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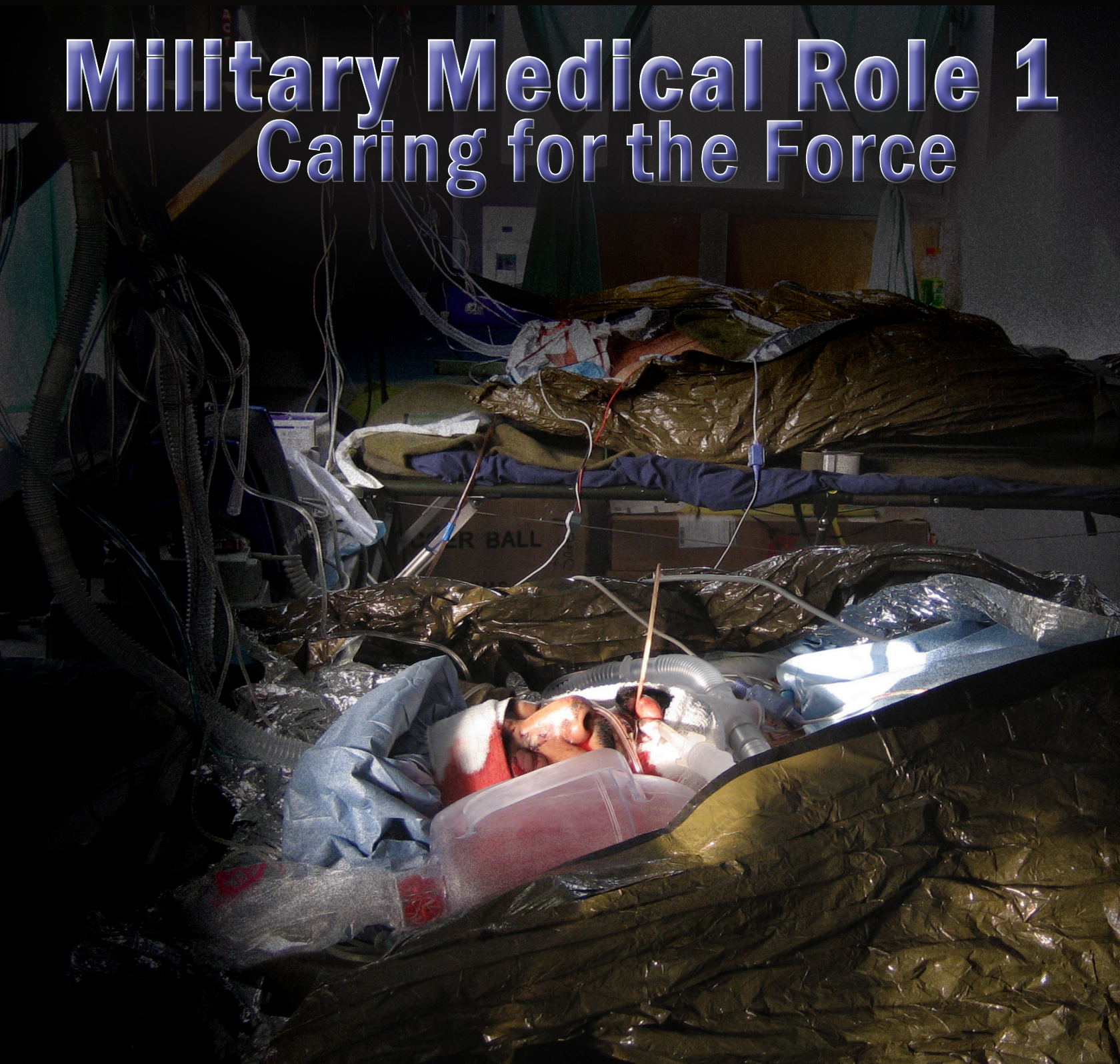
Military Medical Role 1
Caring for the Force



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Two soldiers in the 759th Forward Surgical Team building at forward operating base Lagman, Qalat, Afghanistan, 2006. Image courtesy of COL Jane Shen-Gunther, MD, PhD, a graduate of Jefferson Medical College, Philidelphia, PA; a gynecologic cancer surgeon, who deployed to Afghanistan as a combat surgeon with the 759th in 2006.

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Note from the Editor...

This edition of *The Medical Journal* ushers in a new year for the spring quarterly of 2023, dedicated to the topic of the military Role 1 capabilities, and concerns.

The new year brings some exciting opportunities for groups and agencies to participate with *The Medical Journal*, as several special topic issues are planned and in the works. If your team or unit is working on something noteworthy, please consider sharing it with the military medical community in a special topic issue.

Additionally, *The Medical Journal* accepts general topic submissions year round. Contact us with questions or email submissions to usarmy.jbsa.medical-coe.list.amedd-journal@army.mil. Submission guidelines are included in each issue of the journal, or you can find them on our website at www.medcoe.army.mil/the-medical-journal. Here you can also find more information about the journal, as well as view electronic issues online in the archives. Be on the lookout for new calls for submissions coming soon.

A Narrative Review of Traumatic Pneumothorax Diagnoses and Management

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Abstract

Correct identification and rapid intervention of a traumatic pneumothorax is necessary to avoid hemodynamic collapse and subsequent morbidity and mortality. The purpose of this clinical review is to summarize the evaluation and best treatment strategies to improve outcomes in combat casualties. Blunt, explosive, and penetrating trauma are the 3 etiologies for causing a traumatic pneumothorax. Blunt trauma tends to be more common, but all etiologies require similar treatment. The current standard to diagnose pneumothorax is through imaging to include ultrasound, chest x-ray, or computed tomography. A physical exam aids in the diagnosis especially when few other resources are available. Recent studies on the treatment of a small, closed pneumothorax involve conservative care, which includes close observation of the patient and monitoring supplemental oxygen. For a large, closed pneumothorax, conservative treatment is still a possible option, but manual aspiration may be required. Less often, a needle or tube thoracostomy is needed to reinflate the lung. Large, open pneumothoraxes require the most invasive treatment with current guidelines recommending tube thoracostomy. More invasive management options can result in higher rates of complications. Given the significant variability in practice patterns, most notable in resource limited settings, the areas for potential research are presented.

Keywords: prehospital; pneumothorax, chest, tube, lung, collapse, hemothorax, trauma

Introduction

One of the most prevalent complications of any thoracic trauma, a pneumothorax (PTX), is commonly encountered in emergency settings with a 40%-50% occurrence in all fatal cases.[1,2] Traumatic pneumothoraxes are broken into 2 main categories: iatrogenic and non-iatrogenic. This narrative review focuses on non-iatrogenic traumatic pneumothorax and, specifically, combat-related injuries. The outcome of traumatic pneumothoraxes depends on a combination of diagnosis of the pneumothorax and the choice of treatment. Despite recognizing how critical these aspects of treatment are, there is no consensus on the optimal management strategy.[3] The purpose of this clinical review is to identify the common etiologies, ideal diagnostic modalities, and the best treatment strategies.

Methods

For preparation of this review, the authors used the databases of both PubMed and Google Scholar. The key search terms employed were 'trauma,' 'pneumothorax,' adults,' 'blunt,' 'penetrating,' 'incidence,' and 'treatment.' The authors searched articles written between the years 2012 and 2022 to ensure practices were current. The authors relied on a combination of abstracts, full manuscripts, and supporting citations to obtain as full scope of literature. Restricted terms were those studies focused on children, studies not

Table 1. Search methodology.

Database	Years Searched	Search Terms	Number of Hits
Google Scholar	2012-2022	Trauma Pneumothorax, Treatment, Adults	189
Google Scholar	2012-2022	Piercing, Blunt, Pneumothorax, Adults, Treatment, Diagnostics	645
Google Scholar	2012-2022	Combat, Blast, Trauma, Pneumothorax	978
PubMed	2012-2022	Pneumothorax, Trauma, Adults	859
PubMed	2012-2022	Pneumothorax, Trauma, Diagnostics	286
PubMed	2012-2022	Pneumothorax, Trauma, Incidence	97

written in English, and studies focused on secondary, spontaneous, or iatrogenic spontaneous pneumothoraxes. Table 1 is a detailed breakdown of the database searches.

Review of Literature

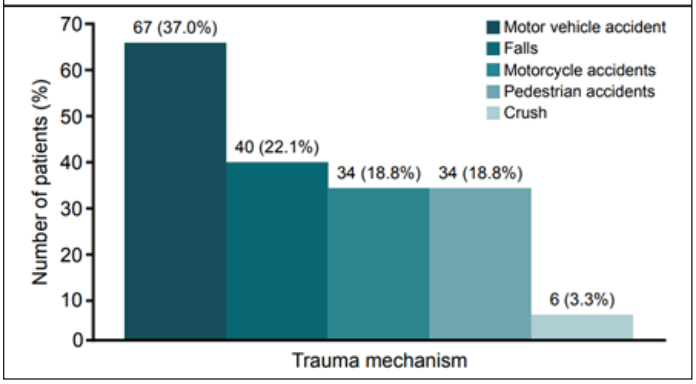
Authors selected a total of 31 research articles from the 2 major databases. The research articles were a combination of retrospective studies, narrative reviews, randomized controlled trials, case studies, and meta-analyses.

Incidence in Trauma: By itself, thoracic trauma accounts for approximately 25% of all trauma-induced mortality and of these cases, almost 50% of the patients have a pneumothorax.[2]

Incidence in Military Trauma: Data collected during Operation Enduring Freedom and Iraqi Freedom, traumatic pneumothorax occurred in over 50% of all thoracic injuries and were the most common complication of thoracic trauma.[4] Of those, 32% of the total thoracic injuries were due to blunt and blast trauma. With modern medicine, the mortality of general chest trauma is 8.6%-16%.[5] Tension pneumothorax was the third leading cause of potentially survivable death on the battlefield.[6]

Etiology: A pneumothorax is a partial or complete collapse of the lung where air leaks into the pleural space. Traumatic pneumothorax can commonly be seen in thoracic traumas. The most common cause of blunt thoracic trauma is motor vehicle collisions but can also be caused by explosions, or impact from falling.[7] A detailed breakdown of the epidemiology of traumatic pneumothorax can be seen in Figure 1.

Figure 1. Distribution of patients based on trauma mechanism.[9]



During combat, potential penetrating injuries are transformed into blunt trauma due to advanced body armor.[5,8] These events can cause rib fractures which may puncture the lung. In military personnel, flail chest is present in quadruple the amount compared to civilians with a blunt chest injury.[5] Blunt force thoracic trauma is the most prevalent type of trauma to the chest, making up 75% of all injuries to this area.[9] It also has a high mortality rate between 20% and 25% with pneumothorax being the primary cause of death.[7,9]

Most commonly, penetrating trauma to the lungs is caused by stabbing, gunshots, impalement, or compound rib fractures. During combat, penetrating trauma is often secondary to blast trauma when flying debris punctures tissue.[5]

Blast trauma results in similar injuries compared to blunt force trauma. Pulmonary injury secondary to blast trauma is further categorized into 3 sections. Primary injury is caused when the direct pressure from the explosion causes tissue damage. Secondary injury occurs due to contact with debris resulting in a combination of penetrating and blunt trauma. Tertiary trauma results from the person being launched into the air upon the initial blast, then falling causing blunt injury.[5] The last 2 pathologies often require hospitalization, whereas those with a primary injury are often fatal prehospital. Blast and other combat traumas may also result in

Figure 2. Ultrasound findings consistent with normal lung movements.

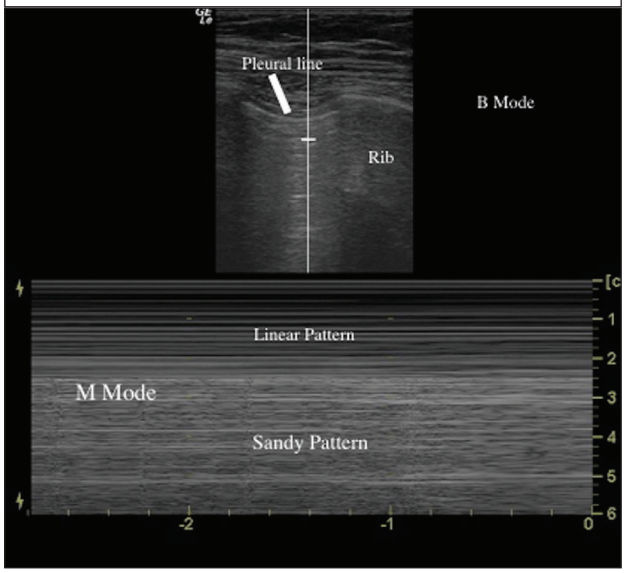
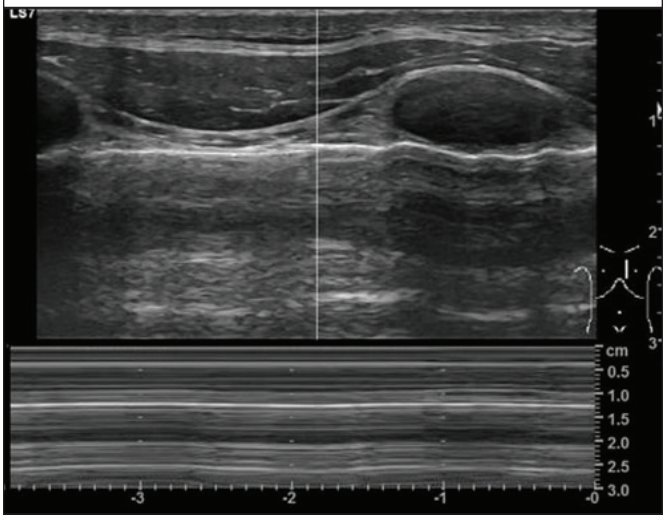


Figure 3. Ultrasound findings consistent with pneumothorax.



lacerations caused by either the initial trauma event or via rib fractures.[5] Due to elastic recoil of the normal pulmonary parenchyma surrounding the injury, displaced ribs or friction caused by fractures can cause lacerations up to 72 hours after injury.[5] Blunt and blast trauma combined make a total of 32% of thoracic combat injuries.[5]

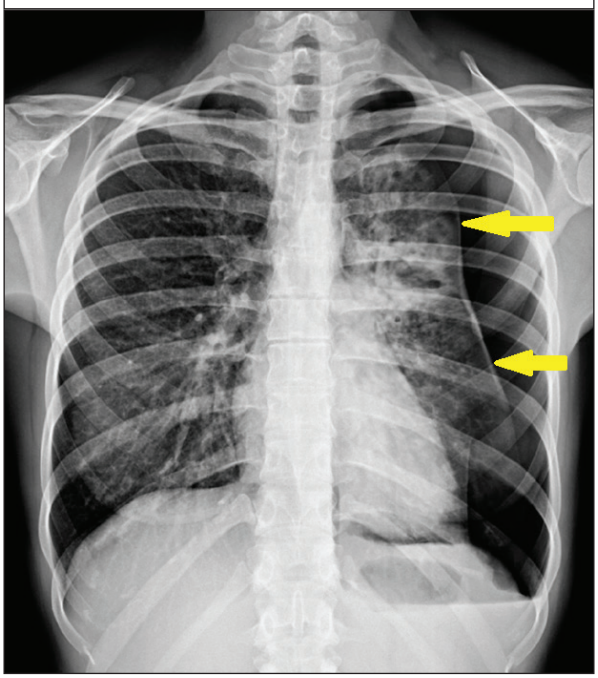
Clinical Diagnosis: A pneumothorax is diagnosed with a combination of physical exam findings and imaging.[10] Most patients' primary complaint is shortness of breath, due to pain during inspiration, usually caused by a fractured rib.[10] On physical exam, there may be tenderness in the area as well as a grating sensation or sound due to the friction of the bone.[10] Chest percussion can also be used in situations where there is no other option for diagnoses of a pneumothorax as it has been shown to have low sensitivity.[11] For penetrating trauma, there is less focus on confirming the diagnosis of a PTX compared to initiating treatment as it can most often be assumed a PTX is present when a penetrating injury is found, and appropriate symptoms are displayed. In the setting of tension PTX, the most common presenting symptom is pulmonary dysfunction with rapid progression to respiratory arrest and/or hypotension.[12]

Ultrasound: Regardless of the etiology, ultrasound has become a reliable tool with increasing popularity in the emergency setting. The shift towards using ultrasound as the first line imaging modality in the diagnosis of PTX has had a favorable effect on length of stay, complications, and pain in trauma patients.[2] In combination with clinical examination and widening of the extended focused assessment with sonography for trauma (eFAST) method, ultrasound studies can be a quick and cost-effective way to diagnose traumatic pneumothoraxes.[13] The most common indicators of a PTX when visualizing the lung through an ultrasound are the absence of lung sliding and comet-tail artefacts.[14] Scanning rib spaces 9, 11, and 12 of the lungs, looking for findings consistent with those seen in Figures 2 and 3, may also help to quickly identify the location of the pneumothorax as 80.4% of right-sided PTX and 83.7% of left-sided PTX can be identified in those regions.[15] Dually noted is "the distribution demonstrated increasing PTX frequency and size from lateral to medial and from superior to inferior," and region 12 also had the largest anterior-to-posterior PTX dimension.[15]

While a clinician can accurately detect many variations of traumatic pneumothoraxes with this tool, using only ultrasound runs a risk of underdiagnosing pneumothorax.[16] The normal eFAST exam has become mainstay of trauma teams but has a low positive predictive value of detecting pneumothoraxes.[17] Ultrasound has shown to have sensitivity of 81% with a 95% confidence interval of 71-88% with another study showing a sensitivity of 65%.[14,16] Ultrasound is also limited when diagnosing the very obese, individuals with subcutaneous emphysema, extensive bandages and dressings, or patients with skin disorders.[13] However, this is generally not as applicable to the military setting. Another main drawback is user error. While ultrasound does have a shorter learning curve, especially in the context of pneumothorax, its ability to correctly diagnose patients often rests in the hands of a skilled technician.[13] Using ultrasound as the primary imaging modality with no follow up test has limitations.[16,17] Serial testing may reduce the risk of missing a PTX on ultrasound.

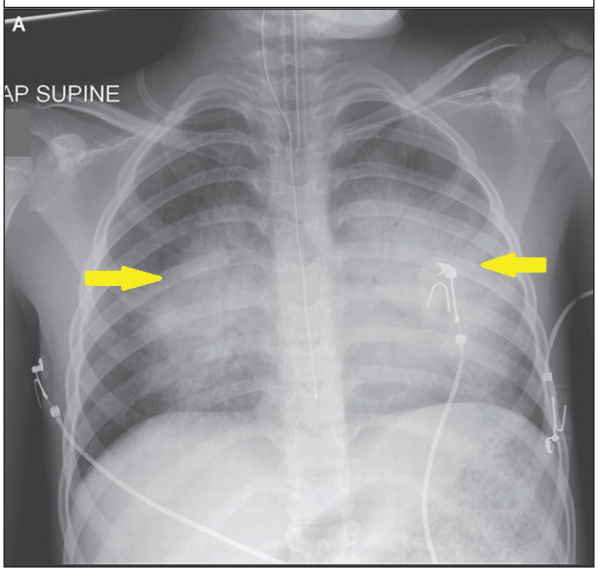
Radiography: Chest radiographs are a very common diagnostic test ordered for anyone who has experienced thoracic trauma. A pneumothorax positive chest x-ray can be seen in Figure 4. However, CT imaging is best for diagnosing rib fractures and possibly pulmonary contusions, which appear as patchy congregations with poorly defined borders on an x-ray.[5,18] Explosive injuries tend to have a specific pattern present on chest x-rays (Figure 5), presenting as butterfly or batwing shaped and is located towards the center of the lung.[5] Though contusions and general trauma to the lungs do not ensure an occurrence of PTX, the unique appearance of chest injuries on radiographs gives an excellent starting point for diagnostics as PTX visible on x-rays are often larger in size. Chest radiographs are not without limitations, however, as it is estimated chest radiographs fail to diagnose PTX around 30% of the time.[13] Because of this, chest radiographs should be treated the same as ultrasound in the context using chest radiographs alone to diagnose a pneumothorax has limitations.[18] When used for follow-up care, however, x-rays can be useful due to their higher predictive values.[18] In a forward setting, though, x-rays may not be readily available.

Figure 4. Chest x-ray findings consistent with pneumothorax.



Computed Tomography (CT): CT can be a useful tool when determining the size of the pneumothorax or if there is a delayed onset.[19] The primary limitation of this modality in the combat setting is the need to transfer a patient to a level of care equipped with a CT scanner; therefore, there is more utility using a CT once the patient has been transferred to a hospital with greater capabilities.[2] For these reasons, physical examination, ultrasound, and chest x-rays are more heavily relied upon for trauma cases in the far-forward setting.

Figure 5. Chest x-ray findings consistent with "blast lung" findings.



Treatment: The overall treatment goal of a pneumothorax is to reinflate the lung to reestablish a typical breathing pattern while limiting the chance of recurrence. If the PTX is 35mm or smaller, then chest tube placement may be unnecessary, meaning fewer resources need to be used to treat a patient, and complications associated with tube placement can be avoided.[3] In a study with 95.5% blunt trauma patients, each with PTX small enough to be seen only on CT scan, chest tubes were not placed.[20] These patients had shorter hospital stays, fewer complications, and decreased mortality than those with chest tubes placed.[20] The results of this study can be found in Table 2. Similarly, PTX between 0.5-2cm may benefit from the same line of treatment. In one study, 33 patients with PTX of that size caused by thoracic trauma, spontaneous reabsorption was observed.[21] Pleural drainage in one patient, and puncture of the pleural cavity in another were required to prevent further complications, but no other intervention was needed.[21] Given this, conservative treatment for small, closed PTX can be an effective treatment that benefits both the patient through having fewer procedures and diminished risk of complications, and the healthcare system as fewer resources are consumed. Though recent literature has challenged the traditional treatment of using a tube thoracostomy for small PTX, combat casualty treatment abides by conventional protocol. In one review, it is recommended military patients with small PTX have a chest thoracostomy immediately as they are at an increased risk of developing a large PTX when flown.[22]

Many patients, especially those with rib fractures, may suffer from a delayed-onset PTX. Plourde et al found 0.9% of patients develop delayed PTX after minor thoracic trauma.[23] Of this

percentage, 87% of the delayed PTX were diagnosed within a week after the initial trauma, and the remainder were diagnosed within 2 weeks.[23] Specifically, at least 1 fracture between the 3rd and 9th ribs had a significant impact on whether a patient would have a delayed diagnosis.[23] Such data indicates even if a patient does not have initial symptoms of PTX, serial exams and high clinical suspicion may be necessary if their condition changes or appears to be evolving.

Table 2. Oucomes of patients with pneumothorax diagnosis before and after 35mm guideline implementation.

Variable	Before Guideline Implementation n = 99	After Guideline Implementation n = 167	Total n = 266	*p*
No. patients receiving chest tubes, n (%)	28 (28.3)	30 (18)	58 (21.8)	0.04
Compliance with 35 mm guideline (4 h), n (%)	90 (90.9)	153 (91.6)	243 (91.4)	0.84
Compliance with 35 mm guideline (24 h), n (%)	81 (81.8)	151 (90.4)	232 (87.2)	0.04
Length of stay, median (SD)	4 (3)	4 (25.1)	4 (20)	0.82
ICU days, median (SD)	0 (1.6)	0 (1.7)	0 (1.7)	0.62
Complications, n (%)	4 (4)	10 (5.9)	14 (5.2)	0.49
Observation, n (%)	84 (84.8)	158 (94.6)	242 (91)	0.007
Observation failure, n (%)	13 (13.1)	21 (12.6)	34 (12.8)	0.62
Reason for failure, n (%)				0.90
New hemothorax	5 (38.4)	9 (42.8)	14 (41.1)	
Physiologic deterioration	0 (0)	0 (0)	0 (0)	
Pneumothorax progression	3 (23)	3 (14.2)	6 (17.6)	
Postsurgery	0 (0)	1 (4.7)	1 (2.9)	
Unclear	5 (38.4)	8 (38)	13 (38.2)	
Thoracic procedure, n (%)				0.63
VATS	1 (1)	2 (0.1)	3 (1.1)	
Rib fixation	1 (1)	2 (0.1)	3 (1.1)	
Pulmonary-related complications, n (%)	5 (5.1)	5 (3)	10 (3.8)	0.39
W Pneumonia	0 (0)	2 (1.1)	2 (0.8)	0.53
Empyema	0 (0)	0 (0)	0 (0)	—
Lung abscess	0 (0)	0 (0)	0 (0)	—
Pulmonary embolism	1 (1)	1 (0.6)	2 (0.8)	1
Postpull pneumothorax	4 (14.8)	3 (10)	7 (12.1)	0.61
Readmission, n (%)	1 (1)	5 (3)	6 (2.3)	0.41
Mortality, n (%)	1 (1)	0 (0)	1 (0.3)	0.37

Observation failure: Patient who after 4 hours of observation underwent a TT.
ICU, intensive care unit; VATS, video-assisted thoracoscopic surgery.

Conservative treatment might remain the preferred method of treatment even in large PTX. As much as 90% of all traumatic PTX patients are treated successfully without surgical intervention or subsequent tube drainage. Whether the patient was on positive pressure ventilation made no difference in the success rate of conservative treatment.[3] Manual aspiration is a valid conservative option to treat large PTX in an attempt to stave off the need for chest tube. Traditionally, 16-gauge (G) catheters are used for this procedure, but 20- or 22-G needles may be effective as well. Aspirations using needles of 20- or 22-G size were 53.3% effective after one attempt, and 80% effective by the third attempt.[24] Aspiration failure "was correlated with an inter-pleural distance >20 mm at the level of the hilum (odds ratio [OR]: 4.93; 95% confidence interval [CI]: 1.49–22.71)" and "twenty-four hours or more from onset to presentation (OR: 2.95; 95% CI: 1.12–8.26)".[24] Other factors such as "severe collapsed lung according to the Japan Society for Pneumothorax and Cystic Lung Disease (JSPCLD) classification system, severe pneumothorax using the Light index (P<0.001), ≥10mm midline shift distance at the level of the carina, and high intrathoracic pressure before aspiration" were correlated to have an increased risk of aspiration failure. The results of this study can be seen in Table 3.

Table 3. Multivariable logistic regression analysis of patients with aspiration failure.[24]

Variables	OR	95% CI	P value
Chest X-ray findings			
Inter pleural distance at level of the hilum >20 mm	4.93	1.49–22.71	0.0075
Type of pneumothorax			
Spontaneous secondary	3.11	1.14–8.76	0.027
Time from onset to visiting the clinic			
≤24 h	2.95	1.12–8.26	0.028

OR, odds ratio; CI, confidence interval

When the aspiration volume is less than 2500mL or the lung fails to expand, a chest tube is placed.[24] Manual aspiration is also easier to perform on outpatients and may reduce hospital time which would greatly benefit the military and reduce return to duty time.[25] In this study, all patients, even those who later needed chest tubes, reported decreased pain, and those with PTX caused by trauma had a 100% success rate.[24] When aspiration fails a chest tube is the next line of treatment. Decompression of the pleura is required before placing a chest tube. Kelly clamps are commonly used for this type of procedure, but with a large surface area more force is required to penetrate the pleura. To reduce force and consequently the risk of secondary injury to the patient, fine artery forceps are an advantageous option,

Advanced Trauma Life Support (ATLS) recommends the course of treatment for open pneumothorax involves first applying a 3-way occlusive dressing and then a chest tube, similar to the Tactical Combat Casualty Care guidelines with the current recommendation to use a vented chest seal. Another important consideration with open pneumothorax injuries is infection. Due to an open wound in the chest, especially when made by a foreign object, broad-spectrum antibiotics should be administered.[1] The detailed steps of this procedure are outside the scope of this review.

In the US, civilian and military in-patient PTX and/or hemothorax (PTX-HTX) clinical management often lasts 13.7 ± 11.9 days before the patient is discharged,

resulting in protracted morbidity.[27] In the deployed environment, US service members with PTX-HTX are often prioritized for evacuation and thus are unable to return to duty, further straining combat capabilities.[28] In future combat operations with delays in evacuation, an accelerated protocol to manage the PTX-HTX may conserve the fighting force.[28,29] An accelerated PTX-HTX protocol may also reduce morbidity and health system costs for civilian populations across all income brackets. However, there is no formal literature or research on the topic. This is likely because the predominance of literature and research on traumatic PTX has emerged from high-income countries, like the USA and Canada.

Complications: Complications surrounding traumatic pneumothorax can vary depending on the original etiology of the injury and the course of treatment. Small, closed pneumothorax complications can be diminished by correct diagnosis and using conservative treatment strategies.[20,30] Large, closed traumatic pneumothorax cases tend to have more complications due to requiring chest tube placement.[31] Complications with chest tubes fall under 3 main categories, post removal, insertional, and positional with the latter being the most common of these complications.[31] In cases with complications, the overage cost of the procedure becomes 9 times greater than non-complicated chest tube insertions.[31]

Another complication is tension PTX, a condition that can theoretically develop in any PTX case and can lead to cardiovascular collapse and death.[2] The details of this complication are otherwise beyond the scope of this narrative review.

Potential Future Research: An area of potential research should focus on far-forward diagnostics and treatments, such as highly portable, automated methods to monitor for pneumothorax that do not require constant ultrasound measurements. This would cognitively offload the reoccurring need for monitoring and potentially identify a PTX before tension physiology occurs. Once a PTX develops, noninvasive or minimally invasive methods to resolve PTX and potentially increase rapid return to duty rates would be optimal. In particular, there is a need to treat a PTX without requiring evacuation from theater, and potentially return them to the fight within a few days.

Conclusions

Traumatic pneumothorax is a common condition among thoracic trauma patients despite a scarceness of studies surrounding it. Current standards of treatment involve thoracic thoracostomy, but recent literature have pointed toward a more conservative treatment (e.g. high-flow oxygen, needle decompression) being the most advantageous route for any patients. Future research should be directed towards portable methods for rapid diagnosis and treatment methods to increase return to duty rates.

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Massive Transfusion Thresholds Associated with Combat Casualty Mortality during Operations in Afghanistan and Iraq: Implications for Role 1 Logistical Support Chains

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Abstract

Introduction: Limited literature exists examining outcomes associated with alternative thresholds for massive transfusion outside of the historical definition of 10 units of packed red blood cells (PRBC) in 24 hours. This study reports the predictive accuracy of alternative thresholds for 24-hour mortality and explores implications for Role 1 care supply requirements.

Methods: We conducted a secondary analysis of data from the Department of Defense Trauma Registry (DOD-TR) spanning encounters from 1 January 2007 through 17 March 2020. We included all casualties who received at least 1 unit of either PRBC or whole blood. We calculated area under the receiver operator curve (AUROC) of blood product quantity received, including both PRBC and whole blood, as a predictor for mortality within 24 hours of arrival to a military treatment facility. We identified optimal predictive thresholds per Youden's index.

Results: We identified 28,950 encounters of which 2,608 (9.0%) entailed receipt of at least 1 unit of PRBC or whole blood. Most casualties sustained battle injuries (2,437, 93.4%) with explosives as the most common mechanism (1,900, 72.8%) followed by firearms (609, 23.3%). The AUROC for blood product received within 24 hours was 0.59. The optimal threshold for predicting 24-hour mortality per Youden's Index was 20 units (sensitivity of 34.9% and specificity of 78.6%). The threshold exceeding 90% sensitivity was 2 units; whereas, the threshold exceeding 90% specificity was 33 units.

Conclusions: We identified a wide range of numbers of received blood products associated with short-term mortality based upon prioritization of sensitivity or specificity. This study found only 2 units of blood product received had a 90% sensitivity for predicting 24-hour mortality, highlighting the resource mobilization challenges that confront healthcare providers during resuscitation at the Role 1.

Keywords: massive transfusion, combat, trauma, blood, resuscitation

Introduction

Contemporary data from combat casualties consistently highlight hemorrhage as the most common cause of potentially survivable death on the battlefield.[1-3] Accordingly, the central focus of Tactical Combat Casualty Care (TCCC) is hemorrhage control of compressible massive hemorrhage, namely through the use of limb and junctional tourniquets.[4-7] Additional interventions include the use of topical hemostatic agents[8,9] and systemic medications such as tranexamic acid.[10-14]

Alongside hemorrhage control, volume resuscitation is an essential component of managing non-compressible torso hemorrhage and hemorrhagic shock. In patients with depleted intravascular volumes and active hemorrhage, the use of alternative strategies to maintain perfusion such as crystalloid fluids appear detrimental to

casualty outcomes.[15-17] Instead, the foundation of current TCCC guidelines focuses on the restoration of the functionality of blood[18,19] and volume with blood— whole blood preferred, followed by a balanced approach with components if whole blood is not available.[20,21] Data from practices during the recent conflicts in Afghanistan and Iraq suggest whole blood, ideally cold stored low titer group O whole blood[22] followed by fresh low titer group O whole blood,[23-25] provides an optimal resuscitation fluid. When using component therapy, optimal transfusion ratios approach 1:1:1 ratios of packed red blood cells (PRBC), fresh frozen plasma (FFP), and platelets.[26] The recently released Prolonged Casualty Care guidelines state to transfuse per the Defense Committee on Trauma and TCCC guidelines.[27]

These guidelines become increasingly important for those patients requiring significant volumes of blood product. The literature studying these events has historically classified massive transfusion as receipt of 10 or more units of whole blood within a 24-hour time period; this value is somewhat arbitrary in that it approximates replacement of 1 blood volume (10 x 500 mL bags versus RBC 10 x 350 ml) but does not necessarily represent a threshold associated with changes in physiology or outcomes.[28-30] Additionally, this is a retrospective classification possibly lacking utility in the midst of resuscitation. This definition is not universal; although, other definitions similarly align with replacement of the equivalent of a patient's blood volume. The Association for the Advancement of Blood & Biotherapies (AABB), formerly the American Association of Blood Banks, specifically defines massive transfusion as the replacement of a volume equivalent to a patient's blood volume in 24 hours.[31] Emerging literature has explored the implications of using alternative cut off values to define massive transfusion.[32]

This study contributes to these efforts by exploring the quantity of blood product most predictive of mortality within 24 hours. Specifically, we sought to determine the volume of blood predictive of death as defined by 3 different measures. Those measures were Youden's index, 90% sensitivity, and 90% specificity.

Table 1. Demographics, injury, and outcome data of the cohort.

Demographics	**Age**	24 (21-28)
	Male	98.5% (2571)
Affiliation	**US Military**	81.1% (2117)
	NATO	18.8% (491)
Classification	**Battle**	93.4% (2437)
	Non-battle	6.5% (171)
Mechanism of injury	**Explosive**	72.8% (1900)
	Firearm	23.3% (609)
	Fall	0.4% (12)
	Motor vehicle	1.2% (32)
	Other	2.1% (55)
Injury Severity Score	**Composite**	21 (14-29)
Serious injuries by body region	**Head/neck**	19.0% (498)
	Face	0.8% (23)
	Thorax	24.5% (639)
	Abdomen	21.2% (555)
	Extremities	70.5% (1840)
	Skin	7.5% (197)
Outcome	**24-hour survival**	94.9% (2476)
	Final discharge survival	91.4% (2384)

Methods

Study Design & Setting: We conducted a secondary analysis of data from the Department of Defense Trauma Registry (DODTR), formerly known as the Joint Theater Trauma Registry (JTTR). This registry is the data repository for the DoD of trauma-related injuries.[8,33-35] The US Army Institute of Surgical Research regulatory office reviewed this protocol (H-20-015) and determined it was exempt from Institutional Review Board oversight. We obtained only de-identified data.

Study Population: The DODTR includes documentation regarding demographics, injury-producing incidents, diagnoses, treatments, and outcomes following injuries. The registry includes US and non-US military as well as US and non-US civilian personnel from the point of injury to final disposition during war and peacetime. The DODTR is comprised of patients admitted to a Role 3 (fixed-facility) or forward resuscitative surgical detachment (FRSD) with an injury diagnosis using the International Classification of Disease 9th Edition (ICD-9) between 800-959.9, near-drowning/drowning with associated injury (ICD-9 994.1) or inhalational injury (ICD-9 987.9) and trauma occurring within 72 hours from presentation to a facility with surgical capabilities. For this study, we included all casualties with documented receipt of at least one unit of either PRBC or whole blood from point of injury to evacuation from theater of operation.

Data Collection: We performed a retrospective review of the prospectively collected DODTR data. Via automated data abstraction, we queried the DODTR for data spanning 1 January 2007 to 17 March 2020 using a series of prehospital procedural and diagnostic codes as previously described.[35] These methods allowed us to retrieve encounters for combat casualties arriving to a military treatment facility. We collected data on patient demographics including age, sex, affiliation, and military operation location. We reviewed intervention data regarding receipt of at least 1 unit of either PRBC or whole blood within 24 hours of arrival to a military treatment facility. Finally, we abstracted data regarding mortality within 24 hours during this same time horizon.

Table 2. Predictive accuracy of blood product receipt for death within 24 hours of arrival to military treatment facility.

Blood Product	AUROC	Threshold	Sensitivity	Specificity
PRBC and whole blood	0.59154	20	0.3485	0.7859
PRBC only	0.59253	20	0.3333	0.8029
Whole Blood only	0.54481	66	0.1500	0.9774

Table 3. Blood product thresholds predictive of death within 24 hours of arrival to military treatment facility with sensitivity values exceeding 90%.

Blood Product	Threshold	Sensitivity	Specificity
PRBC and whole blood	3	0.9196	0.2131
PRBC only	2	0.9621	0.0743
Whole Blood only	2	0.9000	0.1170

Table 4. Blood product thresholds predictive of death within 24 hours of arrival to military treatment facility with specificity values exceeding 90%.

Blood Product	Threshold	Sensitivity	Specificity
PRBC and whole blood	33	0.1970	0.9047
PRBC only	31	0.1894	0.9006
Whole Blood only	19	0.0771	0.9057

Outcome Measures: We included data on all patients and their interventions delivered throughout the echelons of care, but our primary outcome measure was mortality within 24 hours of arrival to a Role 3 military treatment facility. We selected this outcome in lieu of survival to discharge to better focus on an outcome related to transfusion administered in the first 24 hours of the care of the casualty. Our intent was also to avoid potential confounders arising from subsequent hospitalization, treatments, and survival bias.

Data Analysis: We utilized descriptive statistics to portray our patient population. We presented continuous variables as means and 95% confidence intervals (CIs). We reported medians and interquartile ranges for nonparametric continuous variables and ordinal variables. We presented nominal variables as percentages and numbers. We presented limited inferential statistics using the chi-square test for nominal variables, t-test for continuous variables with normal distribution, and Wilcoxon ranked sum test for skewed continuous variables and ordinal data.

We built a receiver operator curve (ROC) of blood product receipt including both PRBC and whole blood. We calculated the area under the ROC (AUROC). We then identified the optimal cut-off value for blood product volume predictive of mortality within 24 hours of arrival to a military treatment facility using Youden's Index.[36,37] We then stratified these analyses for PRBC and whole blood separately. We repeated these analyses to identify thresholds associated with a sensitivity for mortality of 90% or greater. Finally, we identified those thresholds associated with a specificity for mortality of 90% or greater. We performed all analyses using commercially available software for database management and statistical analysis.

Results

Within the DODTR, our original data request resulted in 28,950 encounters spanning 1 January 2007 to 17 March 2020. Of these, 2,608 (9.0%) met the inclusion for this sub-analysis with receipt of at least 1 unit of PRBC or whole blood. The median age was 24, and almost all (98.5%) were male. Most casualties sustained battle injuries (2,437, 93.4%) with explosives as the most common mechanism (1,900, 72.8%) followed by firearms (609, 23.3%). The median composite injury severity score was 21, with serious injuries to the extremities (70.5%) predominating. Both 24-hour (94.9%) and survival to discharge (91.4%) were high (Table 1).

The AUROC for both PRBC and whole blood products (n=2,608) in units administered within 24 hours as a predictor of mortality within 24 hours of presentation to a military treatment facility was modest at 0.59. The optimal blood product threshold including both PRBC and whole blood per Youden's Index was 20 units. This value predicted death within 24 hours with a sensitivity of 34.9% and a specificity of 78.6%. Analysis stratified by PRBC products only (n=2,608) yielded similar results. Analysis stratified by whole blood products only (n=285) yielded a slightly lower AUROC (0.54) and a significantly higher threshold per Youden's index of 66 units. This threshold portended mortality with a sensitivity of 15.0% and a specificity of 97.7% (Table 2).

The quantity of combined PRBC and whole blood products predictive of mortality with >90% sensitivity for death within 24 hours was 3 units. The threshold was 2 units for both PRBC alone and whole blood alone (Table 3). The threshold value for specificity exceeding 90% was 33 units in the case of combined PRBC and whole blood products. In patients with PRBC resuscitation alone, the threshold was 31 units. Finally, for whole blood alone, this threshold was 19 units (Table 4).

Discussion

Hemorrhage is the leading cause of potentially preventable death on the battlefield.[1-3] A paucity of literature has explored alternative thresholds for massive transfusion other than the historical definition of 10 units of PRBC

in 24 hours. An example of an alternative thresholds explored includes >4 PRBC units within 1 hour with anticipation of continued need for blood products.[38] Another example is replacement of >50% of the casualty's total blood volume by blood products within 3 hours.[39] Our study expands upon these explorations by reporting the predictive accuracy of alternative thresholds including whole blood product for mortality within 24 hours of arrival to a military treatment facility. We found optimal thresholds of various combinations of PRBC and whole blood per Youden's index ranging between 20-66 units. Thresholds ranging from 2-3 units predicted mortality with a sensitivity exceeding 90%. Thresholds ranging from 19-31 units predicted mortality with a specificity of 90% or greater.

The historical definition of massive transfusion has been 10 or more units of whole blood in a 24-hour period.[28-30] This number originated from early study of transfusion of non-traumatic surgical patients in the early 20th century who commonly experienced bleeding diatheses. Volumes transfused varied, but 3,000 milliliters, a volume approximating 6 units of PRBCs, generally represented the lower limit received by these patients.[40] Subsequent papers studying patient populations receiving "massive transfusions," to include combat casualties in Vietnam, started to use the 10 units within 24 hours threshold.[41]

The definition of massive transfusion should accurately reflect the threshold beyond which patients' physiology and clinical outcomes change, and our analysis suggests a higher threshold may better serve this purpose. A recent study attempted to redefine massive transfusion using whole blood. In the study, they used a threshold of 7 units for whole blood massive transfusion. They found it the most accurate predictor of early mortality in comparison with other equations by AUC analysis.[42] Our DODTR analysis specifically indicates the volume of blood most predictive of death within 24 hours of arrival to a military treatment facility is 20 units, which is double the historical definition. If replicated by other studies, this has significant implications for the prognosis of casualties receiving more than the 10 units historically meeting criteria for massive transfusion but less than the 20 units identified by our study as most predictive of mortality. The prognosis of these patients, while guarded, may be more favorable, warranting ongoing aggressive intervention through all echelons of care to include Role 1. Planners may conceivably use the thresholds we have identified as approximate amounts of blood product required per critically ill patient based on the presumption after infusion of 20 units, the clinical return on blood product investment will decrease, so providers should consider termination of further blood product infusion or explore alternative therapeutics for shock resuscitation including vasopressors. Even with this presumption, 20 units poses a significant logistical burden. Our findings highlight many casualties will require increasingly large volumes of blood product, which will be challenging to procure and store in a contested environment, particularly as far forward as the Role 1.

The difference in quantity of blood for the traditional definition of massive transfusion and the 20 units identified as a more reliability specific threshold associated with short-term mortality may reflect modern advances in blood storage techniques and donor screening. Unfortunately, this remains purely conjecture at this time as robust data from clinical trials do not yet exist to speak to the impact of alternative storage techniques on patients' coagulopathy and survival. Ongoing improvements in blood product storage and administrative methodology spanning from the publication of these historical articles and the current era may have mitigated the impact of significant volumes of blood product on patient coagulopathy. Thus, patients would need to receive more blood product before developing the deranged physiology associated with mortality risk, hence the higher thresholds we identified in our study when compared to the historical 10 units in 24 hours value. Of course, this is purely conjecture, given we can only identify associations and not causation with this study design. Nevertheless, our results suggest the AABB definition of massive transfusion as replacement of one blood volume threshold, approximately 20 units for a 90 kilogram adult, may better identify those patients at highest risk of mortality.

The need for higher thresholds to better correlate with the risk of adverse outcomes appears particularly true for whole blood transfusions. Emerging data indicate the use of fresh whole blood[21,23-25] and low titer group O whole blood[22] may yield a mortality benefit for combat casualties. It is interesting to note the optimal threshold predictive of mortality for whole blood in our study (66) was markedly higher than that for PRBC alone (20). Survival bias notwithstanding, higher numbers of blood products transfused are likely to indicate sicker trauma patients with higher risks of untoward outcomes. The fact patients could receive more than 3 times the volume of blood product as casualties receiving component therapy before experiencing the highest risk of mortality might indicate improved patient physiology and higher likelihood of survival for patients resuscitated with whole blood as compared to PRBCs. This further highlights the incredibly large volume of product potentially will be necessary to resuscitate patients as far forward

as the Role 1. This finding is preliminary due to limited available data as only 285 of the 2,608 encounters in our study included patients receiving whole blood. Nevertheless, military healthcare providers and planners training to provide combat casualty care during large scale combat operations must prepare for the possibility of needing to manage patients requiring transfusion of such large volumes of blood product.

It is important to bear in mind the modest AUROC values, none of which exceeded 0.6, indicate a limited correlation between blood product administration and short-term mortality outcomes. Practically speaking, no threshold identified in our dataset will simultaneously achieve high sensitivity and high specificity. Indeed, the 20-unit threshold we identified per Youden's index has only a modest specificity (78.6%). Should researchers wish to more reliably identify patients likely experiencing altered physiological states placing them at increased risk for mortality, a threshold predicting 24-hour mortality with a specificity greater than 90% is higher still: 33 units. Using these higher thresholds can predict patient populations likely to require distinct clinical treatments to optimize outcomes. Future studies of massive transfusion could add clarity to the literature on this issue by stratifying their analyses to examine characteristics and outcomes of patients receiving these higher thresholds of blood product.

These higher thresholds come at the expense of sensitivity and as a result would not be appropriate for early identification of patients likely to require mobilization of additional blood resources. Such early identification would be better served by the lower 2-3 unit thresholds we identified which achieved sensitivity values exceeding 90%.

Our study has several limitations. First, a retrospective analysis is limited by data available in a combat setting, which may be inaccurate secondary to recall bias and other errors in data entry. Second, as a strictly observational study, we are unable to establish causation. Third, we do not have data to specify transport times or tactical situation, both of which are incredibly important considerations which may impact mortality due to delays in care. Fourth, for recipients of whole blood, our data does not distinguish between fresh whole blood versus low titer group O whole blood. We imagine the majority of whole blood in our dataset represents fresh whole blood based upon our experience with whole blood availability in theater. We must also note the inherent survival bias built into a study of this design. The casualty had to survive long enough to receive such a large volume of blood, or in some cases any blood at all, to contribute to the volumes noted. To this end, we are also unable to characterize those who may have benefitted from aggressive blood transfusions but did not survive long enough to receive it. Finally, our results arise from data stemming from 2 decades of principally counterinsurgency operations which may not necessarily extrapolate to casualty care scenarios occurring during large scale combat operations. That said, the only other likely source of data to inform massive transfusion processes and outcomes in such settings would likely be notional casualties from combat training centers.[43] Finally, our AUROC analyses are only capable of assessing the predictive value of a single variable at a time and do not control for myriad confounders such as receipt of tranexamic acid (TXA), vasopressors, or other interventions as potential confounders. Strengths of this study include the size of the study population as well as the general relevance of our results to the target combat casualty population.

Future research will be necessary to further expand upon our findings. Given the nature of battlefield research, future investigations utilizing data from combat zones will likely continue to rely on registry data and suffer from similar limitations. Inclusion of prospective civilian massive transfusion studies could allow for stratification of their results using alternative thresholds. Such analyses may yield further insights into the merits of alternative cut-off values to define those patients experiencing unique physiology and risks for adverse outcomes, warranting further studies to optimize management. Future studies would also ideally stratify by receipt of TXA to better clarify the relationship between intervention and patient outcomes.

Conclusions

Based on available DODTR data, we found a threshold of blood product receipt associated with short-term mortality of 20 units, double the historical definition of 10 units within 24 hours. Our data suggest higher thresholds to define massive transfusion may better isolate a patient population with unique pathology and risk for untoward outcomes requiring further focused investigation.

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Airway Management during Large-Scale Combat Operations: A Narrative Review of Capability Requirements

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Abstract

Large-scale combat and multi-domain operations will pose unprecedented challenges to the military healthcare system. This scoping review examines the specific challenges related to the management of airway compromise, the second leading cause of potentially preventable death on the battlefield. Closing existing capability gaps will require a comprehensive approach across all components of the Joint Capabilities Integration Development System. In this, we present the case for a change in doctrine to selectively provide definitive airway management in prehospital settings to maximize the effectiveness of limited resources. Organizational changes to optimize training and efficiency in delivery of complex airway intervention include centralization of assigned healthcare personnel. Training must vastly increase opportunities for live tissue and patient experiences to obtain repetitions of both non-invasive and definitive airway procedures. Potential materiel solutions include extra-glottic devices, bag-valve masks, video laryngoscopes, and oxygen generators all ruggedized and capable of operations in austere settings. Leadership and education changes must formalize more robust airway skills into the initial training curricula for more healthcare personnel who will potentially need to perform these life-saving interventions. Simultaneously, personnel changes should expand authorizations for clinicians with advanced airway skills to the lowest echelons of care. Finally, existing medical training and treatment facilities must expand as necessary to accommodate the training and skill maintenance of these personnel.

Keywords: airway management; intubation; cricothyrotomy; extra-glottic airway device; military medicine; supraglottic; extraglottic

Introduction

Background: Combat casualties present with unique wound patterns most clinicians have relatively little experience encountering during domestic healthcare delivery.[1] Each successive conflict in which the US has participated from World War II through Operating Enduring Freedom has seen incremental improvements in casualty survival.[2] Studies typically assess case fatality based on casualties who arrive to a military treatment facility (MTF) alive and subsequently die of wounds (DOW). This is distinct from prehospital deaths classified as killed in action (KIA), which denotes persons killed on the battlefield prior to reaching a MTF. During the recent wars in Iraq and Afghanistan, the US Army's elite units have achieved DOW percentages as low as 1.7%.[3]

However, these accomplishments are unlikely to be due to advances in clinical care delivery alone. In addition to medical advances, these sequential conflicts also saw increasing overmatch in tactical capabilities for the US compared to its adversaries such as almost complete freedom of air movement and combat against a relatively untrained, gorilla-warfare style combatants.[4,5] In particular, World War II represented the last experience

of the US military with a near peer competitor. The National Defense Strategy, released in 2018, states the US now views the geopolitical environment as one of great power competition in which the US must prepare for the possibility of large-scale combat operations (LSCO) with contests in all domains (air, land, sea, cyber, and space). It is not at all certain the military health system will be able to achieve the impressively low DOW rates seen in recent conflicts when transitioned to such hyperkinetic environments.

While data from Ukraine is pending, experience from simulated environments, such as the military combat training centers and warfighter exercises, indicate multiple features, complicating casualty care in these scenarios. These will include contested battlefields precluding rapid medical evacuation, chemical and biological threats, and disease and non-battle injuries given casualty isolation from MTFs.[6] Contested environments precluding casualty transportation rearward will require prolonged casualty care (PCC) for hours or even days.[7] This will require military healthcare personnel proficiency in many advanced nursing skills such as patient positioning, vital sign monitoring, diet, hydration, wound care, intravenous medication administration, noninvasive monitoring such as electrocardiography and pulse oximetry, and ventilator management, and management of tubes, lines, and drains.[8,9] These settings will also pose unique challenges related to airway management ranging from difficulties with performing intubation and subsequent ventilation management with limited lighting, loud noises, and dangers associated with kinetic environments.[10,11]

Importance: Airway management is critical to the treatment of the combat casualty. During operations in Iraq and Afghanistan, airway compromise was the second leading cause of potentially preventable death on the battlefield.[12] Recent data underscores the continued importance of airway compromise as a major contributor of potentially survivable combat injuries.[13] First responders, such as combat medics, receive training to perform surgical airway management forward on the battlefield, the success of which has been as low as 68% in these settings.[14] Endotracheal intubation has higher first-pass success but generally occurs strictly in higher roles of care by providers and is not a procedure outlined in the Tactical Combat Casualty Care (TCCC) guidelines.[15] There is relatively little data on the use of extra-glottic devices in combat but the data that does exist indicates low casualty survival comparable to those for patients undergoing cricothyrotomy.[16] There exists a critical knowledge gap in the clinical implications of multi-domain operations (MDO) and LSCO in relation to the airway management needs of combat casualties.

Goals of this Paper: This paper comprises a review outlining the capability gaps and potential solutions related to trauma airway management during MDO to include LSCO. To this end, it will comprise a narrative review. We will organize the discussion of potential solutions using a Joint Capabilities Integration Development System (JCIDS) construct.[17] To focus the endpoints on the needs of the military, we organized the review around doctrine, organization, training, materiel, leadership and education, personnel, and facility (DOTMLPF) changes. In conducting the review, we followed the general outline of the Scale for the Assessment of Narrative Review Articles (SANRA).[18]

Doctrine

Existing TCCC guidelines encapsulate current doctrine for prehospital airway management on the battlefield. "Prehospital" as defined in doctrine and the Department of Defense Trauma Registry (DODTR) encompasses the point of injury through Role 1 Battalion Aid Stations (small mobile medical units typically staffed with a generalist physician or physician assistant).[1,19] These guidelines recommend various airway management initiatives forward on the battlefield as part of the prehospital tactical field care phase. These include non-invasive maneuvers such as airway positioning and use of nasopharyngeal airway (NPA) and oropharyngeal airway (OPA) devices to maintain airway patency. When these maneuvers prove inadequate, current guidelines recommend placement of an extra-glottic airway or surgical airway by cricothyrotomy.[20]

The Joint Trauma System (JTS) Clinical Practice Guidelines (CPGs) offer an alternative doctrinal source with comparable recommendations. The CPGs for airway management for traumatic injuries in general and during PCC specifically provide a similar recommendation for stepwise progression from non-invasive positioning techniques and airway adjuncts prior to definitive airway management. One principal difference is the recommendation operators attempt endotracheal intubation prior to surgical airway management.[21,22] This difference reflects the relative focus of the JTS CPGs on higher echelons of care staffed by more extensively trained providers compared to TCCC guidelines, which focus exclusively on the care rendered by combat medics and other first-responders.

There are several concerns with these existing doctrinal guidelines. Regarding extra-glottic airway device use, the data of its success and outcomes on the battlefield are scant with only 22 observations in the DODTR.[23]

More data exists regarding cricothyrotomy for which success is dangerously poor, particularly among prehospital providers.[10,14,15] The appropriateness of these interventions in prolonged field care scenarios is even less certain given the potential for acute and long-term sequelae of airway placement.[24] Nevertheless, alternatives such as tracheal intubation suffer their own limitations, necessitating a Hobson's choice of highly imperfect airway solutions or avoidance of invasive airway procedures altogether.

As a result of the frustrating choices in definitive airway management options in prehospital settings, particularly outside of Role 1 MTFs, an argument can be offered for a more selective use of airway procedures in the prehospital phases in MDO and LSCO. This is because definitive airway management is resource intensive in terms of equipment, medications, and skilled manpower required for the procedure. Such demands continue after securing an airway to monitor patient oxygenation, ventilation, and sedation. Under circumstances of high numbers of casualties and contested lines of communication, providers should reserve intubation or surgical airway placement for the casualties most likely to benefit. The basis for this recommendation is patients undergoing airway interventions have comparatively low likelihood of survival compared to other casualties.[25,26] This is particularly true if airway management occurs in the prehospital setting.[27,28] To accomplish this, new evidence-based guidelines must be developed to provide specifics on selecting candidates for advanced airway management.

As a major shift in medical thinking, selective use of prehospital advanced airway management faces significant counterarguments. Mazuchowski et al found nearly 1 in 6 potentially survivable deaths resulted from airway obstruction, indicating airway management is a critical component of damage control resuscitation.[13] Deemphasizing any one major body system will likely result in poor outcomes. Taken to its limit, a selective approach could be applied to all except the simplest prehospital interventions to include hemorrhage control, wound care, etc. This could preclude lifesaving care for a wide range of combat casualties.

While pragmatic, a selective approach obscures the reason for the stubbornly poor prehospital combat performance in advanced airway procedures: inadequate combat medical skill and a lack of technology development.[29] Addressing training and material solutions may obviate the need to selectively defer airway care in casualties who might otherwise survive. Another important caveat focuses on the very nature of LSCO and MDO: chemical and biological threats. Depending on the agent used, the acute effects are likely to primarily affect the airway and respiratory system.[30] The ability to provide advanced airway management and positive pressure ventilation will be the major focus of casualty management in these scenarios. Selective airway management may be untenable in these circumstances.

Under a selective airway paradigm, if a provider treats a casualty in a prehospital setting in which resources are available and evacuation is possible, definitive airway placement may be reasonable. Conversely, doctrine should normalize provider decision-making to designate these casualties as expectant to conserve resources to achieve better outcomes for greater numbers of less severely wounded casualties. This is in line with a growing body of military medical literature examining the potential role of reverse triage in LSCO settings, prioritizing healthcare resource for casualties more likely to survive and potential return to duty.[31] Reverse triage, originally developed for civilian hospitals, creates inpatient surge capacity by identifying and discharging hospitalized patients not requiring major medical intervention for the next 96 hours or more and having reduced risk for poor outcome directly resulting from early discharge.[32]

Organization

Organizational changes necessary to optimize airway management during LSCO entail centralization of medical personnel. For example, within the Army this should start with centralization within battalion maneuver units with advocacy by the Medical Center of Excellence (MEDCoE) Field Forces Integration Directorate (FFID). According to the modified table of organization and equipment (MTOE) for most maneuver battalions, all medical personnel, including combat medics, undergo assignment to the headquarters and headquarters company (HHC). However, common practice is to attach or even assign these soldiers to other companies within the battalion for the purposes of training and meeting administrative requirements, such as individual and collective task requirements. Commanders at battalion and higher echelons should enforce adherence to the MTOE structure whereby these soldiers reside strictly within the headquarters elements.

An operational extension of this adherence should be increasing transition in support relationships to emphasize area over direct support.[33] A medical unit operating under an area support construct would provide all the combat medical care above the level of combat lifesavers for a group of combat units or a geographical area.[34] Much like civilian emergency medical services respond to citizens within a given municipality, the area support unit

combat medics would likewise respond where needed. This has multiple potential positive effects including a reduction in the number of medics needed to support the line combat units, an increase in per capita combat medic clinical exposure, and improved clinical training focus within the medical unit. Drawbacks include loss of maneuver commander control over medical personnel, less opportunity to synchronize maneuver and sustainment soldiers in training, and undermining of the bonds between combat medics and the soldiers they support. However, the general support model does not preclude attaching one or more combat medics to the line unit, as this can help maintain strong relationships.

Centralization by any means will facilitate the increased training requirements associated with educating medics in the complexities of airway management on the modern battlefield. First, all healthcare personnel will belong to the same organization in which the staff and clinical healthcare personnel reside, enabling the latter to advocate for increased training opportunities for all medical service members. Second, training synchronization will be easier to achieve with all members of the airway training audience falling under a single command team. Finally, by making a single command team responsible for the training readiness of the entirety of the battalion's medical force, it is more likely this command team will exercise extreme ownership of this training for the combat casualty care problem set.[35] Moreover, it allows for better command and control oversight by the unit-level physician who would, presumably, maintain a better focus on ensuring their daily workload is medic task-specific. Accordingly, health service support delivery will occur on an area support as opposed to direct support basis. This will enable these personnel to flex their efforts to those maneuver formations most in need of medical care. This will likely also result in increased procedural volume and hence competency across these healthcare providers.

Over the longer term, the Army should examine further centralization of healthcare personnel to further achieve these ends. The Medical Capabilities Development and Integration Directorate (CDID) under Army Futures Command (AFC) should lead these efforts over the next decade. While retaining some healthcare force structure within the battalion maneuver elements, these efforts would ideally shift more of this force structure into the support medical companies at the brigade combat team level and into medical operational units such as area support medical companies. Such moves are likely to be contentious insofar as they remove medical assets from maneuver battalion commanders. Nevertheless, these moves would further optimize training opportunities in garrison and efficiencies in healthcare delivery during combat operations. These benefits are particularly important for complex interventions such as airway management, which require extensive training and are manpower intensive upon execution.

Training

Among the most important lines of effort for the military to optimize airway management during future conflicts will be evolution of training strategies. After action reports from combat operations routinely highlight the need for more training on airway interventions.[11,36] The need for training extends across the spectrum of airway interventions from positioning maneuvers to surgical airway management. This is particularly true for more complex airway interventions such as cricothyrotomy for which success in prehospital combat environments has been as low as 68%.[14]

The resources and time required for training likely increases significantly for more complex procedures.[37,38] In particular, endotracheal intubations and surgical cricothyrotomy pose significant challenges. The medical literature lacks robust data to indicate exactly how many procedures are necessary to achieve clinical proficiency. Estimates based on expert opinion and longitudinal study of airway management success among learners span from 20-47 intubations to achieve competence.[39,40] The Military Health System lacks capacity to provide this procedural volume. A 12-month descriptive analysis of airway management at Brooke Army Medical Center, the Department of Defense's largest trauma center, yielded only 259 intubations.[41] Based on the aforementioned numbers of intubations believed necessary to achieve procedural competency, this would satisfy the training requirements for no more than 13 providers. In other words, the volumes are insufficient to maintain Army force levels. Other emergency procedures occur with similarly low volumes in MTF settings.[42,43] While didactics, simulations, and live tissue training may close some of this gap, there is no substitute for patient care experiences. Increasing civilian-military partnerships to provide service members from medic through specialist physician more repetitions on patients with complex injury patterns will be imperative.[44,45]

When definitive airway management does occur, providers must have requisite training to manage both sedation and ventilation over prolonged time periods. Military training plans for new accessions and sustainment training for medical personnel must train the post-intubation skill set. This includes sedation, ventilator management, and monitoring. These skills traditionally fall under the responsibility of respiratory therapists, anesthesiologists,

and intensivists. However, in a LSCO context, any provider who might perform definitive airway management, including the combat medic, must have training to perform these functions.

Materiel

Materiel solutions offer another pathway to improved outcomes in combat casualty care. Technological advances can also potentially decrease training requirements and mitigate costs.[46,47] None of these potential advantages are a guarantee, but a resolute and collaborative effort in technology research and development can overcome many of the material challenges in airway management facing the medical force.[48]

Materiel solutions for extraglottic airway devices will be important for airway management on the battlefield. Military healthcare personnel have rarely used these devices during the Global War on Terrorism, so making materiel requirements transparent is important. A recent qualitative study of combat medics identified several different properties end users believe would benefit from refinements to existing products. These included designs facilitating easier insertion, namely via adjustments to material to improve tactile sensation for the end user during insertion. The medics also highlighted the importance of ruggedized design facilitating use in a wide range of temperatures and environments. Lastly, the study identified the need for portability design elements to include ease of carrying and storage.[49]

There are other devices for non-invasive and non-definitive airway management which would benefit from materiel solutions. Novel devices exist to optimize bag valve mask (BVM) function through the incorporation of associated handles to facilitate downward pressure for achieving a better mask seal. Studies of the ability of these devices to optimize tidal volume delivery in manikin models have been inconsistent, but further refinement may yield a simple and inexpensive mechanism to facilitate non-invasive positive pressure ventilation.[50,51] Another promising possibility are intraoral airway masks as alternative to typical BVM face masks. These devices situate inside the casualty's mouth behind the lips and in front of the gums. In a cadaver model, this device showed promise for optimizing tidal volume delivery compared to a conventional cuffed face mask.[52]

Materiel solutions for video laryngoscopy capability must also be a top priority. Observational data in multicenter emergency departments suggests an association between video laryngoscopy and higher first pass success.[53,54] This is an important outcome measure given the association between multiple intubation attempts and peri-intubation adverse events. Randomized trials comparing video to direct laryngoscopy show fewer differences in outcomes between these two modalities but still generally support the finding of better outcomes with video laryngoscopy.[55] It is likely the benefits of video laryngoscopy are greatest among novice users.[56] Given this, availability of a video laryngoscope option for operational medical units is of paramount importance.

The specific materiel solution for a video laryngoscope will have specific requirements for military use. Given the fragility of many video laryngoscopes, there exists a need for a ruggedized device able to operate on battery power. Alternatively, a disposable video laryngoscope offers an expendable solution. This device is single use at a cost of approximately $100-200 per unit and requires no maintenance or additional power sources.[57,58] Among emergency medicine providers, a standard non-disposable video laryngoscope slightly outperformed the disposable laryngoscope with regards to intubation time (22.2 versus 30.2 seconds), but users acknowledged the advantages this device could offer in austere settings.[59]

An additional feature for future video laryngoscope designs would be valuable is in-line suction. While understudied, devices combining video laryngoscopy with suction capability can mitigate the loss of visualization in simulated airways with liquid, so maintaining superior outcomes compared to direct laryngoscopy.[60] Furthermore, any airway devices selected by the military for operational fielding must be capable of operation in a wide range of temperatures.

Contrary to the above airway management requirements, there is little data to support ongoing investment in cricothyrotomy materiel solutions. Multiple trials using manikin models to compare combat medic procedural success with alternative kits have failed to identify any superior devices.[61,62] While reports exist of myriad kits in combat settings,[63] the existing literature does not support any specific alternative to a standard open technique using a scalpel, tracheal hook, stylet, and dilator. Medics report significantly higher comfort level and proficiency with supraglottic airways as compared to surgical airway management, providing further support for emphasizing use of these devices in lieu of cricothyrotomy equipment.[64]

Given the likelihood of a combat airway obscured by secretions, blood, and debris, a means to clear the airway is imperative. Portable suction remains the gold standard but is often too heavy and bulky, and not often carried in a medic's kit.[65] Unfortunately, so-called "luggable" commercial devices have limitations making their use on the battlefield suboptimal.[66] A recent systematic

review showed a lack of randomized controlled trials or other high-quality evidence to address the issue of acute airway clearance using suction.[66,67] Future work in this area involves the setting of military requirements and technical standards.[68]

Lastly, oxygen supply represents another capability requiring new materiel solutions. Operational medical units in the Army still have the oxygen generator field portable (OGFP) devices on their MTOE. The concept behind these devices was to offer a relatively light-weight (12 lbs), battery-operated device capable of producing 3 liters of 93% oxygen per minute, so reducing the logistical burden associated with oxygen delivery in field environments.[69] Unfortunately, maintenance issues precluded ongoing use of this device, compelling the force to return to the use of heavy, logistically burdensome D cylinders.[70] Hence, portable and robust oxygen generation remains a significant capability gap for the care of combat casualties undergoing airway management.[71]

Leadership & Education

In the context of treatment of airway emergencies on the modern battlefield, leadership applies to providers at all levels who may perform airway management as leaders of patient resuscitation. Those providers most in need of augmented airway management in their curricula are combat medics and physician assistants. Advanced Individual Training (AIT) for medics and the Inter-Service Physician Assistant Program (IPAP) for physician assistants would both benefit from incorporation of further airway training in living patients. A clinical ladder for combat medics to acquire experiences in resuscitation while advancing in military rank is an essential component of skill retention.[72] While patient airway experiences would ideally take the form of emergency airway management, more realistic is likely to incorporate anesthesia rotations into the curricula for these students. To the extent MTFs are already saturated with learners requiring procedural repetitions, it may again become necessary to leverage civilian-military partnerships.[37]

Personnel

Combat casualty care, by necessity, focuses on the combat medic and its equivalent members in other services such as Navy corpsmen. This is natural, as the combat medic is the first medically trained responder on the battlefield. However, the combat medic is only as clinically competent as their supervising physicians.[73] Thus, it will be necessary to augment the force structure with clinicians with more extensive airway experience. This includes, ideally, adding emergency physicians to every Role 1 MTF and above. Arguably, other physicians with airway experience could fill this role to include intensivists or anesthesiologists. However, the diverse skill set of emergency physicians render them capable of managing trauma and medical emergencies in addition to airway management. Indeed, data from Iraq and Afghanistan indicated these facilities experienced up to 44% higher combat casualty survival when staffed by an emergency physician in addition to management of larger volumes of casualties.[74,75]

Policy makers should also consider the incorporation of other specialists into all roles of care to further expand capacity to manage ventilated patients. This includes additional registered nurses with critical care training and respiratory therapists. These service members would provide invaluable expertise related to the longitudinal management of ventilated patients.

Of course, manpower limitations are likely to preclude the addition of many of these personnel to all roles of care soon pending significant force structure changes. Yet, flight paramedics represent a population with requisite airway and ventilator expertise who may be more readily available. Casualties in Afghanistan undergoing evacuation by helicopter staffed with critical care flight paramedics as compared to medics trained at the Emergency Medical Technician-Basic level experienced lower 48-hour mortality (8% versus 15%).[76] As a result of these findings, the Army established a critical care flight paramedic training course which provides a pipeline for providing medics with critical care skills every year. This population currently serves primarily within the aviation community but assigning these soldiers to lower echelon roles of care could provide an important interim solution for augmentation of airway expertise closer to the point of injury.

Facilities

Facilities are likely to have an indirect contribution to closing capability gaps for airway management on the modern battlefield given the need for mobility to preserve medical personnel survival. Facility investments will need to focus primarily on training facilities.[37] These may build upon existing Medical Simulation and Training Center facilities but must ensure adequate infrastructure to support advanced simulation and, ideally, live tissue and cadaver labs. As for existing Military Healthcare System facilities, these brick and mortar buildings must embrace the ongoing direction at the behest of recent National Defense Authorization Acts and the Defense Health Agency to focus on leveraging beneficiary care delivery to build readiness for deployment.

Conclusions

Airway management during large-scale combat operations will pose unprecedented challenges to the military health system. Health service support will require increased capacity for airway management in step with increasing numbers of casualties with devastating injury patterns. Military healthcare providers will further need to manage these casualties over prolonged periods of time. Closing current gaps related to these capabilities will require solutions across all components of the JCIDS process.

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An Assessment of Casualties Undergoing Delayed Surgical Intervention in the Combat Setting

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Abstract

Introduction: The US military is transitioning into a posture preparing for large-scale combat operations in which delays in evacuation may become common. It remains unclear which casualty population can have their initial surgical interventions delayed, thus reducing the evacuation demands.

Methods: We performed a secondary analysis of a previously described dataset from the Department of Defense Trauma Registry (DODTR) focused on casualties who received prehospital care. In this, we sought to determine (1) of those who underwent operative intervention, the proportion of surgeries occurring ≥3 days post-injury, and (2) of those who underwent early versus delayed surgery, the proportions who required blood products.

Results: There were 6,558 US military casualties who underwent surgical intervention—6,224 early (< 3 days from injury) and 333 delayed (> 3 days from injury). The median Injury Severity Score (ISS) was higher in the early cohort (10 versus 6, p<0.001). Serious injuries to the head were more common in the early cohort (12% versus 5%, p<0.001), as were the thorax (13% versus 9%, p=0.041), abdomen (10% versus 5%, p=0.001), extremities (37% versus 14%, p<0.001), and skin (4% versus <1%, p=0.001). Survival to discharge was lower in the early cohort (97% versus 100%, p<0.001). Mean whole blood consumption was higher in the early co-hort (0.5 versus 0 units, p<0.001), as was packed red blood cells (6.3 versus 0.5, p<0.001), platelets (0.9 versus 0, p<0.001), and fresh frozen plasma (4.5 versus 0.2, p<0.001). The administration of any units of packed red blood cells and whole blood was higher for the early cohort (37% versus 7%, p<0.001), as was a ≥3 units thresh-old (30% versus 3%, p<0.001), and ≥10 units threshold (18% versus 1%, p<0.001).

Conclusions: Few combat casualties underwent delayed surgical interventions defined as ≥3 days post injury, and only a small number of casualties with delayed surgical intervention received blood products. Casualties who received early surgical intervention were more likely to have higher injury severity scores, and more likely to receive blood.

Keywords: blood; whole; delayed; surgery; military; trauma

Introduction

Background: Over the past 22 years of war in Afghanistan, Iraq, Syria, and the African continent, the US military has made great strides in resuscitation of critically wounded casualties. Early in the course of the wars, the US military found early resuscitation with blood products, either whole blood or component therapy in a 1:1:1 ratio, offers the lowest mortality rates.[1] Shackelford et al found prehospital transfusion associated with significantly reduced 24-hour and 30-day mortality.[1] O'Reilly et al corroborated this evidence, finding improvement in mortality from combat injuries in patients who received prehospital blood transfusion compared to those who did not.[4] As a result, both Tactical Combat Casualty Care (TCCC) and Damage Control Resuscitation (DCR) guidelines from the Joint Trauma System recommend blood transfusion as the first-line therapy for fluid

resuscitation in combat wounded.[2,3]

Another cornerstone in the effort to improve casualty care has been to move surgical teams capable of providing Damage Control Surgery (DCS) as far forward as possible. After instituting the "Golden Hour" policy in an attempt to treat as many traumatically injured patients with damage control surgery within 60 minutes of receiving their injuries, casualties saw a 52% median overall transport time reduction, from 90 to 43 minutes.[5] This transition also saw a drop in the case fatality rate from 13.7 (469 of 3,429) to 7.6 (1,344 of 17,660), another remarkable achievement. However, as the US military prepares to fight in a large-scale combat operation (LSCO), the military medical community must be prepared to care for these patients under differing circumstances, including scenarios without immediate access to surgical capabilities. For a variety of potential reasons, such as lack of air superiority and a large number of casualties requiring evacuation, it may not be feasible to evacuate casualties who require DCS interventions for several days. There exists a gap in the available literature regarding care for patients who experienced a delay to surgical care, and what temporizing measures, such as blood product resuscitation, were provided.

Goal of this Study: We determined the proportion of casualties who underwent delayed operative intervention, defined as surgical intervention ≥3 days post-injury. We also determined the proportions of casualties receiving blood products who underwent early versus delayed operative intervention.

Methods

Data Acquisition: This is a secondary analysis of a previously described dataset of prehospital casualty care delivered and recorded in the combat environment.[6] The US Army Institute of Surgical Research (USAISR) regulatory office reviewed protocol H-20-015nh and determined it was exempt from Institutional Review Board oversight. We obtained and used only de-identified data.

Department of Defense Trauma Registry (DODTR): The DODTR, formerly known as the Joint Theater Trauma Registry (JTTR), is the data repository for DoD combat trauma-related injuries.[7,8] The DODTR includes documentation regarding demographics, injury-producing incidents, diagnoses, treatments, and outcomes of injuries sustained by US and non-US military and civilian personnel deployed in support of military operations. It includes host nation civilians treated in US facilities and covers care delivered from the point of injury to final disposition. Only short-term outcomes data are available for non-US casualties transferred to non-US facilities after initial stabilization. The DODTR comprises all patients admitted to a Role 3 (fixed-facility) or Role 2 (e.g., forward resuscitative surgical detachment (FRSD) with trauma occurring within 72 hours from presentation. The registry defines prehospital care as being rendered prior to arrival at a facility with surgical capabilities.

Patient Selection: For this analysis, we focused on casualties who required operative intervention. We defined operative intervention as any procedure documented in the operating room or a similar variant within the registry without a specific focus on which procedure was performed, given our overarching goal was to determine if a proportion of casualties who require surgery can do so in a delayed fashion and be sustained in the meantime with or without blood products. The operational relevance of this is based on the likely future need for sustaining casualties forward without surgical capability.

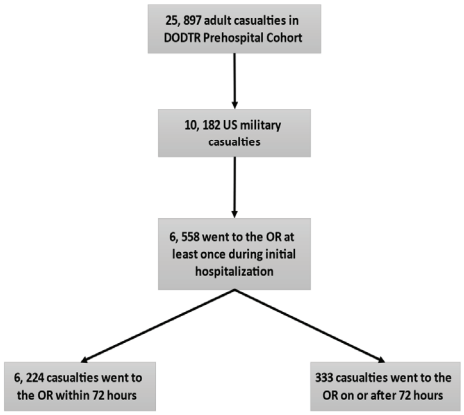
Data Analysis: We performed all statistical analysis using commercially available software. We presented continuous variables as means with 95% confidence intervals; we compared these variables with t-test comparisons. We presented non-parametric continuous variables and ordinal variables as medians with interquartile ranges; we compared these variables using Wilcoxon rank sum comparisons. We presented nominal variables as percentages with numbers; we compared these variables using chi square comparisons versus Fisher's exact test (2-tail) if the expected event count was <5. We converted injury scale scores into binary variables as serious (≥3) versus not serious (<3) as we have done with previous studies.[6,9,10] We analyzed the data under the assumption of accurate documentation of all care rendered.

While there is no universally accepted definition of prolonged casualty care, we used 3 days as our threshold with groups of <3 days (early cohort) versus ≥ 3 days (delayed cohort). We chose to use this threshold because we estimated it would reasonably separate patients into a cohort and allow us to identify relevant characteristics to be applied to future evacuation planning considerations. We further analyzed data based on previously published thresholds of blood product administration (packed red blood cells and whole blood) within the 2 groups of ≥1 unit, ≥3 units, and ≥10 units.[11,12] We used the threshold of ≥1 unit to identify all patients who received any blood product, and a threshold of ≥10 units as this is a common definition of massive transfusion. A threshold of ≥3 units was also utilized in an attempt to further stratify patients who received blood products, but did not meet massive transfusion criteria.

We also reviewed the ICD codes from the delayed cohort,

and these procedure codes were sorted into categories to evaluate for trends in the type of procedures these patients underwent. Categories included general wound care procedures, extremity orthopedic procedures, orthopedic spine and neurosurgical procedures, ear, nose and throat and oral maxillofacial procedures, other general surgery procedures, and ophthalmologic procedures. Some procedures were non-surgical in nature, such as codes related to diagnostic or basic, non-surgical care procedures and were placed in their own category. Finally, some procedure codes did not fit any of the above categories and remained unclassified.

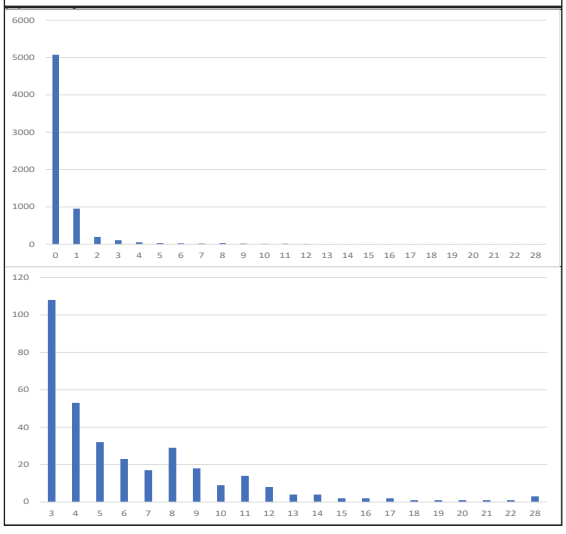
Figure 1. Consort flow diagram.



Results

Our original dataset comprised 25,897 adult casualties. Of these, 10,182 were US military with 6,558 who went to the operating room (OR) at least once during initial hospitalization. The 6,558 comprised the dataset of interest for this analysis (Figure 1). The majority of the casualties who went to the OR did so within 3 days (n=6224), which comprised the early cohort with 333 casualties going to the OR on or after 72 hours (Figure 2). Both groups were predominantly male with a median age of 24. Explosives were the most common mechanism of injury in both groups (58% versus 40%). The median ISS was higher in the early cohort (10 versus 6, p<0.001). Serious injuries to the head were more common in the early cohort (12% versus 5%, p<0.001), as were the thorax (13% versus 9%, p=0.041), abdomen (10% versus 5%, p=0.001), extremities (37% versus 14%, p<0.001), and skin (4% versus <1%, p=0.001). Survival to discharge was lower in the early cohort (97% versus 100%, p<0.001, Table 1). Mean whole blood consumption was higher in the early cohort (0.5 versus 0 units, p<0.001), as was packed red blood cells (6.3 versus 0.5, p<0.001), platelets (0.9 versus 0, p<0.001), and fresh frozen plasma (4.5 versus 0.2, p<0.001) (Table 2). The administration of any units of packed red blood cells and whole blood was higher for the early cohort (37% versus 7%, p<0.001), as was a ≥3 units threshold (30% versus 3%, p<0.001), and ≥10 units threshold (18% versus 1%, p<0.001) (Table 3).

Figure 2. Distribution of the total count versus first day of surgery with (a) 0-28 days and (b) 3-28 days.



A review of the ICD codes from the delayed cohort revealed 918 coded procedures. Extremity orthopedic procedures accounted for 38.2% (n=351), with a majority of these being reductions (open or closed) with internal fixation. Wound care procedures accounted for another 36.1% (n=331) of procedural codes, predominantly wound debridement, skin closures and skin grafts. Other categories included ear, nose, and throat and oral and maxillofacial surgical procedures (4.9%; n=45), orthopedic spine and neurosurgery codes (4.6%; n=42), other general surgery codes (1.31%; n=12) and ophthalmologic procedural codes (0.01%; n=5). There were 52 codes (5.7%) covering diagnostic, monitoring, labs and basic non-surgical procedures, and another 96 codes (10.45%) remained unclassified from these categories.

Discussion

Within our dataset, 64% of all casualties underwent surgical intervention of some kind at least once during their initial hospitalization. Of these wounded patients who went to the OR during their initial hospitalization, only 5% underwent delayed surgery at or after 3 days from their admission; the overwhelming majority went to the operating room in under 72 hours. Of these patients who had delayed surgical intervention, the data revealed there was a 100% survival rate. Additionally, compared to the vast majority of patients who underwent surgery in the first 72 hours of their hospitalization, these delayed surgical patients also had a lower injury severity score, and they were far less likely to receive any kind of blood product as part of their resuscitation.

Table 1. Casualty characteristics.

		OR < 3 days n=6224	OR ≥ 3 days n=333	p-value
Demographics	Age	24 (22-28)	24 (22-29)	0.239
	Male	98% (6118)	95% (318)	<0.001
Mechanism of injury	Explosive	58% (3608)	40% (133)	<0.001
	Fall	3% (172)	16% (53)	
	Firearm	26% (1610)	9% (31)	
	Motor vehicle	3% (184)	6% (20)	
	Other	10% (650)	29% (96)	
Injury severity score		10 (5-18)	6 (4-11)	<0.001
	Head/neck	12% (752)	5% (15)	<0.001
	Face	1% (32)	0% (0)	0.408
	Thorax	13% (798)	9% (30)	0.041
	Abdomen	10% (600)	5% (15)	0.001
	Extremities	37% (2329)	14% (47)	<0.001
	Skin	4% (222)	<1% (1)	0.001
Outcome	Alive	97% (6056)	100% (333)	<0.001

The past 20-plus years of combat have largely been in environments with uncontested ability to evacuate patients quickly to theatre hospitals with surgical capabilities. Even before the institution of the "Golden Hour" policy in 2009 with its resultant 50% reduction in overall transport time, patients were still arriving to surgical teams within an average of 90 minutes of their injury.[5] Given this capability to perform surgery quickly on wounded patients, it is not surprising only 5% of patients had their initial surgical intervention delayed later than 72 hours. It is also not surprising these patients had lower injury severity scores and were vastly less likely to need blood product resuscitation. Patients who were more severely injured received more intensive resuscitation measures, more blood products, and faster time to surgical intervention. It is not possible to know in this study how many patients received early surgical intervention simply because the capability for surgical intervention was available, and not because it was necessary to ensure the survival of the patient. It is possible a much larger cohort of patients could have survived a longer period of resuscitation prior to surgical intervention. The relative lack of patients undergoing delayed surgical intervention as we defined it *a priori* is the primary limitation of this data analysis. It is also not possible to draw any conclusions regarding the potential impact of blood product resuscitation as a temporizing measure in patients experiencing prolonged evacuation times to surgical intervention in this cohort, given this group received less blood than the early surgical group and had a 100% survival rate.

In preparation for future combat, more research will be necessary to ascertain the optimal care and resuscitation of patients who require surgical intervention for their wounds but are delayed in doing so. Patients who received surgical intervention with a delay of just 12 or 24 hours could also be considered to have delayed intervention compared to the average. A sensitivity analysis of shorter thresholds could further define this, and using a shorter threshold could increase the size of the cohort, and perhaps give additional insights into which patient injuries can be delayed to receive surgery and what temporizing measures would provide the best chance for survival.

It may be useful to conduct an in-depth, case-by-case analysis of these 333 patients who received surgical intervention greater than 72 hours from their time of injury. Given 100% of these patients survived despite their delayed surgical intervention, it could be hypothesized these patients might serve as a guide as to which patients are most appropriately held in place if medical evacuation capabilities are limited, delayed, or non-existent in future combat environments. Further study into the casualties who required no surgical intervention are needed as these patients could, in theory, completely bypass a location with surgical capabilities, requiring only medical management instead.

There are several limitations to this study. First, the data set only allows for inquires of information recorded and does not account for incomplete records or absent data. This limitation has been well described, and it is well known prehospital documentation is often poor, though not without valid reason.[13] Second, as mentioned previously, this dataset only looks at the occurrence of delayed surgical intervention and blood product administration. It cannot infer why a particular course of action

Table 2. Mean blood products by group.

Product	OR < 3 days n=6224	OR ≥ 3 days n=333	p-value
Whole blood	0.5 (0.3-0.6)	0 (0-0)	<0.001
Packed red cells	6.3 (5.8-6.8)	0.5 (0.1-0.8)	<0.001
Platelets	0.9 (0.8-1.0)	0.0 (0.0-0.1)	<0.001
Fresh frozen plasma	4.5 (4.1-4.9)	0.2 (0.0-0.3)	<0.001

Table 3. Blood products thresholds met by group.

Product	OR < 3 days n=6224	OR ≥ 3 days n=333	p-value
Any PRBC or WB	37% (2309)	7% (23)	<0.001
PRBC or WB ≥ 3	30% (1882)	3% (11)	<0.001
PRBC or WB ≥ 10	18% (1132)	1% (4)	<0.001

was taken, such as if delayed surgical intervention was the more ideal clinical course, or if the intervention was truly necessary or only taken because the capability was present. Another limitation also previously mentioned is the small size of the data set. Of the already small number of patients who only received surgical intervention after 72 hours, only 7% received blood products, and they had less severe injury severity scores. This small sample size cannot provide any definitive evidence on the role that blood product resuscitation might play as a temporizing measure to delayed surgical intervention. Other confounding variables of this study include a lack of data regarding the supply and logistics status at each Role of care (i.e., whether and how many blood products were available), how quickly these patients were evacuated to a location with surgical capabilities, and which surgical specialties and sub-specialties were available during their initial surgical intervention.

Conclusions

In this analysis, we attempted to identify characteristics of casualties who had their initial surgical intervention delayed beyond 3 days, and if blood product administration served as a temporizing measure for these patients. We found only a small fraction of combat casualties received delayed surgical interventions, defined as ≥3 days post injury, and only a small number of casualties with delayed surgical intervention received blood products. Our analysis was primarily limited by the small number of these patients in our dataset. Further study in this area is necessary to seek better sensitivity of patients considered to receive delayed evacuation, and if there are characteristics of these patients that could better inform evacuation decisions in the future.

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Tranexamic Acid Improves Survival in the Setting of Severe Head Injury in Combat Casualties

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Abstract

Introduction: Approximately 1.7 million people sustain traumatic brain injuries (TBI) annually in the US. To reduce morbidity and mortality, management strategies aim to control progressive intracranial bleeding. This study analyzes the association between Tranexamic Acid (TXA) administration and mortality among casualties within the Department of Defense Trauma Registry, specifically focusing on subsets of patients with varying degree of head injury severities.

Methods: Besides descriptive statistics, we used inverse probability weighted (for age, military service category, mechanism of injury, total units of blood units administered), and injury severity (ISS) and Abbreviated Injury Scale (AIS) head score adjusted generalized linear models to analyze the association between TXA and mortality. Specific subgroups of interest were increasing severities of head injury and further stratifying these by Glasgow Coma Score of 3-8 and severe overall bodily injuries (ISS>=15).

Results: 25,866 patients were included in the analysis. 2,352 (9.1%) received TXA and 23,514 (90.9%) did not receive TXA. Among those with ISS>=15 (n=6,420), 21.2% received TXA. Among those with any head injury (AIS head injury severity score>=1; n=9,153), 7.2% received TXA. The median ISS scores were greater in the TXA versus no-TXA group (17 versus 6). Weighted and adjusted models showed overall, there was 25% lower mortality risk between those who received TXA at any point and those who did not (OR:0.75, 95% CI: 0.59, 0.95). Further, as the AIS severity score increased from >=1 (1.08; 0.80, 1.47) to >=5 (0.56; 0.33, 0.97), the odds of mortality decreased.

Conclusions: TXA may potentially be beneficial in patients with severe head injuries, especially those with severe overall injury profiles. There is a need of definitive studies to confirm this association.

Keywords: TXA; TBI; mortality; interventions; military; trauma

Introduction

In the US, there are approximately 1.7 million people who sustain traumatic brain injuries (TBI) yearly, leading to approximately 275,000 hospitalizations and 52,000 deaths.[1] Though the majority of TBI's are categorized as mild, 80-90,000 people experience long-term disability.[1] Reports from the wars in Iraq and Afghanistan have estimated over 350,000 casualties sustained a TBI with largest proportion (33%) caused by explosives.[2] In order to reduce morbidity and mortality, management strategies aim to control progressive intracranial bleeding and to avoid secondary brain injury caused by elevated intracranial pressure and cerebral ischemia.[3] Intensive research efforts over the past decade focused on tranexamic acid (TXA) as a therapeutic intervention to reduce morbidity and mortality from TBI.[4]

TXA is a synthetically derived antifibrinolytic that blocks the conversion of plasminogen to plasmin in

the blood. The inhibition of plasminogen conversion to plasmin reduces fibrin breakdown while maintaining fibrin meshwork.[5,6] CRASH-2 reported when administered within 3 hours of injury and/or hemorrhage, TXA provided patients with a 1.5% decrease in mortality rate, and a 2.1% decrease in mortality rate when administered within 1 hour.[7] In CRASH-3, a multi-national randomized-control trial of TXA versus placebo in a cohort of over 12,000 patients, there was a decreased mortality in mild-moderate head injury and trend towards decreased mortality in severe head injury.[8] Subgroup analysis among those with isolated head injury and without unreactive pupils showed a 20% lower risk of new hemorrhage among the TXA groups.[9] Additional studies have not shown a mortality benefit in TBI patients who receive TXA.[10-12] To help strengthen the evidence base, there is a need to better understand if TXA should be used in patients with severe head injuries and for which subset of patients TXA is most beneficial.

Methods

Data Acquisition: This is a secondary cross-sectional analysis of previously published de-identified data from the DODTR which has been described elsewhere.[13] The US Army Institute of Surgical Research (USAISR) regulatory office reviewed protocol H-20-015nh and determined it was exempt from Institutional Review Board oversight.

Department of Defense Trauma Registry: The DODTR, formerly known as the Joint Theater Trauma Registry (JTTR), is the data repository for DOD trauma-related injuries.[14,15] The DODTR includes documentation regarding demographics, injury event related characteristics, diagnoses, treatments, and outcomes of injuries sustained by US/non-US military and US/non-US civilian personnel. Short-term outcome data are available for non-US casualties. The DODTR comprises all patients admitted to a Role 3 (fixed facility) or forward surgical team (FST) with an injury diagnosis and trauma occurring within 72 hours from presentation. The registry defines the prehospital setting as any location prior to reaching an FST, field hospital, or a combat support hospital to include the Role 1 (point of injury, casualty collection point, battalion aid station) and Role 2 without surgical capabilities (temporary limited-capability forward-positioned hospital inside combat zone). We included all patients in the DODTR aged 18 and above with a diagnosis of head injury.

Variables: The primary outcome of interest was mortality (at any time point) for patients who received prehospital or hospital TXA compared to those who did not receive TXA, specifically focusing on those with head injuries. Specific subgroups of interest were increasing gradients of maximum abbreviated injury scale (AIS) head injury scores and further stratifying these by those with Glasgow Coma Score [GCS]: 3-8 and severe bodily injuries (injury severity score [ISS]>=15).

Demographic variables included age, sex (male, female), and military service category (US military, coalition military, non-coalition military, humanitarian). Injury characteristic variables included classification of injury (battle, non-battle, disease, unknown), mechanism of injury (explosives, firearm wound, fall, motor vehicle crash, other), AIS head maximum severity score, ISS, if immediate assistance was available/provided and what resources were used (combat medic, battalion aid station, ground transportation, air transportation.

Data regarding additional interventions received included hemostatic dressing, wound dressing, chest seal, chest tube, chest needle, junctional tourniquet, limb tourniquet, pelvic binder, external splint, nasopharyngeal airway, airway adjunct, supraglottic airway, c-collar, intraosseous access, cricothyrotomy, warming, and IV fluids. Variables related to medications received included individual blood products given in the first 24 hours (Cryoprecipitate, packed red blood cells, platelets, fresh frozen plasma, whole blood) and specific drugs administered (at any time point). Other critical interventions assessed include prehospital intubation, emergency department intubation, surgical interventions, intra-cranial pressure monitoring, epidural administration, and subdural administration. Injury complications included intracerebral bleeding, subarachnoid hemorrhage, traumatic brain injury, and any intracranial hemorrhage. Other morbidity-related outcomes were measured using emergency department GCS score, total ICU days, total ventilator days, and total hospital days.

Analysis: We present frequencies and percentages for categorical variables and median and interquartile ranges for continuous variables. Chi-squared tests and t-tests were respectively used for significance testing. Primary analyses involved using inverse probability weighted (for age, military service category, mechanism of injury, and total units of blood transfusion) and injury severity and AIS score adjusted generalized linear models to analyze the association between prehospital or hospital TXA administration and overall mortality and among the specified subgroups.[16-18] All analysis were conducted using commercially available software.

Results

A total of 25,866 patients were included in the analysis. There were 2,352 (9.1%) who received TXA, and 23,514

Table 1. Demographic and operational characteristics, stratified by tranexamic acid (TXA) administration.

Characteristics	N (%) No (n=23514)	Yes (n=2352)	p-values
Age			0.121
<=30 years	18370 (78.1)	1870 (79.5)	
>30 years	5144 (21.9)	482 (20.5)	
Gender			<0.0001
Male	22862 (97.2)	2330 (99.1)	
Female	652 (2.8)	22 (0.9)	
Military service category			<0.0001
Humanitarian	5661 (24.1)	911 (38.7)	
NATO Military	1946 (8.3)	138 (5.9)	
Non-NATO Military	6301 (26.8)	728 (31.0)	
United States Military	9606 (40.8)	575 (24.4)	
Classification of injury			<0.0001
Battle	18518 (78.8)	2249 (95.6)	
Non-battle	4952 (21.1)	103 (4.4)	
Mechanism of injury			<0.0001
Explosive	12303 (52.3)	1435 (61.0)	
Fall	905 (3.9)	3 (0.1)	
Firearm wound	6674 (28.4)	848 (36.1)	
Motor vehicle crash	1739 (7.4)	34 (1.5)	
Other	1893 (8.1)	32 (1.4)	
Combat medic present			<0.0001
No	17589 (74.8)	635 (27.0)	
Yes	5921 (25.2)	1717 (73.0)	
Battalion aid station present			<0.0001
No	22799 (97.0)	2230 (94.8)	
Yes	711 (3.0)	122 (5.2)	
Transportation via ground			<0.0001
No	20565 (87.5)	1867 (79.4)	
Yes	2945 (12.5)	485 (20.6)	
Transported via air			0.781
No	4875 (20.7)	494 (21.0)	
Yes	18635 (79.3)	1858 (79.0)	

(90.9%) who did not receive TXA. Almost 80% patients in both the TXA and no-TXA group were aged 30 years or below and almost all were males. Explosives and firearm wounds were the most common mechanisms of injury in both groups. While among the TXA group, explosives and firearms attributed to 61% and 36.1% of the injuries, among the no-TXA group they attributed to 52.3% and 28.4% of the injuries, respectively (Table 1).

Among those with severe overall bodily injuries (n=6420), 21.2% received TXA. Among those with any head injury, i.e., AIS head injury severity score >=1 (n=9153), 7.2% received TXA. Similar proportions of those within the TXA group and those in the no-TXA group experienced intracerebral bleeding (not otherwise specified), subarachnoid hemorrhage, and any intracranial hemorrhage respectively. Within the TXA group as opposed to no-TXA group, the median ISS scores were greater (17 vs 6). While median units of blood received in the TXA group was 14 (Interquartile Range [IQR]: 4-35), it was 0 (IQR: 0-1) in the no-TXA group. The TXA group also had longer median ICU, ventilator, and hospital days. T-tests comparing the two groups showed significant differences across almost all characteristics (p-value <0.0001). Deaths occurred in 8.5% of the TXA and 4% of the no-TXA group (Table 2).

Table 2. Injury characteristics and rates of complications, stratified by tranexamic acid (TXA) administration.

Characteristics	TXA administered prehospital or in-hospital N (%)/Median (IQR) No (n=23514)	Yes (n=2352)	p-value
Injury Severity Characteristics			<0.0001
Any head injury (AIS Head max score >=1)	8492 (92.8)	661 (7.2)	
AIS Head max score >=2	6094 (92.0)	529 (8.0)	
AIS Head max score >=3	3049 (89.4)	361 (10.6)	
AIS Head max score >=4	1529 (89.0)	186 (11.0)	
AIS Head max score >=5	719 (88.9)	90 (11.1)	
Composite ISS	6 (2-14)	17 (10-25)	
Emergency department GCS score	15 (14-15)	6 (3-15)	
Total units of blood administered (first 24 hours)	0 (0-1)	14 (4-35)	
Total ICU days	0 (0-2)	2 (0-7)	
Total ventilator days	0 (0-1)	2 (0-4)	
Total hospital days	2 (1-6)	4 (1-12)	
Death			<0.0001
No	22573 (96.0)	2153 (91.5)	
Yes	941 (4.0)	199 (8.5)	

ISS: Injury Severity Score; ICU: Intensive Care Unit; GCS: Glasgow Coma Scale; IQR: Interquartile Range; TXA: Tranexamic Acid

Greater proportions of those in the TXA as opposed to no TXA group were administered limb tourniquet application, chest needle insertion, pelvic binder application, intraosseous needle placement and IV fluids (Figure 1).

Table 3 shows that greater proportions of patients in the TXA group versus no TXA were intubated (either prehospital or in the emergency department) and had

Figure 1. Proportion of patients receiving interventions, stratified by tranexamic acid (TXA) administration.

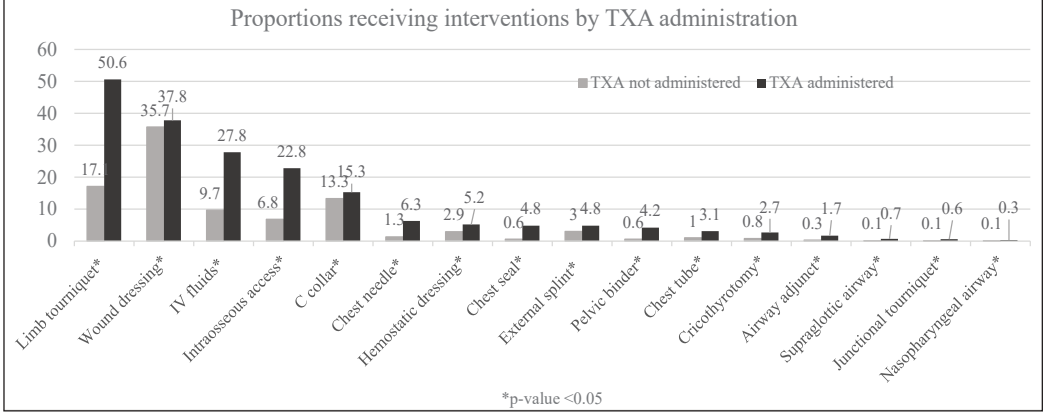


Table 3.Critical interventions, blood product, and medication administration, stratified by (TXA) administration.

Characteristics	TXA administered prehospital or in-hospital N (%)		
	No (n=23514)	Yes(n=2352)	p-values
Critical Interventions			
Prehospital intubation			<0.0001
No	22669 (96.4)	2048 (87.1)	
Yes	845 (3.6)	304 (12.9)	
Emergency department intubation			<0.0001
No	21028 (89.4)	1476 (62.8)	
Yes	2486 (10.6)	876 (37.2)	
Surgical interventions			0.764
No	23065 (98.1)	2305 (98.0)	
Yes	449 (1.9)	47 (2.0)	
Intra-cranial pressure monitoring			<0.0001
No	23290 (99.1)	2289 (97.3)	
Yes	224 (0.9)	63 (2.7)	
Epidural administration			0.165
No	21918 (93.2)	2190 (93.1)	
Yes	276 (1.2)	20 (0.9)	
Subdural administration			0.394
No	21918 (96.3)	2190 (96.0)	
Yes	837 (3.7)	92 (4.0)	
Blood products administered (first 24 hours)			
Packed Red Blood Cells			<0.0001
No	18031 (76.7)	479 (20.4)	
Yes	5466 (23.3)	1873 (79.6)	
Platelets			<0.0001
No	21628 (92.0)	1295 (55.1)	
Yes	1865 (7.9)	1057 (44.9)	
Cryoprecipitate			<0.0001
No	22448 (95.5)	1465 (62.3)	
Yes	1045 (4.4)	887 (37.7)	
Whole blood			<0.0001
No	23072 (98.1)	1871 (79.6)	
Yes	419 (1.8)	481 (20.5)	
Fresh Frozen Plasma			<0.0001
No	5514 (23.5)	1441 (61.3)	
Yes	14 (0.1)	16 (0.7)	
Medication Administration			
Acetaminophen			<0.0001
No	23229 (98.8)	2273 (96.6)	
Yes	281 (1.2)	79 (3.4)	
Meloxicam			0.359
No	23434 (99.7)	2347 (99.8)	
Yes	76 (0.3)	5 (0.2)	
Ketamine			<0.0001
No	22090 (93.9)	1424 (60.5)	
Yes	1420 (6.0)	928 (39.5)	
Fentanyl			<0.0001
No	20447 (87.0)	1636 (69.6)	
Yes	3063 (13.0)	716 (30.4)	
Morphine			0.427
No	18993 (80.8)	1916 (81.5)	
Yes	4517 (19.2)	436 (18.5)	
Hydromorphone			<0.0001
No	23349 (99.3)	2288 (97.3)	
Yes	161 (0.7)	64 (2.7)	
Antibiotics			<0.0001
No	21237 (90.3)	1869 (79.5)	
Yes	2273 (9.7)	483 (20.5)	

Table 4. Odds of mortality for tranexamic acid (TXA) vs no-TXA from inverse probability weighted (IPW) and adjusted generalized linear models accounting for injury characteristics and severity.

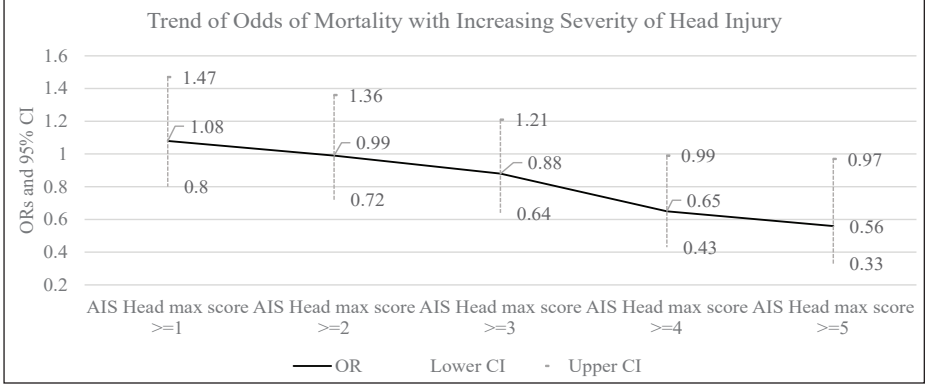
**Analyzed group/subset	N	IPW and multivariable adjusted models	
		*OR (95% CI)	p-value
All patients	25866	0.75 (0.59, 0.95)	0.016
ISS >=15	6420	0.66 (0.51, 0.86)	0.002
GCS 3-8	4995	0.66 (0.51, 0.84)	0.010
Any head injury (AIS Head max score >=1)	9153	1.08 (0.80, 1.47)	0.615
and GCS 3-8	2779	0.82 (0.60, 1.12)	0.215
and GCS 3-8 and ISS >= 15	2128	0.69 (0.49, 0.98)	0.040
AIS Head max score >=2	6623	0.99 (0.72, 1.36)	0.963
and GCS 3-8	2455	0.81 (0.58, 1.11)	0.189
and GCS 3-8 and ISS >= 15	1952	0.71 (0.50, 1.02)	0.064
AIS Head max score >=3	3410	0.88 (0.64, 1.21)	0.444
and GCS 3-8	1982	0.80 (0.57, 1.13)	0.205
and GCS 3-8 and ISS >= 15	1661	0.68 (0.47, 0.98)	0.040
AIS Head max score >=4	1715	0.65 (0.43, 0.99)	0.043
and GCS 3-8	1199	0.53 (0.34, 0.81)	0.004
and GCS 3-8 and ISS >= 15	1198	0.53 (0.34, 0.81)	0.003
AIS Head max score >=5	809	0.56 (0.33, 0.97)	0.037
and GCS 3-8	669	0.63 (0.35, 1.12)	0.117
and GCS 3-8 and ISS >= 15	668	0.62 (0.35, 1.11)	0.110

ISS: Injury Severity Score; AIS: Abbreviated Injury Scale; GCS: Glasgow Coma Scale
*IPW for age, military service category, mechanism of injury (explosive, firearm wound, others), total blood units administered in the first 24 hours
**Additionally adjusted models for AIS Head injury severity max score [max score from 0-6] and/or ISS scores, unless included in the subgroup

intracranial pressure monitoring. Patients in the TXA group were also significantly more likely to receive blood products in the first 24 hours. A total of 76.7% patients in the TXA group received packed red blood cells, 44.9% received platelets, 37.7% received cryoprecipitate and 20.5% received whole blood. Patients who received TXA were more likely to also be administered acetaminophen, fentanyl, hydromorphone, or antibiotics but not more likely to receive meloxicam, morphine or ketamine.

Inverse probability weighted and adjusted models showed overall, there was 25% lower mortality risk between those who received TXA at any point and those who did not (OR:0.75, 95%CI: 0.59, 0.95). The odds of mortality were 44% lower among subgroup of patients with severe bodily injuries (ISS>=15) and depressed mental status (GCS 3-8). Further, as AIS head injury severity maximum scores increased from >=1 to >=5, the odds of mortality comparing the TXA group with no TXA group decreased. The ORs and CIs were 1.08; 0.80, 1.47 and 0.56; 0.33, 0.97 respectively (Table 4). This trend is observed in Figure 2.

Figure 2. Odds ratios and 95% confidence intervals from inverse probability weighted (IPW) and multivariable adjusted models analyzing the association between head injury severity and mortality.



Discussion

This retrospective analysis of head injured patients from the DODTR found there was significantly decreased (25%) mortality among patients who received TXA compared to those who did not. As the AIS head injury severity score increased from >=1 to >=5, the odds of mortality significantly decreased (1.08; 0.80, 1.47 and 0.56; 0.33, 0.97, respectively). Though not significant, those with any head injury (AIS head injury maximum score >=1) and depressed GCS 3-8 had an 18% lower mortality risk. Further, our results showed those with most severe head injuries (AIS head injury severity score >=5 and GCS 3-8) experienced 37% lower odds of mortality; although, it was statistically non-significant. Similar to our study, CRASH-3 found among adults with moderate to severe TBI (GCS of 12 or lower or any intracranial bleeding) the relative risk of 28-day mortality was about 6% lower in patients who received TXA (RR:0.94; 0.86, 1.02). However, we cannot make direct comparisons between our study and CRASH-3 since both studies differ in terms of patient populations (military versus civilian) and differing criterion-referenced subgroups.[8]

Using a similar analytic methodology to our study, a previous German Trauma Registry study conducted a propensity-score matched retrospective analysis of prehospital TXA administration among severely injured civilian patients (defined as ISS >= 9). Massive transfusion rates were significantly lower in TXA vs no-TXA group (5.5% vs 7.2%). Mortality rates among the prehospital TXA vs no-TXA groups were similar beyond 12 hours. 19 In our DODTR study, which included both pre- and in-hospital TXA administration, we found that patients who received TXA also received a significantly greater proportion of blood products. This may be because the combat setting patients in the DODTR who received TXA also had a more severe injury profile given their higher ISS scores (median ISS of 17 in our study vs. 6 in the German study). While the goal of our study was not to assess if the likelihood of massive transfusions was lower in patients receiving TXA, this will be important to assess in the future as access to blood products remains a significant challenge in the field.

TXA has been shown to be safe for patients with severe head injuries both in this study cohort and in a systematic review. However, balancing risk versus benefit is an important consideration. First, it is important to note TBI is accompanied by intracranial bleeding in 25%-45% patients with severe TBI and in 3%-12% and 0.2% in patients with moderate and mild TBI respectively. Between 11-51% of patients with TBI are prone to hematoma expansion. Further, hyperfibrinolysis contributes to bleeding in 37% of such cases.[20] These are compelling factors to administer TXA to TBI patients, especially those with severe TBI who are at highest risk. A systematic review evaluated the effectiveness of TXA administration in patients with TBI, reported the risk of critical outcomes (all-cause mortality, neurological outcome rates, enlargement of bleeding, incidence of ischemia, and hemorrhagic intracranial complications) was lower in TXA group (RR:0.93; 0.86, 1.01). The review noted estimates from the 3 randomized controlled trials that reported the incidence of ischemic complication, and one study that reported hemorrhagic complications, there was no significant difference in complications between the TXA versus no-TXA groups (RR: 1.33; 0.35, 5.04, and RR 0.71; 0.37, 1.35, respectively).[21] A randomized controlled trial, by Yutthakasemsunt et al, also found no increased thrombotic events in the TXA group.[22] These data, amongst similar data from several other studies, provide a basis to suggest TXA can be safe when administered early to the appropriate head injured patient.

Limitations: As a retrospective analysis of a registry, the conclusions are limited to associations and not causation, and the study shares the same bias previously described with using data from the DODTR. Inclusion into the DODTR requires arrival at a deployed military treatment facility with surgical capabilities as an entry point for capture into the registry. Data in the trauma registry is dependent upon documentation in austere combat conditions, and previous studies have demonstrated suboptimal adherence with completion of documentation, especially in the prehospital setting.[23,24] Our findings likely represent under documentation, and it is likely the effect sizes presented in this study underestimate the true effect.

Conclusions

TXA may be potentially lifesaving in patients with head injuries with intracranial hemorrhage. The mortality benefit may be largest in casualties with severe head injuries associated with depressed mental status and overall severe bodily injuries. There is a need for additional definitive studies to confirm this association. The benefits of TXA may outweigh the risks, especially if TXA is administered early to severe head injured patients.

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Antarctic Evacuation: A Retrospective Epidemiological Study of Medical Evacuations on US Military Aircraft in Antarctica

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Abstract

Background: The international community has shown increasing interest in the Arctic and Antarctic due to the value polar regions have in terms of environmental research, natural resources, and national defense. The US Government maintains several permanent research and military facilities in polar regions. Medical evacuation (MEDEVAC) from these facilities can be limited for prolonged periods of time due to their extreme climates. Published data regarding MEDEVACs from these facilities is extremely limited.

Methods: Evacuations on military aircraft registered in the Transportation Command Regulation and Command and Control Evacuation System (TRAC2ES) database in a previously de-identified dataset were queried for events from McMurdo, Antarctica. The data was analyzed to determine the number of evacuations, reasons for evacuation, and additional demographic data.

Results: There were 31 evacuations from McMurdo Station and Scott Amundsen South Pole Station for 29 unique patients recorded in the available TRAC2ES dataset. Reasons for evacuation included traumatic brain/head injury, behavioral health concerns, extremity injuries, pregnancy, and various other medical/surgical concerns.

Conclusions: MEDEVAC was typically required for advanced diagnostic/treatment modalities or if a patient could no longer fulfill his/her duties. Most evacuations were not directly related to environmental exposure. Given the climate in polar regions can preclude timely evacuation for large periods of time, the need for evacuation must be anticipated and mitigated whenever possible. Better data is needed to guide staffing and mission planning in this remote location.

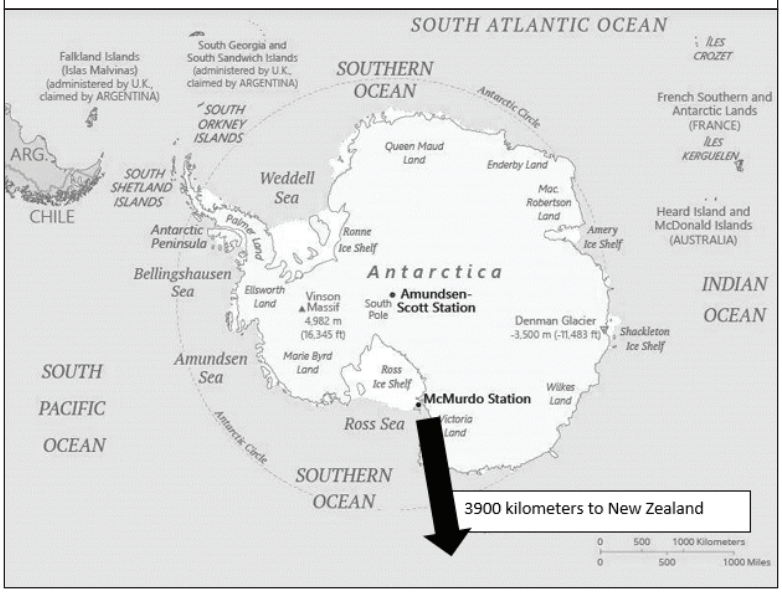
Introduction

Background: Around the world, US military personnel defend and support operations in remote areas with environmental and distance considerations that can make medical evacuation difficult. The Arctic and Antarctic regions challenge even the most prepared with bad weather, freezing temperatures, and long travel times to advanced medical management. Currently, US military operations above the Arctic circle generally support border operations in Alaska and various space-based and nuclear early warning missions vital to the current national defense strategy, but there are concerns multidomain/large scale combat operations could occur in this region.[1] Below the Antarctic circle, US military missions are supportive of noncombat, scientific missions on the Antarctic continent but still carry many of the same challenges posed by the Arctic environment.

A significant obstacle to polar operations is the distance involved for aircraft support, the current preferred method of patient transport for critical injury and illness. This is becoming a more prominent challenge for the US military as we transition into a posture focused

on combat operations against adversaries with similar military strength, projection capabilities, and competing interest in polar regions.[2] McMurdo Station, the largest Antarctic station, is approximately 3,900 kilometers (km) from its primary air supply port at Christchurch, New Zealand (Figure 1). Thule Air Base (AB) in Northern Greenland is approximately 3,000 km from a suitably large logistics hub at St. John's, Canada. These distances are approximately 6-7 hours each way for a modern C-130 transport, necessitating significant planning from the aircrew as the mission may require refueling and crew rest requirements.[3] Bad weather and high winds, both of which are common to the polar regions, delay and/or prolong transport times, and in a conflict, these problems would be exacerbated by potential adversarial action. When evacuation is required from Antarctica, The Transportation Command (TRANSCOM) often helps coordinate these highly technical and risky operations.

Figure 1. Map of Antarctica adapted from the Central Intelligence Agency World Factbook.[17]



The National Science Foundation's (NSF) McMurdo Station provides a unique opportunity to study military evacuation trains from Polar regions. McMurdo marks a unique intersection of civilian and military cooperation as TRANSCOM is integrally linked in the logistic train for the station's peaceful, civilian research operations. McMurdo is primarily accessed during the austral summer (October to February), but limited flights are available during the winter as well. The station can host approximately 1,000 personnel in the summer and roughly 200 in the winter with an international population, which is approximately two-thirds male. There is a small group of USAF active duty airman and reservists, including medical personnel, deployed on a rotational basis. McMurdo is also a major waypoint for approximately 3,000 researchers and field staff who deploy to various locations across the continent every year.[4]

The holding facilities for patients at McMurdo, like many austere outposts, are not nearly as well-equipped as their contiguous counterparts. Careful utilization of these limited resources is paramount as resupply is often limited by the same issues highlighted above. However, evacuation poses its own set of unique dangers to the patient. During an attempted evacuation, patients are exposed to extreme temperatures as well as significant changes in air pressure which can create new medical problems or worsen existing pathology (e.g. subcutaneous emphysema, pneumothorax, various sinus/inner ear pathology, hypothermia, etc.).[5] In addition to the risk posed to the patient, aeromedical evacuation requires mobilization of significant resources as well as exposure of the patient and aircrew to the inherent risk of aviation (e.g.-mechanical failure), compounded by flight in an austere environment.[6]

In order to facilitate medical movements using military aircraft, TRANSCOM uses the TRANSCOM Regulating and Command and Control Evacuation System (TRAC2ES) to plan and record patient movements. Providers and planners can input specific patient data and transportation/medical requirements in this global system to help execute medical movements throughout a theater of operations.[7] Data captured in this system includes various patient demographics, diagnoses, date/time of movement, and specific aeromedical considerations and techniques. In some cases, narratives detailing treatments and future plans are given, but this is not uniform across the system as the system is designed for movement tracking and not for communication amongst medical personnel.[8,9]

To date, there is limited literature about medical events occurring at these remote military and research bases in polar regions. A literature search revealed several case studies/series as well as a handful of epidemiological articles about clinic utilization at various international research facilities.[5,10,11] One case report included the number of evacuations from McMurdo from 1998-2001 and reasons for emergent evacuation.[12] No articles were found detailing reasons for all medical movements and

evacuations, and no clear military transport analysis exists in medical literature despite the military presence in Antarctica for nearly a century.

Goal of this Study: We sought to report on a dataset of aeromedical evacuation which occurred out of a US Antarctic research facility highlighting the patient population, conditions leading to evacuation, and specific challenges unique to these environs.

Table 1. Demographics of the patients evacuated and precedence of the evacuation.

Demographics/Characteristics			
		Patient Nationality/Military	
Total Evacuations:	31	**Status:**	*n (%)*
Unique Patients:	29	U.S. Civilian:	14 (48)
		U.S. Military:	3 (10)
Patients by Gender:	*n (%)*	Non-U.S. Partners:	3 (10)
Female:	5 (17)	Unknown:	9 (31)
Male:	24 (83)		
		Evacuations by Precedence:	*n*
Average Age:	39 years	Priority:	10
Median Age:	32 years	Routine:	21

Methods

De-identified data, part of another study examining patient movement in the INDOPACOM region, was used to analyze medical movements in Antarctica.[13,14] The original protocol was reviewed by the 59th Medical Wing regulatory office under protocol number FWH20180147N and determined to be exempt from Institutional Review Board oversight. We obtained only de-identified data.

TRACE2S, a military database, provides patient and transport information on TRANSCOM evacuations. Data in TRACE2S includes case numbers, type of aircraft, originating and receiving facilities, basic demographic information, date of evacuation, chief complaint, and it often provides a brief narrative regarding the clinical circumstances and logistical concerns surrounding the evacuation. The narrative descriptions provided in TRACE2S do not follow a pre-specified format and range in complexity from non-existent to detailed descriptions of the patient, conditions, and reasons evacuation is necessary.

This was a retrospective, observational study. We analyzed data from the TRACE2S dataset for evacuations between 2013-2018 in INDOPACOM. All medical evacuations beginning in or terminating at McMurdo Station, Antarctica, were included. Basic age, sex, diagnosis code, date of evacuation, and a non-standardized narrative description of the patient presentation were reviewed. Two emergency medicine physicians reviewed all cases in the data set to determine if the evacuations were due to traumatic or medical processes. The chief complaints and narrative descriptions were used to generalize diagnoses leading to evacuation into 12 broad categories. The number of trauma compared to non-trauma (medical) related incidents was also analyzed.

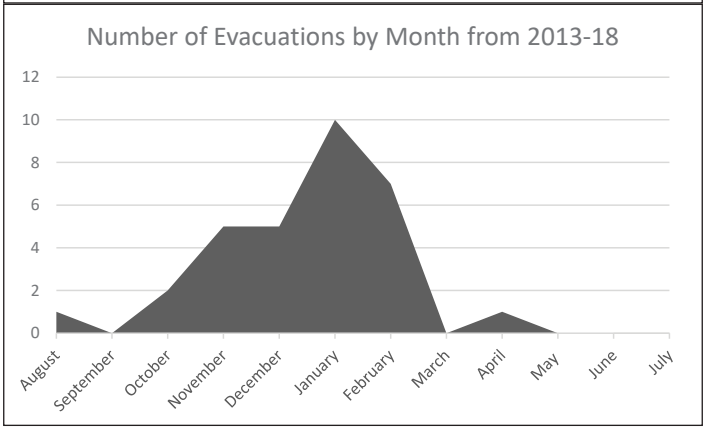
Descriptive methods were used to analyze the data. All statistical analysis was performed using a commercial database software package. Prevalence of diagnosis by category, number of evacuations by month, and demographic information are reported in the following section of this paper.

Results

On review of the data, there were 31 cases of evacuation to or from McMurdo Station found in the TRAC-2ES dataset. These were the result of 29 unique cases with 2 data entries representing patients who were initially evacuated to McMurdo by air and then underwent subsequent movement off the Antarctic continent. The patient population was predominately male, civilian researchers/contractors, and the average age was 39 years old. Further characteristics are documented in Table 1.

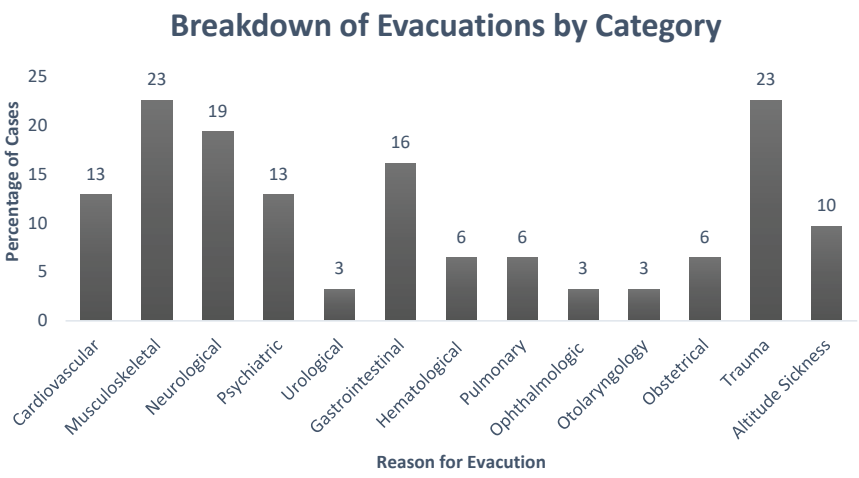
In regard to the evacuations, 11 evacuations were designated "priority" evacuations while 20 were "routine." Overall, evacuations were more commonly recorded in the summer season, and the number of seasonal evacuations recorded in TRAC2ES varied from as few as 1 in the 2013-14 season to as many as 14 during the 2016-17 season. Figure 2 details the number of medical evacuations entered in this dataset by month and shows most evacuations occurred during the austral summer with no evacuations recorded in the middle of winter.

Figure 2. Seasonal variation of evacuations.



The medical reasons for

Figure 3. Relative prevalence of evacuations by diagnosis category.



evacuation varied significantly from evacuation for obstetrical care after a positive pregnancy test to definitive management of cardiovascular and surgical emergencies. A summary of broad categories for evacuations is provided in Figure 3. Overall, medical causes for evacuation (24 cases) exceeded acute traumatic causes. Upon further subgroup analysis of medical causes for evacuation, musculoskeletal complaints predominated reasons for evacuation followed closely by neurological, psychiatric and gastrointestinal concerns. Only 3 evacuations in this dataset were related directly to environmental exposure, and all environmental illnesses were result of exposure to high altitude at the South Pole. No records were found for frostbite or thermal injuries in this dataset.

The TRACE2S data does not fully capture what prompted evacuation (e.g., need for further diagnostics, inability to provide definitive care, or inability to perform duties). However, review of available narrative data regarding certain cases does reveal patients were often transported out of McMurdo due to need for advanced imaging, specialty care not available in Antarctica, or for concerns the patient may decompensate further. These resource limitations are largely inferred from reading the text. Table 2 provides several examples where the narrative portions explicitly stated resources limitations and evacuation considerations in Antarctica. Overall, the limitations within the McMurdo health system which ultimately led to evacuation cannot be adequately evaluated by this dataset due to the lack of reporting and variable nature of the narrative sections.

Table 2. Narrative descriptions of logistical considerations for evacuation.

Diagnosis	Evacuation Considerations
Chest Pain, High Risk	"Troponin neg x2... At this time the runway won't be cleared until at least Monday."
Abdominal Pain	"Started antibiotics. Sending to [New Zealand] for CAT Scan."
Deep Vein Thrombosis despite Anticoagulation	"Therapeutic on 8mg of Coumadin, needs outpatient workup."
Facial Trauma, Possible Orbital Wall Fracture	"...facial xray to confirm trapped gas. [P]atient will move to New Zealand for head and face CT."
Joint Effusion	"...for follow up with this orthopedic surgeon."

Discussion

With this data, we would like to highlight some of the possible pathology encountered in polar operational environments. The patient population described herein is representative, albeit slightly older, of the population one may see during a military surge of operations to these colder areas of the world. The population studied was rigorously screened by medical professionals prior to their deployment to Antarctica, and they are sent for what is expected to be short period of time before redeployment.[4] While the cohort described above may have a slightly higher median age compared to most military units, the cohorts are likely similar enough to extrapolate some of the data.

Overall, the dataset seems to suggest the most prominent diagnoses leading to evacuation were related to workplace/recreational injuries, psychiatric crises, and medical pathologies which could be encountered anywhere but required specialty care not available at the originating facility. Musculoskeletal concerns were the most common reason for evacuation. Not surprisingly, this is similar to military operations, as most pathology arises as the result of disease/non-battle injuries. While non-traumatic diagnoses exceeded traumatic diagnoses, trauma on and off duty contributed to many evacuations. Notably, only 3 individuals required evacuation purely due to environmental factors (altitude sickness) despite the extreme environment. It is not clear if other environmental injuries (hypothermia, frostbite, etc.) may have been evacuated using means not captured in TRAC2ES, or more likely, managed locally given robust methods for treatment of this are likely available onsite. Data from Japanese research expeditions suggest exposure injuries

still occur with relative frequency despite aggressive preparation for the polar environment;[11] however, given cold weather injuries are expected, treatment in place may decrease the number of overall cold weather injuries requiring evacuation.

Interestingly, our data shows mental health issues contributed significantly to total evacuations (approximately 13%), but data on clinic utilization at various facilities shows psychiatric illness was lower in volume than other processes (as low as 0.5% in one study).[11,15] Given the extreme psychological burdens which can exist in austere environments, the higher evacuation rate may be due to concerns the patients would be unable to continue their duties or would continue to suffer while deployed. However, this is conjecture and further research is needed to understand this trend.

The data collected in the TRAC2ES is relatively scant for this 5-year period with only 29 unique cases requiring 31 evacuations. When compared to other literature regarding the number of evacuations from Antarctica, it is clear this dataset does not capture all medical movements to or from McMurdo. Notably, research published by Pattarini regarding clinic utilization in McMurdo in 2013-14 shows more than 30 medical evacuations/movements, but only 2 evacuations were captured in TRAC-2ES for this same time period.[10] It is unclear whether the evacuations simply were not documented in TRAC2ES or if they occurred on non-military platforms.

Similarly, an abstract presented at the 2015 Aerospace Medical Association Meeting by Reyes et al demonstrated there were 165 evacuations from McMurdo between 2001 and 2014 suggesting evacuation rates are higher than what was captured in TRACE2S. According to Reyes et al, trauma, gastrointestinal, and cardiological emergencies were the most common medical conditions needing evacuation. Generally, this appears consistent with our data, but detailed information regarding timing of evacuation or resource limitations driving evacuation were not available for review.[16] No PubMed indexed articles were found pertaining to this topic prior to the writing of this paper. Thus, there exists a significant gap in literature regarding Antarctic medical evacuations.

Overall, our analysis provides information for why a cohort of personnel were evacuated from McMurdo Station in Antarctica. However, this research is limited as it is a single site analysis of evacuations listed in the TRAC2ES. Based on comparison to existing literature, this does not capture all evacuations from Antarctica in the study period. Unfortunately, the database is also insufficient to draw conclusions regarding the role pre-existing conditions/comorbidities and need for evacuation. Furthermore, TRAC2ES does not provide information regarding non-evacuated patients, so it is impossible to determine an evacuation rate based purely on this data.

While TRACE2S provides a good starting point for analyzing evacuations, more detailed medical records would be helpful in elucidating useful information and trends. Conclusions from this data should be drawn carefully and only used with the understanding this is incomplete data requiring further research and development of more robust datasets with a focus on medical evacuation. Future research could seek to merge data from the various entities operating in Antarctica to better capture and characterize all reasons for medical encounters and evacuations from circumpolar regions as well as to better describe sending facility limitations necessitating evacuation.

Conclusions

Most evacuations were due to medical problems with musculoskeletal issues predominating; however, trauma contributed to evacuations as well. Challenges and delays to evacuation were noted to occur, but data regarding this is limited. Better data would be useful for mission planning in similar environments.

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Prehospital Pharmacotherapy in Moderate and Severe Traumatic Brain Injury: A Systematic Review

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Abstract

Background: Traumatic brain injury (TBI) affects civilian and military populations with high morbidity and mortality rates and devastating sequelae. As the US military shifts its operational paradigm to prepare for future large-scale combat operations, the need for prolonged casualty care is expected to intensify. Identifying efficacious prehospital TBI management strategies is therefore vital. Numerous pharmacotherapies are beneficial in the inpatient management of TBI, including beta blockers, calcium channel blockers, statins, and other agents. However, their utility in prehospital management of moderate or severe TBI is not well understood. We performed a systematic review to elucidate agents of potential prehospital benefit in moderate and severe TBI.

Methods: We searched 6 databases from January 2000 through December 2021 without limitations in outcome metrics using a variety of search terms designed to encapsulate all studies pertaining to prehospital TBI management. We identified 2,142 unique articles, which netted 114 studies for full review. Seven studies met stringent inclusion criteria for our aims.

Results: Studies meeting inclusion criteria assessed tranexamic acid (TXA) (n=6) and ethanol (n=1). Of the TXA studies, 3 were randomized controlled trials, 2 were retrospective cohort studies, 1 was a prospective cohort study, and 1 was a meta-analysis. Notably absent were papers investigating therapeutics shown to be beneficial in inpatient hospital treatment of TBI. Overall, data suggest TXA administration is potentially beneficial in moderate or severe TBI with or without intracranial hemorrhage. Severe TBI with or without penetrating trauma was associated with worse overall outcomes, regardless of TXA use.

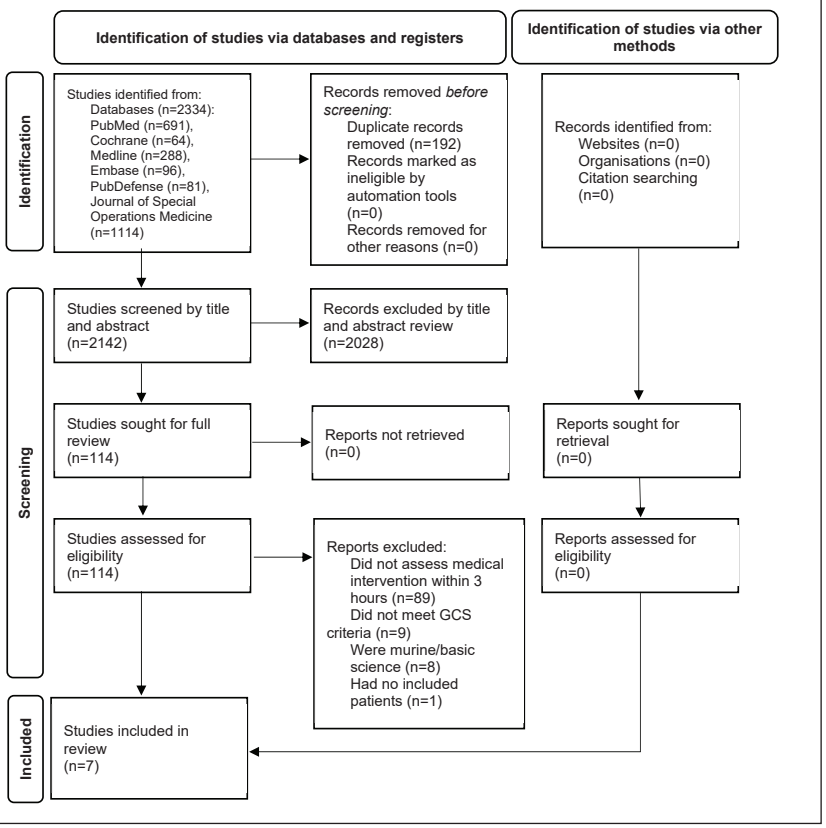
Conclusion: Effective interventions for treating moderate or severe TBI are lacking. TXA is the most widely studied pharmacologic intervention and appears to offer some benefit without adverse effects in moderate TBI (with or without intracranial hemorrhage) in the pre-hospital setting despite heterogeneous results. Limitations of these studies include heterogeneity in outcome metrics, patient populations, and circumstances of TXA use. We identified a gap in the literature in translating agents with demonstrated inpatient benefit to the prehospital setting. Further investigation into these and other novel therapeutic options in the prehospital arena is crucial to improving clinical outcomes in TBI.

Keywords: TBI; traumatic brain injury; prehospital; military

Introduction

Traumatic brain injury (TBI) is a disruption in typical neural function due to an applied external force causing temporary or permanent neurocognitive and/or functional impairment.[1-4] TBI affects global civilian and military populations, has high morbidity and mortality rates, and is a significant resource and cost burden. Prolonged casualty care (PCC) will become increasingly important as the US military shifts its operational paradigm to prepare for future peer and near-peer large-scale combat operations (LSCOs).[5] Therefore, identifying efficacious prehospital TBI management strategies is vital.

Figure 1. PRISMA flow diagram of search methodology.



Moderate and severe TBI present an increasing burden on individual, medical, societal, and economic stakeholders at an estimated annual cost of $400 billion worldwide.[6,7] Though hospital management of TBI is costly, most of this burden results from lost productivity, disability, reduced quality of life, and the need for family members to provide care.[6-8] The impact is magnified in US military service members and veterans. TBI is considered a signature injury of Operation Iraqi Freedom (OIF) and Operation Enduring Freedom (OEF). According to data from the Department of Defense Trauma Registry, TBI accounted for 20-25% of combat casualties from 2000-2011 and affected over 400,000 service members from 2000-2021.[6,9-11]

Injury mechanisms in the military (explosive trauma, extracranial polytrauma) are complex and likely contribute to poor outcomes,[6] alongside loss of consciousness and exposure to explosive weaponry.[10,12] Although other wounds have decreased, a significant rise in head and neck injuries have been recorded due to improvements in individual body armor, training, and other precautions.[10] Despite increased survival after battlefield injury, TBI and related sequelae may persist and/or evolve during the transition from acute injury to the chronic recovery phase.[3,4,13,14]

Fortunately, the mechanisms underlying TBI and potential therapeutic mitigation strategies are targets of active research. TBI is increasingly recognized as a multifactorial pathophysiologic process with the potential for irreversible and progressive neurocognitive and neuropsychiatric decline.[3,15] Primary and secondary brain injury are thought to encompass the pathogenesis of TBI.[16,17] The primary injury involves the initial insult to the cranium, whereas the secondary injury encompasses the subsequent cerebrovascular, coagulopathic, and metabolic dysregulation that occur following primary injury.[18-20] The coagulopathic axis in TBI manifests as acute disseminated intracranial hemorrhage, delayed hematoma formation, and systemic bleeding, although the mechanisms driving early hypercoagulable and hyperfibrinolytic states may differ from other pathologies such as extracranial trauma and hemorrhagic shock.[21] TBI-induced coagulopathy is a well-known risk for poor clinical outcome which remains poorly understood.[22] Additional patient characteristics contributing to poor outcomes include age, sex, existing comorbidities, alcohol use, genetics, metabolic factors, and prior TBI.[4,16,17,23,24]

Moderate and severe TBI sequelae include a spectrum of neurobehavioral and neuropsychiatric pathologies, and growing evidence indicates TBI is a risk factor for future neurodegenerative disease.[16,25-43] Long term outcomes paint a grim picture. Per the Extended Glasgow Outcome Scale (GOS-E), between years 1-5 post-injury, only 26% of patients with moderate or severe TBI showed improvement, 35% declined, and an estimated 20% of patients died.[42]

Various pharmacologic agents have been studied in TBI in the inpatient setting. Beta-blockers significantly reduced in-hospital and 6-month mortality while improving long-term functional outcomes and delivering time-dependent neuroprotective effects.[44-46] A meta-analysis assessing calcium channel blockers found nimodipine is beneficial in patients with subarachnoid hemorrhage,

though it was also associated with an increase in adverse events.[47] Pravastatin and simvastatin were shown to attenuate cerebral vasospasm (pravastatin by 32%), modulate cerebral autoregulation, mitigate serum markers associated with brain injury, and improve overall mortality in acute subarachnoid hemorrhage (a common TBI comorbidity).[48,49] Erythropoietin offers a possible in-hospital mortality benefit at 6-month follow-up without adverse events.[50] One randomized controlled trial (RCT) found progesterone administration in patients with severe TBI significantly improved Functional Independence Measure at 6-month follow-up,[51] while another found oral glibenclamide significantly decreased contusional volume expansion versus placebo.[46] One meta-analysis suggested magnesium sulfate improves Glasgow Outcome Scale (GOS) and Glasgow Coma Scale (GCS) outcomes.[52]

Table 1. Summary of included studies.

Author	Country	Number of Patients	Pharmacologic Agent	Study Design	Primary Outcome Metric
Roberts (2021)	Multiple (29)	9127	Tranexamic Acid	RCT	28-Day Mortality
Rowell (2020)	United States and Canada	966	Tranexamic Acid	RCT	6-Month Neurologic Outcome (GOS-E)
Jokar (2017)	Iran	80	Tranexamic Acid	RCT	Growth of ICH
Walker (2020)	United States and Canada	71	Tranexamic Acid	RCS	Neurologic Outcome (GCS, GOS)
Morte (2019)	Multiple*	174	Tranexamic Acid	RCS	In-Hospital Mortality, GCS on Discharge
Bossers (2020)	Netherlands	1827	Tranexamic Acid	PCS	30-Day Mortality
Raj (2016)	Multiple**	95,941	Ethanol	MA	Hospital Mortality
	*All NATO hospitals in Iraq and Afghanistan				
	**11 included studies				

Unfortunately, despite the robust and promising investigation into inpatient pharmacologic management, little is known regarding prehospital TBI treatment. The continued epidemiologic consequences and US military focus on future LSCOs emphasize the importance of developing effective prehospital therapeutic strategies to improve TBI outcomes. This systematic review seeks to identify pharmaceutical agents with potential prehospital benefit in moderate or severe TBI.

Methods

We searched for published and unpublished studies from January 2000 through December 2021 in the following databases: PubMed, Medline, Embase, Web of Science, Cochrane, and PubDefense. Our search was designed to capture any study of prehospital traumatic brain injury management in civilian and military medicine. We limited included study designs to randomized controlled trials, meta-analyses, and prospective and retrospective cohort studies. We further limited study participants to those with moderate or severe TBI (GCS<12, as defined across studies) without regard to injury mechanism. While there was variability in time-to-treatment across studies, we limited results to those with interventions used within 3 hours, a timeframe more generalizable to the wide range of treatment environments encountered in combat settings. We included any type of pharmacologic intervention and excluded studies emphasizing non-pharmacologic interventions, such as intubation, cooling, and hyperventilation. We did not limit our studies by outcome metric to best comply with Cochrane guidelines for systematic review. Metrics include (but are not limited to) mortality, neurologic recovery, disability, progression of ICH, and adverse effects.

Our search parameters produced 2,334 articles from the 7 databases (Figure 1). After controlling for duplicates, 2,142 articles remained. Two authors independently evaluated each title and abstract, netting 114 studies for full review. Upon full paper review, 7 studies met inclusion criteria.

Results

The 7 studies we included analyzed tranexamic acid (TXA) (n=6) 53-58 and ethanol (n=1).[59] Of the TXA studies, 3 were RCTs,[53,54,57] 2 were retrospective cohort studies (RCSs),[55,56] and 1 was a prospective cohort study (PCS).[58] The study assessing ethanol was a meta-analysis.[59] A summary of included studies can be found in Table 1.

Tranexamic Acid—Randomized Controlled Trials: The Roberts CRASH-3 trial compared intravenous infusion of TXA versus placebo within 3 hours following TBI in 9,127 patients at 175 hospitals across 29 countries.[53] Patients were randomized to either TXA (one gram [g] loading dose followed by 1g infusion over 8 hours; n=6406) or 0.9% normal saline (n=6331) intervention group. The primary outcome was 28-day mortality, which demonstrated an 18.5% mortality in the TXA group versus 19.8% in the placebo group (RR=0.94; 95% CI 0.86-1.02). One group controlled to exclude those with a GCS of 3 or bilateral unreactive pupils at baseline, noting a 12.5% mortality in the TXA group compared to 14.0% in the placebo group (relative risk [RR]=0.89; 95% CI 0.80-1.00).

These authors also reported a mortality risk reduction overall and at 24- and 48-hours post-injury in moderate TBI (RR=0.81 and 0.89, respectively), but no risk

reduction in severe TBI, in the TXA group. Further, while all study patients received treatment or placebo within 3 hours of injury, the authors noted earlier post-injury TXA treatment within the timeframe correlated with lower mortality (p=0.005) in the moderate TBI group. There was no improvement in the severe TBI group. There were no significant differences in disability risk or the incidence of vaso-occlusive events or seizures between groups.[53]

Rowell and colleagues evaluated administration of prehospital TXA bolus (1g) and in-hospital TXA infusion (1g over 8 hours; bolus maintenance group), prehospital TXA bolus (2g) and in-hospital placebo infusion over 8 hours (bolus only group), and prehospital placebo and in-hospital placebo over 8 hours in 966 patients at 20 trauma centers and 30 emergency medical service agencies in the US and Canada.[54] The primary outcome measure was favorable neurologic recovery by GOS-Extended (GOS-E; quantifies functional neurologic outcomes) at 6-month follow-up. Authors pre-specified patients were to be stratified into 2 groups: GOSE>4, indicating moderate disability or good recovery; and GOSE≤4, indicating severe disability, a vegetative state, or death. Secondary outcome measures included mortality at 28 days, and 6-month scores on the Disability Rating Score (DRS: a 30-point scale quantifying severity of neurologic disability) such that lower scores indicate more favorable outcomes. The study protocol does not specify whether TXA was administered at the point of injury or en route, but does report standard of care life-saving procedures were followed.

These authors reported no significant improvement by GOSE>4 in the treated group (95% CI:-0.9%–10.2%). Additionally, they found no significant differences between the combined TXA groups versus placebo in either 28-day mortality or 6-month DRS score. However, the bolus-only subgroup with image-confirmed ICH expansion experienced significantly lower mortality (18% compared to 27% in the placebo group, p=0.03) and a significantly lower DRS score (95% CI: -4.3 to -0.1,). Within this same subgroup, the bolus-only group experienced significantly lower mortality (95% CI: -15.6 to -0.8) and a significant reduction in DRS (95% -4.2 to -0.08) compared to the bolus maintenance group.

Though this study reports incidence of adverse events, authors acknowledged statistical analysis of such secondary outcomes were not included in this study. Additionally, these authors note limitations including potential survival bias, heterogeneity in time from injury to time of TXA administration, difficulty assessing ICH using only out-of-hospital GCS as a qualifier, and a 3% rate of penetrating head injury, thus limiting this study's generalizability to military populations. These results suggest while a prehospital bolus confers some benefit compared to placebo, subsequent treatment with TXA possibly confers harm.

The Jokar team randomized 80 TBI patients with CT-confirmed intracranial hemorrhage (ICH) into equal groups to receive a "conservative treatment" for ICH and either intravenous TXA (1g bolus followed by 1g infusion over eight hours) or placebo within 2 hours of injury.[60] Initial ICH volume was similar between the TXA and placebo groups (21.6±5.37 and 22.2±4.9, respectively). They found although there was a significant increase in ICH volume in both groups after 48 hours, the volume increase in the TXA group was significantly less than placebo (1.7±9.7 mL and 4.3±12.9 mL, respectively; $p < 0.001$). They detected no significant differences in gender, age, ICH type, and duration of hospital stay between groups. No long-term outcomes (e.g., mortality, functional neurologic outcomes) were assessed.

Retrospective Cohort Studies: The group led by Walker retrospectively evaluated all military patients with ICH arriving at an individual military treatment facility from October 2010 through December 2015 (n=71).[55] Fourteen patients received TXA and 57 did not. The authors reported patients receiving TXA had lower initial GCS (9.2±4.4 vs. 12.5±3.4, p=0.008), similar discharge GCS (13.3±4.0 vs. 13.8±3.2, p=0.58), and a larger improvement between presenting and discharge GCS (3.7±3.9 vs. 1.3±3.1, p=0.02). One caveat the authors noted was a greater proportion of patients who received TXA also received a massive transfusion (28.6% versus 8.8%); however, there was no statistical difference in mortality, mean 6-month GOS, or need for decompressive craniectomy despite the significant initial differences in injury severity.

Morte and colleagues assessed all trauma admissions who received TXA (n=174) in North Atlantic Treaty Organization (NATO) hospitals in Iraq and Afghanistan from 2008 through 2015.[56] Characteristics of patients receiving TXA include a higher injury severity score, more penetrating injuries, a lower presenting GCS, and a higher incidence of head injury. Patients receiving TXA, per pre-existing hospital administration guidelines, were those requiring blood product resuscitation and those judged likely to require massive transfusion. The authors included 92 patients in the propensity-matched cohort. Patients receiving TXA had a significantly lower mortality (0% vs. 10.1%, p=0.02) and improvement of GCS from 14 to 15 irrespective of admission GCS (100%, p=0.01). They found no significant differences in rate or number of thromboembolic events between the groups.

Prospective Cohort Study: The Bossers group enrolled patients in a prospective multicenter cohort study for treatment of suspected severe TBI by the Dutch Helicopter Emergency Medical Services with subsequent 1-year follow-up (n=1827).[58] These authors used the Abbreviated Injury Score (AIS) to stratify patients into severe confirmed TBI (Head AIS>3) or isolated severe TBI (Head AIS>3 and all other AIS<2) subgroups. They reported higher 30-day mortality in patients with severe isolated TBI who received prehospital TXA (OR 1.34, 95% CI 1.16-1.55, p<0.001) compared to similar patients who did not receive prehospital TXA. After adjusting for confounding variables, 30-day mortality remained statistically significant (OR 2.05, 95% CI 1.22-3.45, p=0.007). However, median arrival GCS for treated and untreated groups were 4 and 5, respectively. Furthermore, patients receiving TXA had a higher median injury severity score (27, IQR 21-38 and 26, IQR 17-34, respectively; p <0.001) than those receiving placebo. This could confound results in patients who had a high likelihood of mortality prior to TXA treatment.

Ethanol Meta-Analysis: The Raj group performed a meta-analysis of 11 observational studies assessing the effect of blood alcohol content (BAC) on mortality after moderate to severe TBI (n=95,941).[59] In their primary analysis, they stratified patients into a BAC-positive group and BAC-negative group. They reported a significant decrease in mortality in the BAC-positive group compared to the BAC-negative group (pooled OR 0.84, 95% CI 0.81-0.0.88, Z=8.13, p<0.00001), though their results were expectedly flawed by heterogeneity (I2=68%). Sensitivity analyses included 55,949 patients, and 51,772 patients produced similar results to the primary analysis: one found a pooled OR 0.87, 95% CI 0.83-0.92, Z=5.36, and p<0.00001, and the other supplied a pooled OR 0.78, 95% CI 0.74-0.83, Z=7.79, and p<0.00001. However, these analyses offered improved heterogeneity rates of I2=36% and I2=14%, respectively. Variability in the data of included studies precluded the authors from assessing the impact of different BAC levels on outcomes.

Discussion

Tranexamic Acid: TXA is a synthetic analog of lysine and acts as an antifibrinolytic agent via reversible competitive binding to lysine receptor sites on plasminogen. Blocking plasminogen to plasmin conversion prevents fibrin degradation, preserves the fibrin matrix structure, and ensures clot stability.[61] This mitigates subsequent bleeding and explains TXA's approved on-label clinical uses, including treatment of menorrhagia and management of short-term bleeding for patients with coagulopathies.[62,63] TXA may also be used off-label in massive transfusion protocols, hyper-fibrinolysis, non-traumatic subarachnoid hemorrhage, postpartum hemorrhage, gastrointestinal bleeding, traumatic bleeding, and various dental and surgical procedures.[61-63] Currently, TXA is only authorized for intravascular (IV) and intraosseous (IO) use, though an intramuscular formulation shows promise.[64] Prior studies indicate TXA can offer benefit in polytrauma.[65-67]

Only Bossers et al[58] and Rowell et al[54] administered different doses of TXA, ranging from 1-2g boluses with 1g infusions. However, Bossers et al did not stratify outcomes by dose. Rowell et al found the subgroup receiving a 2g prehospital TXA bolus with ICH experienced significantly lower 28-day mortality compared to placebo. Future studies could consider administering various doses and stratifying by outcome. All included studies administered TXA within three hours of injury; however, the studies did not clarify whether prehospital TXA was delivered at point of injury or en route. Delayed arrival to the hospital due to point-of-injury administration could confound outcomes. Stratifying patients by location of administration with subsequent comparison of outcome metrics is a reasonable next step.

Jokar et al[57] and Walker et al[55] reported TXA reduces ICH expansion in patients with ICH secondary to TBI, possibly via modulation of the coagulopathic axis to preserve hemostasis at sites of injury. These results possibly underlie the Rowell et al findings of a benefit in mortality. Unfortunately, the Jokar and Walker teams did not assess long-term neurologic outcomes associated with reduced ICH volume expansion from TXA use. Though TXA mitigates ICH expansion and improves mortality, further research is needed to determine whether this improves subsequent clinical outcomes.

The benefit of TXA in patients with TBI without active ICH is less clear. The CRASH-3 RCT provided evidence TXA reduced acute mortality in patients with moderate TBI and found a strong correlation between time-to-treatment and reduced mortality. Rowell et al did not corroborate these findings and found no benefit to functional neurologic outcomes 6 months post-injury. These 2 studies were consistent in that TXA use in severe TBI patients had no clear benefit but may prove useful in patients with isolated moderate TBI. Neither study found a significant incidence of the major adverse events of venous thromboembolism (VTE) or seizures.

In included cohort studies, TXA administration depended on the existing standards of care in each medical system. In these studies, patients receiving TXA were generally more severely injured, had associated polytrauma, and/or were likely to receive a blood transfusion. This selection bias for TXA patients among RCSs and PCSs

clouds the interpretation of results. Future RCTs should seek to minimize these biases.

The benefits of TXA in acute TBI appear to depend on injury mechanism, severity, and time to treatment. The availability of imaging equipment to assess hemorrhage and the wide variability in time to treatment in the combat or austere environment may further complicate therapeutic management. Logistical challenges to TXA use include transportation and route of administration. TXA is currently only approved for IV/IO delivery, whereas the intramuscular route is more practical for transportation and acute administration during care under fire.[68] TXA IV formulations require storage at temperatures ranging from 15° to 30° Celsius, making climate and storage environment crucial when considering transportation in a combat setting.[69] Though included studies incorporated patients with various injury severities and mechanisms of trauma, these civilian studies may fail to effectively model the types of trauma common in the military battlespace, thus obscuring potential benefits. Future studies of TBI coagulopathic states may elucidate the optimal therapeutic dosage and timing requirements for TXA in acute treatment regimens.

Given early TXA administration is associated with decreased mortality, can reduce ICH, and is not a significant source of adverse events, it is reasonable to consider TXA administration in patients who clinically meet moderate or severe TBI criteria. As of 2020, Tactical Combat Casualty Care guidelines added a TXA indication for service members who either demonstrated clinical TBI or were exposed to blast trauma. Additionally, these guidelines reflect an increase in the TXA bolus from 1g to 2g over 10 minutes.[70] This change should be tracked in military medicine and modeled broadly in civilian medicine to better assess prehospital mortality and long-term recovery.

Ethanol: The meta-analysis from Raj et al[59] found reduced mortality in TBI patients with ethanol in the blood at the time of injury. This study raised questions about the utility of gamma-aminobutyric acid (GABA) modulators in blunting the acute excitotoxicity central to TBI pathophysiology. Given the near-instantaneous excitotoxic responses occurring after TBI, the benefits observed in this study are likely due to intoxication at the time of injury. Furthermore, it is unclear what pathways may be affected by GABA modulators in TBI and how these may be modulated by ethanol use prior to injury. Whether GABAergic agents including ethanol remain beneficial when administered following TBI in the pre-hospital setting remains unanswered, and poses an interesting question for future studies. Significant questions also remain regarding long term functional neurologic outcomes.

Limitations: Our study was limited by lack of access to closed Department of Defense databases and to non-English literature which may identify other potentially beneficial therapies. Broad heterogeneity in outcome measures, study designs, and treatment groups further limit clear assessment of efficacy for pharmacologic interventions. Additionally, despite our broad and thorough search, the possibility remains we unintentionally excluded investigations of value.

Future Directions: Drugs theorized to provide benefit in TBI via minimization of secondary brain injury include anti-epileptic agents (phenytoin, valproic acid, levetiracetam), histone deacetylase inhibitors, and anti-inflammatory agents (mannitol, indomethacin, aminosteroids, and interleukin-1 receptor antagonists).[71] Several murine models suggest acid sphingomyelinase inhibitors,[72] triiodothyronine,[73] and mannose-binding lectins[74] also improve TBI outcomes. Despite a variety of agents mechanistically theorized to treat TBI and its sequelae, data is limited, and the toxicity of the drugs (often required in supra-therapeutic doses) is not yet well-characterized.

Our search indicated several therapeutics theorized to be beneficial in the early treatment of TBI have not been studied in the prehospital setting. Pharmacotherapies including beta blockers, statins, progesterone, calcium channel blockers, erythropoietin, and NSAIDs have undergone significant investigation in long-term management of TBI patients. However, this review failed to identify published studies investigating their application in the prehospital setting. This large gap in the literature demands further investigation. The study of established agents and novel interventions in acute TBI treatment provide an exciting direction for future research.

Conclusions

TXA has undergone extensive investigation in the prehospital setting, yet the results vary considerably in both consistency and applicability. Although some studies show promise in reducing mortality and improving neurologic outcomes without increased incidence of thromboembolic events, a clear consensus has yet to be reached. Collectively, these studies suggest TXA is safe and likely beneficial in moderate TBI with or without ICH while severe TBI outcomes are worse overall regardless of TXA administration. Further stratification of outcomes by time to treatment, TBI severity, associated polytrauma, and TXA dosage will be crucial in identifying candidate patients for rapid TXA intervention.

As TBI continues to exact a significant socioeconomic toll on military and civilian populations, investigating novel and effective therapeutic strategies in the prehospital setting remains crucial. Optimizing TBI outcomes is essential for the individual, the family, the US Military Health System (MHS), and the broader civilian healthcare systems. Prehospital pharmacologic TBI management is an ideal yet understudied interventional point to improve individual clinical outcomes and reduce systemic burdens.

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Can Military Role 1 Practitioners Maintain Their Skills Working at Civilian Level 1 Trauma Centers: A Retrospective, Cross-Sectional Study

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Abstract

Introduction: Military Role 1 practitioners have difficulty maintaining skill competency by working solely in military medical treatment facilities. Recognizing this, the Army Medical Department has renewed focus on physician specialty-specific Individual Critical Task Lists (ICTL) and is increasing the number of military-civilian partnerships, wherein small military treatment teams work full-time in civilian trauma centers. Yet, data to validate this approach is lacking. We hypothesize military Role 1 practitioners working full-time at a civilian Level 1 trauma center would attain similar resuscitation-specific procedural frequency to providers deployed to an active combat zone, and use the emergency medicine (EM) ICTL to compare select procedural frequency between a cohort of trauma patients from a civilian Level 1 trauma center and a cohort of combat casualties from the Department of Defense Trauma Registry (DODTR).

Methods: We compared a selected subset of critically-injured, military-aged (18-35 years) trauma patients who were seen in a Level I Trauma Center emergency department (ED) between January 1, 2016 and December 31, 2017 and dispositioned directly either to the operating room, intensive care unit, or morgue to a selected cohort from the Department of Defense Trauma Registry (DODTR) who were seen in EDs in Iraq and Afghanistan between January 2007 and August 2016 using descriptive statistics. The primary outcome was the frequency of ICTL procedures performed, and the secondary outcome was injury severity.

Results: We identified 843 civilian patients meeting inclusion criteria, of 1,719 military-aged patients captured by the trauma registry during the study. The selected cohort from the DODTR included 27,359 patients. Demographics were similar between the 2 groups, except the DODTR cohort included significantly more patients with blast trauma (55% versus 0.4%). We found similar ICTL procedural frequency (1 procedure for every 1.84 patients in the civilian cohort compared to one procedure/1.52 patients in the military cohort).

Conclusion: Role-1 ICTL trauma procedures were performed at similar frequencies between civilian patients seen at a Level 1 trauma center and combat casualties. With proper practice implementation, the opportunity exists for Role 1 practitioners to maintain their trauma resuscitation skills at civilian trauma centers.

Keywords: trauma epidemiology; skills maintenance; trauma procedures; Role 1

Introduction

Medical practitioners in Army Role 1 medical facilities provide pre-surgical resuscitative and stabilizing care. Practitioners at this level can include physicians with or without residency training and with a variable level of trauma exposure, as well as physician assistants, and medics. These practitioners suffer from the same problem: They do not see enough critically ill trauma patients or perform enough trauma-focused procedures to maintain skill competency while practicing in stateside military medical facilities.[1,2] As a result, the National Academies of Science, Engineering, and Medicine concluded providers "lack the necessary expertise to deliver trauma care on the battlefield."[3] Recognizing this need, the US Army Medical Department (AMEDD) has renewed the focus on specialty-specific Individual Critical Task Lists (ICTLs), which delineate critical

procedures US Army providers are required to document performing at a proscribed annual frequency.[4] The purpose of these lists is expanding the number of Army physicians who are able to stay combat-ready while performing their daily non-combat duties. To this end, the Army has been expanding military-civilian partnerships, wherein select physicians, nurses, and certified registered nurse anesthetists work in civilian level 1 trauma centers to increase their exposure to, and comfort with, critically ill patients, as well as their procedural volumes.[5] The only potential Role 1 providers assigned to these teams are trained in emergency medicine (EM), and other potential Role 1 practitioners do not benefit from this training (physician assistants (PA) and medics).

Table 1. Individual critical task list for the emergency physician; all procedures to be performed annually.

Procedure
Place a central venous catheter
Place an arterial catheter
Perform a cricothyroidotomy
Place a chest tube
Perform an extended focused assessment with sonography in trauma (eFAST) ultrasound exam
Perform canthotomy/cantholysis
Perform patient triage
Treat hemorrhagic shock
Perform emergency pericardiocentesis
Perform initial treatment of extremity crush injury
Perform advanced non-surgical airway management
Perform emergency resuscitative thoracotomy (ERT)
Perform resuscitative endovascular balloon occlusion of the aorta (REBOA)
Perform procedural sedation
Perform major burn resuscitation
Manage severe head injury
Manage a patient on mechanical ventilation
Manage agitated delirium/aggressive patient
Place a transvenous pacemaker
Manage a patient with chemical / biological / radiological / nuclear (CBRN) exposure
Perform system-based practices of managing CBRN exposure

Intuitively, working at a civilian level 1 trauma center would guarantee exposure to the highest volume of critically-injured trauma patients, and allow the maintenance of combat readiness among the Medical Corps during times of low combat casualty volume. Yet objective evidence of this in the form of comparisons between combat casualty cohorts and civilian trauma victims are lacking. Schreiber et al compared patients seen during a year at a civilian level 1 trauma center with those seen at a single Army combat support hospital (CSH) in Iraq in 2004-2005.[6] Chambers et al compared patients seen by a single Marine Corps surgical team during 1 year with a cohort of young male patients with gunshot wounds seen at a civilian level 1 trauma center during the same time frame.[7] More recently, Savell et al compared patients seen in 2 level 1 trauma centers with an analysis of patients seen in military emergency departments (ED) in both Iraq and Afghanistan.[8,9]

Our objective was to add to the limited body of literature comparing patients seen in civilian level 1 trauma center EDs with those seen in combat, and specifically to describe ED procedural frequency within the 2 registries. We chose a subset of skills required by the EM physician ICTL (Table 1)[10] (published 23 February 2022), as they are, for the most part, Role 1-applicable, and all Role 1 practitioners should be proficient in them. We describe procedural frequency of these skills amongst a cohort of patients from the trauma registry at a civilian level 1 trauma center compared to a cohort of patients from the Department of Defense Trauma Registry (DODTR). Our hypothesis was procedural volumes would be similar.

Methods

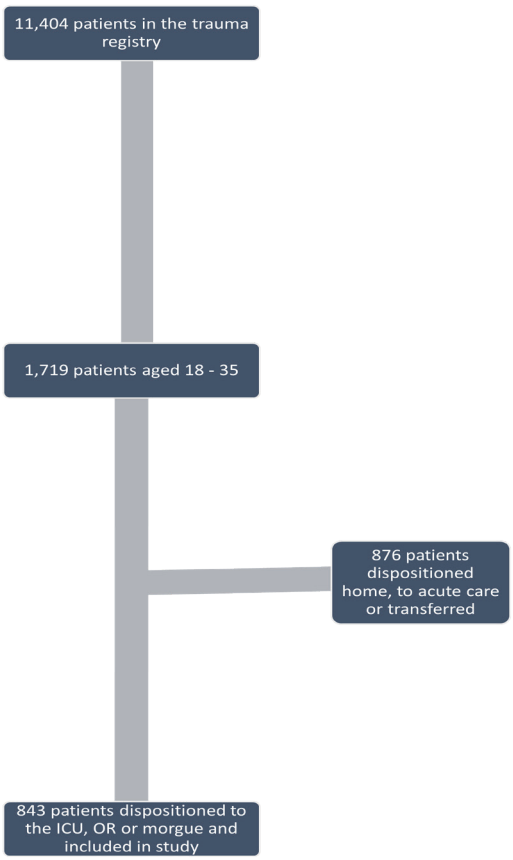
Ethics Approval & Setting—Civilian Site: Harborview Medical Center, located in Seattle WA, is a regional level 1 adult and pediatric trauma center serving a catchment area consisting of 5 states in the US Pacific Northwest. The hospital has 65,000 emergency department (ED) visits annually and 413 inpatient beds. The trauma/surgical intensive care unit (ICU) admits approximately 2,500 patients per year, and the trauma service evaluates approximately 5,500 patients per year. Data from all patients evaluated by the trauma service are collected in the trauma registry. Because only anonymous registry data was used, this study did not meet criteria for human subject research as defined by our institution's Human Subjects Division, thus was exempt from institutional review board oversight.

DoD Trauma Registry: We compared the civilian cohort to a dataset described previously[9] of casualties identified by ED procedure codes from the DODTR and were seen in the ED of a Combat Support Hospital (CSH)/Field Hospital (FH) or forward resuscitative surgical detachment (FRSD) in Iraq or Afghanistan between January 2007 and August 2016. The DODTR, formerly known as the Joint Theater Trauma Registry (JTTR), is the data repository for DoD trauma-related injuries.[11,12] The DODTR includes documentation regarding demographics, injury-producing incidents, diagnoses, treatments, and outcomes of injuries sustained by US/non-US military and US/non-US civilian personnel in wartime and peacetime (including host nation civilians) from the point of injury to final disposition. The DODTR comprises all patients admitted to a Role 3 (fixed-facility) or FRSD with an injury diagnosis using the International Classification of Disease 9th Edition (ICD-9) between 800-959.9, near-drowning/drowning with associated injury (ICD-9 994.1) or inhalational injury (ICD-9 987.9) and trauma occurring within 72 hours from presentation. In this dataset, procedures which were performed at Role 1 or Role 2 medical facilities are categorized as pre-hospital. Of note, all patients who died of wounds prior to reaching the CSH/FH, were excluded. Regulatory approval for the use of this data was previously

obtained for the above-described publication.

Study Design & Civilian Population: This is a retrospective, cross-sectional comparison of our trauma registry data collected over a 2-year period from 1 January 2016 through 30 December 2017 with the subset of the DODTR described above. We selected these dates from the Harborview trauma registry as they were the most recent available at the time of data collection and aligned best with our comparator dataset. To focus on military-relevant trauma patients like those seen by military resuscitation teams, we included only those patients aged 18-35 who were critically injured on arrival to the ED, which we defined as requiring disposition directly to either the operating room (OR), intensive care unit (ICU), or morgue.

Figure 1. Flow diagram for patient inclusion in the Harborview cohort.



Outcomes: Our primary outcome was the frequency of ED procedures performed expressed as the total ratio of patients per procedure. We selected the most Role-1 relevant procedures from the ICTL, including endotracheal intubation, tubal thoracostomy, resuscitative thoracotomy, central venous catheter placement, focused abdominal ultrasound in trauma (FAST) exam, and blood transfusion (used as a surrogate for "treat hemorrhagic shock"). Our secondary outcome was anatomical injury severity calculated by injury severity score (ISS). We hypothesized intubation would be less common in the civilian cohort and the frequency of ED procedures would otherwise be similar. Based on similar comparison studies, we anticipated injury severity would be higher in the civilian cohort than in the combat cohort.

Statistical Analysis: This study is presented in accordance with the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement.[13] Data was summarized using descriptive statistics. Nominal variables were presented as total counts and percentages. We compare the total ratio of patients seen per individual procedure performed between the 2 data sets. Descriptive methods were used as we were seeking to describe the volumes within the 2 registries with a goal of inferring findings from these 2 heterogenous registries to the population at large.

Results

During the study period, the Harborview trauma registry captured 11,404 patients. Of these, 1,719 (15%) were military age (18-35) of which 843 (49%) were dispositioned to either the OR, ICU, or morgue (Figure 1). 78% were male, and 70% suffered blunt trauma with the majority (53%) involving motor vehicle or bicycle collisions. Patients in the civilian cohort and DODTR were of similar age and sex and similar proportions suffered from gunshot wounds (18% vs 24%). There was an obvious difference in explosion-related injuries, where 55% of combat casualties suffered blast injuries compared to only 0.4% of civilian patients.[9] Patient demographics from the Harborview trauma cohort are reported in Table 2 and demographics from the

Table 2. Demographics of the civilian study population.

	Civilian cohort	%	DODTR	%
Total	843		27,359	
Age (median (IQR))	26 (22-30)		25 (21-30)	
Sex				
Male	665	78.8%	26,510	96.9%
Race			Not reported	
White	*563*	*66.7%*		
Black or African American	*125*	*14.8%*		
Asian	*47*	*5.5%*		
Native American	*38*	*4.5%*		
Native Hawaiian or Other Pacific Islander	*17*	*2.0%*		
Other Race	*5*	*0.5%*		
Not Documented	*53*	*6.2%*		

IQR: inter-quartile range

DODTR are reported in Table 3.[9]

Table 3. Demographics of the Department of Defense Trauma Registry study population.

		Overall	Explosive (15606)	GSW (6662)	MVC (2540)	Other (3414)
Demographics	**Age**	25 (21-30)	25 (21-30)	25 (21-30)	31 (25-40)	34 (26-44)
	Gender (male)	96.9% (27359)	97.5% (15217)	97.2% (6474)	96.4% (2447)	94.4% (3221)
Patient Category	**US Military**	41.3% (11665)	62.3% (7266)	15.5% (1805)	5.8% (685)	16.4% (1909)
	Coalition	8.0% (2259)	66.7% (1507)	19.2% (434)	3.5% (79)	10.6% (239)
	Host nation forces	24.1% (6795)	51.6% (3504)	32.3% (2195)	11.5% (780)	4.7% (316)
	Humanitarian	20.4% (5760)	44.4% (2558)	35.6% (2048)	12.6% (726)	7.4% (428)
	Contractor	5.7% (1616)	43.8% (708)	9.5% (154)	15.8% (256)	30.8% (498)
	Other	0.5% (127)	49.6% (63)	20.5% (26)	11.0% (14)	18.9% (24)
Military Operation	**Operation Iraqi Freedom**	30.6% (8638)	50.2% (4335)	24.7% (2136)	10.0% (867)	15.1% (1300)
	Operation Enduring Freedom	66.9% (18868)	58.3% (10999)	23.1% (4363)	8.4% (1590)	10.2% (1916)
	Operation Freedoms Sentinel	1.3% (358)	41.6% (149)	30.2% (108)	8.4% (30)	19.8% (71)
	Operation New Dawn	1.3% (358)	34.4% (123)	15.4% (55)	14.8% (53)	35.5% (127)

GSW: gunshot wound; MVC: motor vehicle collision

Primary Outcome Frequency of ED Procedures Performed:

Of 843 cases included in the civilian cohort, 461 procedures of interest were performed, with a frequency of 1 of the identified procedures being performed for every 1.84 patients seen. As a comparison, there was a frequency of 1 procedure for every 1.52 patients seen in the DODTR. We report and compare the Harborview and DODTR results by type of procedure in terms of both percentage and quantity in Table 4. The most common procedure performed in either setting was blood transfusions, which was performed in 21% and 26% of patients respectively. Intubation was much less common in the civilian cohort (4.3% compared to nearly 12%).

Secondary Outcome Injury Severity Scores: Patients had higher ISS in the civilian setting. Civilian patients had a median ISS of 17 with an interquartile range (IQR) of 9-26, compared with a median of 9 (4-16) in the DODTR cohort. In the DODTR cohort, the body region most frequently seriously injured were the extremities, accounting for 42% of patients. Conversely, serious extremity injury was relatively rare in the civilian cohort, accounting for only 11%. Rather, chest injuries were increased in the civilian cohort (37%) compared to the DODTR cohort (19%). We provide a comparison of composite ISS scores and anatomic injury locations from both cohorts in Table 5.

Table 4. Comparison of Emergency Department procedural volumes by cohort.

Procedure	Civilian Cohort		DODTR Cohort	
Total:	843		28222	
	Count	**%**	**Count**	**%**
Intubation	37	4.3%	3371	11.9%
Ultrasound	125	14.7%	6276	22.2%
Chest tube	79	9.3%	1310	4.6%
Thoracotomy	11	1.3%	130	0.4%
Blood	176	20.7%	7449	26.3%
Central line	33	3.8%	77	0.2%

DODTR: Department of Defense Trauma Registry

Discussion

We compare procedural frequency from a selected cohort of severely-injured military aged trauma patients presenting to a local level I trauma center with a subset of patients from the DODTR which has been previously published. The civilian cohort shared similar demographics to the DODTR cohort, was more severely injured, and had a similar frequency of critical Role-1 ED procedures performed. Mechanisms of injury differed significantly, with almost no blast injuries seen in the civilian cohort.

As expected, intubation was much less common in the civilian cohort. This difference may be attributed to differences in prehospital airway management provided by civilian emergency medical services providers versus combat medical providers.[14-16] Prehospital providers in the civilian setting are much more likely to intubate than are pre-Role 1 providers in the military, as the tactical combat casualty care guidelines do not emphasize intubation for airway management, and the vast majority of pre-Role 1 providers do not intubate.

Focused abdominal ultrasound in trauma (FAST) exams were performed less commonly in the civilian setting, despite seeing a higher proportion of severe thoracoabdominal injuries. This may reflect incomplete data captured in our trauma registry, but may also reflect different practice patterns. Patients with penetrating trauma in our facility are unlikely to have a FAST exam performed.[17] In addition, in a resource-limited combat environment, FAST exams may be performed more

frequently in lieu of computerized tomography (CT) scans given limited availability of both CT scanners, operating rooms, and surgeons.

Chest tube thoracostomy was twice as common in our cohort, which likely reflects prehospital tube placement in the military cohort rather than a truly increased frequency of chest tube placement in the civilian setting, It may also reflect the benefit of wearing body armor in the combat environment.

Table 5. Comparison of composite injury severity scores (ISS) and injuries by cohort.

	Civilian Cohort		DODTR Cohort	
Total:	843		28222	
	Count	**IQR**	**Count**	**IQR**
Composite ISS	17	(9-26)	9	(4-16)
	Count	**%**	**Count**	**%**
Head	309	36.4%	8500	30.1%
Face	129	15.2%	3866	13.7%
Thorax	311	36.6%	5489	19.4%
Abdomen	213	25.1%	4925	17.4%
Extremities	97	11.4%	11937	42.3%

DODTR: Department of Defense Trauma Registry; IQR: inter-quartile range

Resuscitative thoracotomy was rare in both cohorts but 3 times as common in the civilian setting. Frequency of thoracotomy in the combat cohort is consistent with prior literature.[18] The high prevalence of blast injury and poor prognosis of resuscitative thoracotomy in blunt trauma may explain the reduced frequency in the combat setting.[19-21]

While procedural frequencies were similar amongst the 2 groups, important caveats remain when considering whether military Role 1 practitioners can maintain procedural competency while working in civilian trauma centers:

- Our trauma registry does not capture who performed which specific procedure, but procedures are typically distributed between learners (residents and fellows) and attending physicians in academic civilian centers compared with small, dedicated resuscitation teams deployed in the military setting. Trauma responses at level I trauma centers also typically involve a multispecialty response. For example, highest level trauma activations at Harborview Medical Center involve co-management by surgery, EM, and anesthesia. Therefore, close attention to practice implementation is needed when integrating military EM providers into civilian trauma teams to ensure their procedural skill maintenance is prioritized. In one model, the military team embedded in a civilian facility could take care of patients as a team without civilian faculty or residents present. This may not meet standard of care in some civilian hospitals due to team size, composition, and levels of training (absence of a trauma fellowship-trained surgeon). In another model, military staff members are embedded in the normal civilian facility schedule, and much of their procedural exposure is through the teaching of residents and fellows.

- Credentialing and available procedural volume would also significantly impact the ability of non-physician practitioners to obtain and maintain procedural competency in civilian centers.

- Military EM physicians are often, but not always, able to moonlight at local civilian centers to maintain procedural competency. This ability to maintain trauma exposure is not shared by primary care physicians or by medics, and likely is shared to a lesser extent by physician assistants. The procedural volume acquired through civilian moonlighting is also difficult to quantify, and to our knowledge is not captured by ICTL reporting.

- We have used as our comparison dataset 10 years of military data during a period of active conflict. The frequency of procedures performed in war zones during this conflict likely does not reflect casualty or procedural volume during the next conflict.

- Our standard of procedural competency here is the EM physician ICTL. This list is useful as a starting point, but true procedural frequency required to maintain competence for long periods of time remains undefined.

Limitations

Our comparison dataset likely underestimates the procedural volume performed by Role 1 practitioners amongst military trauma patients, because it does not capture procedures performed prior to a Role 2 hospital. We refer to the selected procedures as "Role 1" procedures because they can be and are performed at the first point of battlefield contact with a provider, the Role 1 facility. Additionally, our comparison of patient volumes is limited by comparing a 10-year dataset of patients seen in multiple combat facilities to 2 years of data at a single civilian institution. As mentioned above, our facility is an academic level 1 trauma center. As such, learners at all levels compete for procedures, so the proportion of the procedures performed specifically by emergency medicine attending physicians is not

known. This was also a retrospective, cross-sectional comparison of 2 trauma registries. Therefore, all data collected are from the patients seen and procedures performed over a specified period of time. An ideal study would minimize confounders by comparing procedural volumes per provider by location over a given period of time. Such a comparison would require many providers to participate both in and out of the deployed combat setting to control for variations in operational tempo, population, and catchment area, and may not be immediately feasible. However, as the Army and other DoD medical assets continue to expand cooperation with civilian level 1 trauma centers, and ICTLs for EM physicians continue to be developed, perfected, and implemented, a retrospective comparison using a compilation of these ICTLs might become an efficient way to perform such a comparison. Future research regarding civilian-military partnerships should take these important variables into consideration.

Conclusions

Military-relevant trauma patient demographics, procedural frequencies, and injury severity are similar at this single civilian level 1 trauma center compared to the DODTR. This suggests military Role 1 practitioners can see large volumes of severely injured trauma patients and potentially perform sufficient procedures to meet the requirements of individual critical task lists while practicing at civilian trauma centers.

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A Comparison of Injury Patterns and Interventions among US Military Special Operations Versus Conventional Forces Combatants

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Abstract

Background: Over the course of the US' Global War on Terrorism, its military has utilized both conventional and special operations forces (SOF). These entities have sustained and treated battlefield casualties in the prehospital, Role 1 setting, while also making efforts to mitigate risks to the force and pursuing improved interventions. The goal of this study is to compare outcomes and prehospital medical interventions between SOF and conventional military combat casualties.

Methods: This is a secondary analysis of previously published data from the Department of Defense Trauma Registry. The casualties were categorized as special operations if they were 18-series, Navy SEAL, Pararescue Jumper, Tactical Air Control Party, Combat Controller, and Marine Corps Force Reconnaissance. The remainder with a documented military occupational specialty (MOS) were classified as conventional forces.

Results: Within our dataset, a MOS was categorizable for 1806 conventional and 130 special operations. Conventional forces were younger age (24 versus 30, $p<0.001$). Conventional forces had a higher proportion of explosive injuries (61% versus 44%) but a lower proportion of firearm injuries (22% versus 42%, $p<0.001$). The median injury severity scores were similar between the groups. Conventional forces had lower rates of documentation for all metrics: pulse, respiratory rate, blood pressure, oxygen saturation, Glasgow Coma Scale, and pain score. On adjusted analyses, SOF had higher odds of receiving an extremity splint, packed red blood cells, whole blood, tranexamic acid, ketamine, and fentanyl.

Conclusion: SOF had consistently better medical documentation rates, more use of ketamine and fentanyl, less morphine administration, and lower threshold for use of blood products in both unadjusted and adjusted analyses. Our findings suggest lessons learned from the SOF medics should be extrapolated to the conventional forces for improved medical care.

Keywords: special; operations; forces; conventional; trauma

Introduction

Background: The US military has been involved in conflicts as part of the Global War on Terrorism since October 2001. Two decades of combat have brought advances in Tactical Combat Casualty Care (TCCC) at the point of injury (POI), in-theater stabilization and management, and expedited evacuations to more definitive care.[1-3] These advances contributed to significant declines in overall rates of morbidity and mortality associated with combat. The 'golden hour' evacuation policy of 2009 is considered a prominent contributor.[2] Subsequent analyses suggest decreased rates of morbidity and mortality are multifactorial including early hemorrhage control, adoption of early prehospital blood product transfusion, forward deployed damage control resuscitation and surgery, and decreasing "time to required capability."[4] Other considerations, limited by experiential data, include improvements in tactics, techniques, and procedures (TTP), and enhancements in protective gear and

equipment. The operational threat environments also play a role as enemy combatants adjust tactics, techniques, and procedures.[5] In response, we have changed our TTPs to include better IED detection, and better intelligence, surveillance, and reconnaissance (ISR).

An important aspect regarding this era of US military combat is the level of reliance on special operations forces (SOF). From the initial contact and collaboration with Afghan Northern Alliance forces to the close cooperation with Kurdish militias in northern Iraq, the US has increasingly utilized SOF elements for multiple combat applications while also maintaining a significant requirement for conventional forces. As more SOF engaged in combat, these units pursued mitigation strategies to protect the force from battlefield injuries as well as improved interventions to limit severity of injuries. The US Army's 75th Ranger Regiment, 160th Special Operations Aviation Regiment, Special Forces Groups, US Navy SOF, and US Air Force pararescue stand out as early adopters of what has become the standard of care regarding battlefield injuries.[6,7] The Special Operations Combat Medic course, located in Fort Bragg, North Carolina, has provided standardization of training for all SOF elements. Moreover, this baseline training of SOF medics is substantially longer and more in-depth than medical training for combat medics in conventional forces and augmented by a greater emphasis on skills sustainment training given the austere environments SOF typically operate within.

SOF mission sets have historically diverged from the more traditional objectives of conventional forces. The US Army Special Forces, for example, focus on unconventional warfare, foreign internal defense, special reconnaissance, direct action, and counterterrorism. This ranges from facilitating local nationals conducting an insurgency, advising, and training a host nation's counterterrorism units, gathering intelligence in a non-permissive and/or semi-permissive environment, or conducting raids to capture high-value targets. These foci inherently require a degree of self-sufficiency and autonomy in an austere operational environment distinct from the usual context in which conventional forces are deployed which may result in prolonged evacuation times and limited access to medical and surgical facilities. SOF units have historically prioritized force protection mitigation strategies through robust combat casualty care across all phases, especially in pre-hospital care. The 75th Ranger Regiment was able to achieve zero prehospital preventable deaths during the first decade of conflicts in Afghanistan and Iraq.[7] Eastridge's (2012) analysis highlighted mechanisms and contexts for battlefield deaths, noting potentially survivable (PS) injuries on the battlefield coalesced around hemorrhage control and airway management.[8] As noted, these are areas where SOF units have advanced combat casualty care through the implementation of TCCC, early prehospital blood product administration, tourniquet use, and airway adjuncts to augment survivability likelihood until definitive care can be accessed. Multiple publications have described SOF and/or conventional military unit combat casualty outcomes and medical interventions; however, we are not aware of any study whose aim was directly to compare outcomes and prehospital management between SOF and conventional forces, which can vary significantly in operational environment and organic medic medical proficiency.

Goal of this Study: We compare outcomes and prehospital medical interventions between SOF and conventional military combat casualties.

Methods

Data Acquisition: This is a secondary analysis of previously published data from the Department of Defense Trauma Registry (DoDTR) which is previously described.[9] The US Army Institute of Surgical Research (USAISR) regulatory office reviewed protocol H-20-015nh and determined it was exempt from Institutional Review Board oversight. We obtained only de-identified data. Data was requested in aggregate from the DoDTR from 2007 through the date of submission in 2020. Data was extracted and provided to the study team by the Joint Trauma System, Data Analysis Branch.

Department of Defense Trauma Registry (DoDTR): The DoDTR is the data repository for DoD trauma-related injuries.[10,11] The DoDTR includes documentation regarding demographics, injury-producing incidents, diagnoses, treatments, and outcomes of injuries sustained by US/non-US military and US/non-US civilian personnel in wartime and peacetime (including humanitarian) from the point of injury to final disposition. Short-term outcome data are available for non-US casualties. The DoDTR comprises all patients admitted to a Role 3 (fixed-facility) or forward resuscitative surgical detachment (FRSD) with an injury diagnosis using the International Classification of Disease 9th Edition (ICD-9) between 800-959.9, near-drowning/drowning with associated injury (ICD-9 994.1) or inhalational injury (ICD-9 987.9) and trauma occurring within 72 hours from presentation. The registry defines the prehospital setting as any location prior to reaching a FRSD, field hospital (FH), or a combat support hospital (CSH) to include the Role 1 (point of injury, casualty collection point, battalion aid station) and Role 2 without surgical capabilities (temporary limited-capability forward-positioned

hospital inside combat zone).[9,12]

Analysis: We performed all statistical analysis using commercially available software. We present binomial variables using percentages, frequencies, and chi square or Fisher's exact tests, normally distributed continuous variables using means, confidence intervals, and student's t-test, and ordinal variables and non-normally distributed continuous variables using median, interquartile ranges, and Wilcoxon rank sum test. Multivariable regression models were used to describe associations and interactions between variables. We analyzed the data under the assumption of accurate documentation of all care rendered, to include interventions and measurements

Table 1. Demographic, mechanism of injury, injury severity score, injury locality, outcome metrics.

		Conventional n=1806	Special Operations n=130	p-value
Demographics	Age	24 (21-27)	30 (27-33)	<0.001
	Male	99% (1800)	100% (129)	0.549
Mechanism of injury	Explosive	61% (1115)	44% (58)	<0.001
	Fall	3% (60)	4% (6)	
	Firearm	22% (402)	42% (55)	
	Motor vehicle	3% (54)	3% (4)	
	Other	9% (174)	4% (6)	
Injury Severity Score		8 (4-14)	10 (4-17)	0.387
Serious injury by body region	Head/neck	9% (171)	6% (8)	0.270
	Face	1% (14)	0% (0)	0.617
	Thorax	10% (182)	6% (9)	0.287
	Abdomen	6% (116)	7% (10)	0.555
	Extremities	28% (520)	37% (48)	0.043
	Skin	2% (52)	3% (4)	0.786
Outcome	Alive	98% (1784)	97% (126)	0.212

For this analysis, we isolated only casualties with a documented military occupational specialty (MOS) or ratings. The casualties were categorized as special operations if they were 18-series, Navy SEAL, Pararescue Jumper, Tactical Air Control Party (TACP), Combat Controlled (CCT), and Marine Corps Force Reconnaissance. The remainder with a documented MOS were classified as conventional forces.

Results

From 01 January 2007 to 17 March 2020, the DoDTR documented 28,950 adult casualties. Within those adult casualties, a military occupational specialty was categorizable for 1,806 conventional and 130 special operations. Conventional forces were younger (24 versus 30, p<0.001). Conventional forces had a higher proportion of explosive injuries (61% versus 44%) but lower proportion of firearm injuries (22% versus 42%, p<0.001). The median injury severity scores (ISS) were similar between the compared groups (8 versus 10, p=0.387). Conventional forces had a lower proportion of serious injuries to the extremities (28% versus 37%, p=0.043) with no significant differences within the other injury regions (Table 1). Conventional forces had lower rates of documentation for all metrics: pulse, respiratory rate, blood pressure, oxygen saturation, Glasgow Coma Scale (GCS), and pain score (Table 2). On unadjusted analyses, conventional forces had lower proportions of receiving a chest seal, extremity splint, packed red blood cells (pRBCs), whole blood, intravenous fluids, tranexamic acid, ketamine, fentanyl, and morphine. On adjusted analyses, SOF had higher odds of receiving an extremity splint, packed red blood cells, whole blood, tranexamic acid, ketamine, and fentanyl (Table 3).

Table 2. Documentation metrics.

	Conventional n=1806	Special Operations n=130	p-value
Pulse	52% (943)	72% (94)	<0.001
Respiratory rate	43% (779)	65% (85)	<0.001
Systolic pressure	47% (858)	65% (84)	<0.001
Diastolic pressure	44% (803)	62% (80)	<0.001
Oxygen saturation	46% (835)	68% (88)	<0.001
Glasgow coma scale	46% (848)	73% (95)	<0.001
Pain score	26% (484)	36% (47)	0.018

Discussion

Analysis of the data indicates SOF were more likely to utilize documentation methods in real-time while managing battlefield trauma, more likely to initiate interventions and treatments, and more likely to administer non-morphine analgesics. Consistent with prior studies, interventions noted in this analysis focused on potentially survivable injuries and the opportunities where life-saving measures could have an impact.[8] Additionally, there was variation in types of injuries sustained as well as differentiation in anatomical distribution of injuries. Conventional forces sustained more explosive injuries, fewer firearms injuries, and fewer injuries to the extremities. The data from DoDTR utilized for this analysis is the common thread from other analyses regarding battlefield injuries, mechanisms, and fatalities.

Although definitive statements regarding the underlying rationale for variance between conventional and SOF injuries and subsequent management remain unlikely, several key observations can be made. Mechanism of injury remains unclear. For example, an explosive mechanism could signify indirect artillery, traditional land mines, vehicle borne IEDs, static and roadside IEDs, or explosive devices worn by enemy combatants. Moreover, the specific operational environment associated with each specific injury incident remains unknown. At the height of combat in Iraq, explosively formed penetrator IEDs became such a threat to coalition forces a new personnel transport was rapidly developed and implemented (Mine Resistant Armored Personnel carrier). Alternatively, Afghanistan was

one of the most heavily mined countries in the world prior to the conflict, and the significant threats and injuries associated with rural landmines created the dismounted complex blast injury taxonomy. Another point of consideration is the manner of infiltration and transport utilized by SOF elements compared to conventional forces. Targeted direct-action missions by SOF elements accounted for a significant portion of helicopter infiltrations and transport, likely reducing SOF exposure to roadside threats. The larger proportion of direct-action missions by SOF also likely contributes to the greater percentage in firearm injuries sustained during engagements with a committed hostile force.[13-15]

Table 3. Prehospital interventions.

	Conventional n=1806	Special Operations n=130	p-value	Adjusted odds ratio*
Hemostatic	2% (52)	6% (8)	0.057	1.8 (0.8-4.1)
Chest seal	<1% (7)	2% (3)	0.024	3.9 (0.9-16.0)
Warming	49% (897)	57% (74)	0.092	1.3 (0.9-1.8)
Limb tourniquet	24% (449)	29% (38)	0.246	1.1 (0.7-1.8)
Extremity splint	3% (59)	8% (11)	0.002	3.7 (1.8-7.5)
IO access	3% (54)	4% (6)	0.287	1.8 (0.7-5.0)
PRBC	1% (21)	6% (8)	<0.001	7.8 (2.9-20.6)
Whole blood	<1% (8)	3% (4)	<0.001	3.9 (1.1-14.3)
IV fluids	12% (227)	24% (31)	<0.001	2.1 (1.3-3.2)
TXA	<1% (15)	6% (8)	<0.001	5.8 (2.3-14.6)
Ketamine	6% (119)	22% (29)	<0.001	3.7 (2.3-6.0)
Fentanyl	18% (328)	41% (53)	<0.001	2.9 (1.9-4.3)
Morphine	28% (506)	13% (17)	<0.001	0.3 (0.2-0.6)
Antibiotic	12% (225)	18% (24)	0.044	1.3 (0.8-2.1)

**presented as SOF/CON for OR, adjusted for injury severity score and mechanism of injury*

An evaluation of the vital sign metrics, documentation, and prehospital interventions for conventional versus SOF forces highlights additional differences. Heart rate, Glasgow Coma Scale (GCS), pain score, and other metrics were documented more often for SOF injuries compared to conventional injuries. One explanation is the extent and depth of training were likely significant contributors to the disparity. SOF medics attend a training pipeline known as Special Operations Combat Medic (SOCM) course which emphasizes battlefield injuries and the most effective interventions currently available, with a focus on training personnel to deliver care under high stress situations. The US Army Special Forces Medical Sergeants (18D) complete SOCM as the first iteration of their medical training pipeline. Rangers, Navy corpsman, and Marine Corps Special Operations Command members also attend SOCM. Conventional units, in comparison, train combat medics through an introductory course in combination with basic training at the outset of a servicemember's introduction to the military.[9] A focus on and familiarity with multitasking during high stress situations likely contributed to the disparity in documentation during treatment and transport of the sample population of injuries.

Furthermore, unit level training for medics also likely contributed to the types of interventions initiated by conventional versus SOF medics. Early hemorrhage control, extremity splinting, fluid and blood transfusion administration, and pain control were all implemented to a greater degree in the SOF injuries. Also, SOF unit incorporation of TCCC potentially led to a greater utilization of self-aid, buddy-aid, along with the early adoption of standardized individualized first aid kits. The utilization of oral transmucosal fentanyl citrate (fentanyl 'lollipops') by SOF units compared to morphine utilization by conventional forces can partly be explained by the distribution of fentanyl to the individual service member.[16] At times, SOF units would allow for service members to sign for and carry the opioid analgesic in an upper extremity uniform pouch along with other medication interventions like atropine/pralidoxime as the operational environment dictated. Moreover, SOF units like the US Army 75th Ranger Regiment have led the effort in early prehospital transfusion of blood products to include whole blood with programs like Ranger O Low Titer transfusion protocols.[17]

Limitations

Analysis of registry data has limitations. We assume SOF casualties were treated by SOF medics and likewise for conventional forces given the typical operational practices of US military forces. However, we cannot exclude the possibility of a SOF medic treating a conventional casualty and vice versa given limitations in the identification of the prehospital provider within the DoDTR. Furthermore, because the 75th Ranger Regiment does not utilize a specialized job identifier (18-series, etc.), the results of their care have most likely fallen into the conventional unit section, potentially skewing the results despite having additional training beyond a standard Combat Medical Specialist (68W). Context of injuries for the data remains unknown. This limits analysis somewhat as it becomes difficult to assess the sequence of interventions provided by conventional and SOF forces. It is also difficult to determine whether conventional forces or SOF had shorter evacuation periods until arriving at definitive care, possibly resulting in less interventions that otherwise would most likely have occurred in a protracted pre-hospital phase. Additionally, context of injuries with regards to theater of operations, urban versus rural, and composition of force are unavailable. Information regarding these variables would provide more granular information in the comparison of

conventional and SOF interventions. Additionally, the study period of approximately 13 years limits the characterization of the differences between conventional and SOF; specifically, it is possible some interventions and protocols were comparatively available or introduced at different points during the conflict. For example, this point is noted by Schauer et al with regards to documentation of prehospital injuries by TCCC cards being mandated and broadly implemented in 2013.[18] Finally, only 6.7% (1936 of 28950) of the casualties in the DoD-TR possessed a MOS or unit identifier enabling their inclusion in our analysis. Consequently, limitations in the available data precluded more robust subject populations for our evaluation.

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Outcomes after Prehospital Cricothyrotomy

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Abstract

Background: Prehospital surgical cricothyrotomies and complications from placement are an important and under-evaluated topic for both the military and civilian prehospital populations. This study uses the Department of Defense Trauma Registry to identify complications and the incidence of complications in prehospital combat surgical cricothyrotomies.

Methods: A secondary analysis of previously described prehospital-based dataset from the Department of Defense Trauma Registry (DODTR) was performed. Casualties who had a prehospital cricothyrotomy performed were isolated and assessed for documented airway injuries and surgical procedures after hospital admission.

Results: There were 25,8976 casualties in the original dataset, of which 251 met inclusion for this analysis. The median age was 25 and most (98%) were male. Explosives were most frequent (55%) followed by firearm (33%) mechanisms. Most were host nation partner forces (35%) and humanitarian (32%) casualties. The median injury severity score was 24. The most frequent seriously injured body region was the head/neck (61%). Most (61%) were discharged alive. Within the 251, 14% had a complication noted, most commonly requiring tracheostomy revision (5%).

Conclusions: Cricothyrotomies are rarely performed, but when they are performed and the casualty survives long enough to reach a military treatment facility with surgical capabilities, the incidence of near-term and long-term complications is high. A better understanding of outcomes associated with this procedure will enable more targeted training and technology development.

Keywords: prehospital; combat; battlefield; airway; cricothyrotomy; injury; pattern

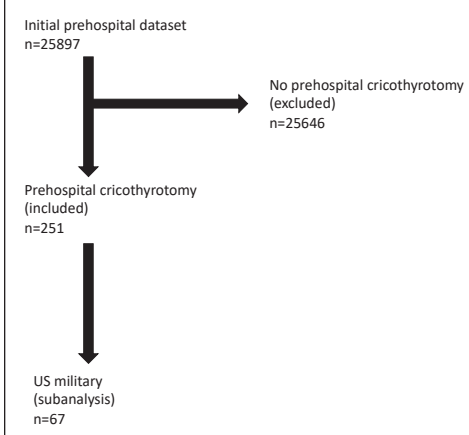
Introduction

The most common mechanisms of injury in the last 2 decades of war are explosions.[1,2] The landmark paper by Eastridge et al found the most common, potentially survivable injuries were associated with hemorrhage and airway obstruction.[3] Upper-airway obstruction can occur due to direct injury to the airway structures of the face and neck and may be associated with vascular injury, potentially compounding the effects of the injuries.[3] More recent data continues to underscore the importance of airway compromise as a leading cause of potentially preventable battlefield death.[4] Many of the more recent battlefield deaths have multiple overlapping problems and attention to non-compressible hemorrhage and airway (and ventilation) is needed to affect survival. Prehospital combat interventions and damage control resuscitation must therefore be multifaceted and simultaneously address airway, breathing, and bleeding. The aggressive use of tourniquet technology and forward-staged whole blood administration directly impact hemorrhage-related deaths.[5,6] However, little in the way of advancements for airway interventions have been made with the US military still primarily relying on the cricothyrotomy as the definitive prehospital airway intervention. Previous studies have demonstrated a high proportion of complications and misplacement, highlighting the complexity of this procedure.[7,8]

The Tactical Combat Casualty Care (TCCC) guidelines recommend the use of positional maneuvers during the tactical phase followed by nasopharyngeal airway and if

unsuccessful, transition to a surgical cricothyrotomy. In the Department of Defense Trauma Registry (DODTR), in the prehospital setting, 4.9% of patients underwent an airway intervention: nasopharyngeal airway in 15.1%, endotracheal intubation in 81.0%, and less than 1% underwent a surgical cricothyrotomy. In one study, surgical cricothyrotomies were successful in 68% of cases; whereas in 26% of cases, the prehospital team failed to cannulate the trachea. There was no documentation on 6% of cases in which patients were dead on arrival.[1,9,10]

Figure 1. Casualty inclusion flow diagram.



It remains unclear what the long-term outcomes are associated with this procedure and the need for surgical revision. With this challenge in mind, this article will revisit cricothyrotomy as a potential prehospital intervention by highlighting the benefits and risks, identifying data gaps, and proposing research directions.

Goals of this Investigation: This study sought to determine the incidence of surgical interventions, survival, and function at discharge.

Methods

Data Acquisition: The data source for this analysis was the Department of Defense Trauma Registry (DODTR), formerly known as the Joint Theater Trauma Registry (JTTR). The US Army Institute of Surgical Research (USAISR) regulatory office reviewed this protocol (H-20-015nh) and determined it was exempt from Institutional Review Board oversight. Only de-identified data was obtained. This is a secondary analysis of a previously published dataset.[11]

Study Population: The DODTR includes documentation regarding demographics, injury-producing incidents, diagnoses, treatments, and outcomes of combat casualties following injuries. We included data from year 2007 to year 2020. The registry includes US and non-US military as well as US and non-US civilian personnel from the point of injury to final disposition during war and peacetime. The DODTR is comprised of patients admitted to a Role 3 (fixed-facility) or forward resuscitative surgical detachment (FRSD) with an injury diagnosis using the International Classification of Disease 9th Edition (ICD-9) between 800-959.9, near-drowning/drowning with associated injury (ICD-9 994.1) or inhalational injury (ICD-9 987.9) and trauma occurring within 72 hours from presentation to a facility with surgical capabilities. The registry defines the prehospital setting as any location prior to reaching a forward surgical team (FST), field hospital (FH), or a combat support hospital (CSH) to include the Role 1 (point of injury, casualty collection point, battalion aid station) and Role 2 without surgical capabilities (temporary limited-capability forward-positioned hospital inside combat zone).

Analysis: We performed all statistical analysis using commercially available software. We present continuous variables as means and 95% confidence intervals, non-parametric continuous variables and ordinal variables as medians and interquartile ranges, and nominal variables as percentages and numbers. We analyzed the data under the assumption of accurate documentation of all care rendered. We linked all the casualties with a documented cricothyrotomy prehospital with the hospital-based procedural code and international classification of diseases version 9 codes (ICD-9). The associated codes were then reviewed for relevance and inclusion into this analysis.

Results

There were 25,897 casualties in our original dataset, of which 251 met inclusion for this analysis (Figure 1). The median age was 25, and most (98%) were male. Explosives were most frequent (55%), followed by firearm (33%) mechanisms. Most were host nation partner forces (35%) and humanitarian (32%) casualties. The median injury severity score (ISS) was 24. The most frequent seriously injured body region was the head/neck (61%). Most (61%) were discharged alive (Table 1). Within the overall dataset from which this data was derived, the survival proportion

Table 1. Casualty characteristics.

		Prehospital cohort	MTF cohort	p-value
Demographics	Age	24 (21-27)	24 (21-28)	0.268
	Male	98% (273)	98% (1818)	0.611
Mechanism of Injury	Explosive	71% (198)	71% (1317)	0.616
	Firearm	22% (60)	21% (381)	
	Motor vehicle	1% (3)	2% (42)	
	Other	6% (17)	6% (106)	
Injury Severity Score		25 (17-34)	22 (14-30)	<0.001
Serious injuries by body region	Head/neck	38% (105)	25% (462)	<0.001
	Facial	2% (5)	1% (23)	0.410
	Thorax	28% (523)	26% (71)	0.333
	Abdomen	19% (52)	23% (423)	0.116
	Extremities	56% (155)	57% (1056)	0.649
	Skin	9% (24)	9% (167)	0.822
Outcome	Ventilator days	5 (2-8)	4 (2-7)	0.005
	ICU days	7 (4-10)	7 (4-12)	0.531
	Hospital days	5(3-21)	17 (5-39)	<0.001
	Discharge Alive	80% (222)	93% (1714)	<0.001

was 98%. Within the 251, 14% had a complication noted, most commonly requiring tracheostomy revision (5%) (Table 2).

Table 2. Surgical revision procedures.

Repair of trachea, open approach	1% (3)
Repair of tracheostomy device in trachea	2% (6)
Repair of larynx, open approach	1% (3)
Repair of neck, open approach	<1% (1)
Suture of laceration of larynx	<1% (1)
Repair of laryngeal fracture	1% (2)
Suture of laceration of trachea	1% (3)
Closure of external fistula	<1% (1)
Revision of tracheostomy	5% (13)
Other plastic operation on trachea	1% (3)
Replacement of tracheostomy tube	2% (5)
Esophageal placement	1% (2)

Within the US military sub-analysis, we found 51% survived to hospital discharge. Of those who had a documented discharge location 22% were discharged home or return to duty, 0% went to an acute care facility, and 78% were placed into a medical hold unit.

Discussion

The ISS average was high with most casualties surviving to hospital discharge yet carrying a substantially higher risk of death than the baseline population.[11] Nearly 1 in 6 required surgical revision of the cricothyrotomy, with the most common procedure being tracheostomy revision. Overall, the data showed a prehospital surgical cricothyrotomy is a potentially complicated procedure with poor outcomes.

In previous data, the most common mechanisms of injury were the same as this study; however, there were variations of percentages with 73.7%, 22.1%, and 4% for explosives, firearms, and other injuries respectively.[3] In a previous study, while hemorrhage was 90.9% of injuries, only 13.5% was peripheral-extremity hemorrhage.[3] This study showed 25% of serious injuries were to the extremities compared to the other percentages of injuries by body regions showing compressible extremity hemorrhage may still be an issue for the US troops. The predominant injury leading to death in non-survivable injuries is traumatic brain injury.[12] In this study, as expected, most had a serious injury or greater to the head.

Emergency cricothyrotomy is necessary in the "cannot intubate, cannot oxygenate" setting. The indications for this procedure include cervical spine trauma, oral hemorrhage, emesis, oral or maxillofacial trauma, and anatomical abnormalities preventing endotracheal intubations. There are no absolute contraindications. The most common immediate complication is bleeding often due to laceration of the adjacent highly vascular structures. Other immediate complications of cricothyrotomies include lacerations of the tracheal cartilage, perforation of the trachea, creation of a false tract, and infections. Long-term complications include voice changes and subglottic stenosis. Subglottic stenosis rates are higher in patients with acute laryngeal diseases.[13] In one study, surgical cricothyrotomies were successful in 68% of cases, and in 26% of cases, there was failure to cannulate the trachea.[7] In another study, there was 64% of acceptable surgical cricothyrotomies, and 16% were functioning with some concern of adequacy.[14] That study had 62% survival to emergency department and 27% with survival to hospital discharge.[14] The abysmal outcomes in that study were generally mirrored within our population. In this study, 61% of people who received a prehospital cricothyrotomy were discharged alive. In the emergency department, the success of cricothyrotomy is between 89-100%, compared to the 61% discharged alive after the procedure.[15] Out of the 251 people who met inclusion criteria, 34 people (14%) had complications compared to the 26% in a prior study.[9] Many factors affect the complication rates of surgical cricothyrotomies including the level of training, location of the procedure, and the clinical scenario.[16]

As a prehospital surgical procedure, cricothyrotomy is rarely performed. One of the limitations of this study was a small inclusion group of only 251 resulting in less data available for what complications can arise.[15] This study only includes patients who were transported to a military treatment facility with surgical capabilities with signs of life or ongoing interventions. It is therefore likely we missed a group of patients with prehospital cricothyrotomies who nonetheless died and were subsequently not transported to the hospital.[17] These patients are not included in the DoDTR. Data on these expired casualties would greatly add to this limited body of science. Previous calls for better data in the prehospital deaths have highlighted this,[18] which would reduce a survivor bias and potentially improve both the success rate and the survival rate associated with this procedure. There may also have been missing data of casualties who received a prehospital cricothyrotomy but were not included in the study.[10] It is unknown if the complications reported in this study arose as a result of the prehospital cricothyrotomy or are related to other injuries or factors. This study excluded those who received a prehospital cricothyrotomy, therefore, we did not total all the trauma causalities who were discharged alive. Another limitation, it was not determined who performed the prehospital cricothyrotomy, whether it was highly-trained personnel (e.g. EM physician, anesthesiologist, anesthetist, head/neck surgeon, etc.) versus less-trained (e.g. medic) personnel. There is no information if the equipment was ineffective or had any malfunctions. A better understanding of outcomes associated with this

procedure will enable more targeted training, and technology development in future research should be directed at improving the data acquisition of cricothyrotomy survivors and non-survivors.

Conclusions

Cricothyrotomies are rarely performed in the prehospital combat setting, but when they are performed and the casualty survives long enough to reach a facility, the incidence of near- and long-term complications is high.

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Clinical Assessment of Low Calcium In traUMa (CALCIUM)

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Abstract

Major trauma frequently occurs in the deployed, combat setting and is especially applicable in the recent conflicts with explosives dominating the combat wounded. In future near-peer conflicts, we will likely face even more profound weapons including mortars and artillery. As such, the number of severely wounded will likely increase. Hypocalcemia frequently occurs after blood transfusions, secondary to the preservatives in the blood products; however, recent data suggests major trauma in and of itself is a risk factor for hypocalcemia. Calcium is a major ion involved in heart contractility; thus, hypocalcemia can lead to poor contractility. Smaller studies have linked hypocalcemia to worse outcomes, but it remains unclear what causes hypocalcemia and if intervening could potentially save lives. The objective of this study is to determine the incidence of hypocalcemia on hospital arrival and the association with survival. We are seeking to address the following scientific questions, (1) Is hypocalcemia present following traumatic injury prior to transfusion during resuscitation? (2) Does hypocalcemia influence the amount of blood products transfused? (3) To what extent is hypocalcemia further exacerbated by transfusion? (4) What is the relationship between hypocalcemia following traumatic injury and mortality? We will conduct a multicenter, prospective, observational study. We will gather ionized calcium levels at 0, 3, 6, 12, 18, and 24 hours as part of scheduled calcium measurements. This will ensure we have accurate data to assess the early and late effects of hypocalcemia throughout the course of resuscitation and hemorrhage control. These data will be captured by a trained study team at every site. Our findings will inform clinical practice guidelines and optimize the care delivered in the combat and civilian trauma setting. We are seeking 391 patients with complete data to meet our *a priori* inclusion criteria. Our study will have major immediate short-term findings including risk prediction modeling to assess who is at risk for hypocalcemia, data assessing interventions associated with the incidence of hypocalcemia, and outcome data including mortality and its link to early hypocalcemia.

Keywords: prehospital; combat; casualty; battlefield; military; hypocalcemia

Introduction

Hypocalcemia occurs frequently in critically ill patients including severely injured trauma patients.[1,2] Hypocalcemia is associated with massive resuscitation with blood products and chelation of serum calcium by the citrate in anticoagulant storage solutions.[3] Currently the Joint Trauma System guideline on Damage Control Resuscitation (Clinical practice guideline [CPG] ID:18, 12 July 2019), recommends, "Earlier calcium use recommended. One gram of calcium (30 ml of 10% calcium gluconate or 10 ml of 10% calcium chloride) IV/IO should be given to patients in hemorrhagic shock during or immediately after transfusion of the first unit of blood product and with ongoing resuscitation after every 4 units of blood products. Ideally, ionized calcium should be monitored, and calcium should be given for ionized calcium less than 1.2mmol/L." The reason for the administration of calcium after 4 units of blood has been attributed to the citrate compounds in the blood preservative which

binds free calcium resulting in hypocalcemia.[4] The hypocalcemia leads to decreased heart contractility and overall hypoperfusion which can occur after massive hemorrhage.[5-7] However, new data suggests our current paradigm with hypocalcemia in trauma may be inadequate. In a study by Conner et al in *Military Medicine*, they prospectively collected data on casualties arriving to one forward surgical team in Afghanistan.[3] In their study, they assessed 101 patients, of which 55 (54.5%) experienced hypocalcemia on arrival to the forward surgical team (FST) with a mean ionized calcium (iCa) of 1.16 mmol/L (95% confidence interval [CI] 1.14 to 1.18) prior to receiving any blood products. They found casualties injured by explosion conferred an increased risk of hypocalcemia compared to all other patterns of injury (odds ratio=2.42, p=0.042). Of the 101 assessed, 38 (37.6%) patients required blood product transfusion, of whom 33 (86.8%) of the patients requiring blood product transfusion were hypocalcemic on arrival. This suggests the major trauma itself may be a contributing factor to the hypocalcemia, and it may not be attributable solely to the blood product administration. In other words, it may be blood product administration exacerbates a pre-existing or developing hypocalcemia.

There is currently limited clinical evidence assessing hypocalcemia in trauma patients and no outcome studies looking at the association of mortality and hypocalcemia or the association of calcium replacement with survival in trauma patients.[2] Giancarelli et al studied the incidence of hypocalcemia during massive transfusion (MT) and found out of 156 patients, 97% experienced hypocalcemia and 71% experienced severe hypocalcemia; hypocalcemia was frequently associated with elevated lactate, other markers of coagulopathy, and lower survival for those with severe hypocalcemia.[8] In this study, hypocalcemia occurred during the MT which does not account for those who may have arrived already hypocalcemic.[8] Vivien et al prospectively studied 212 patients who were given crystalloid or colloid in the prehospital setting, finding 74% became hypocalcemic after fluid infusion without blood suggesting hemodilution itself may exacerbate this finding—before receiving blood products.[9-11] In a study of 99 patients with non-trauma and non-septic who were critically ill, they found up to 88% of them had hypocalcemia—further suggesting critical illness in and of itself may cause hypocalcemia.[12] Webster et al studied 55 trauma patients who were in the ED receiving blood. They found 55% were hypocalcemic on arrival, and 89% were hypocalcemic after blood product administration; however, no mortality effect was examined.[13] Ho et al, unlike in other studies, assessed mortality, finding a linear relationship between decreasing calcium and mortality among 352 patients; however, they only assessed the lowest documented value and did not trend the data over the initial 24 hours or control for the supplementation given.[14] These findings parallel the Li et al review, which states fluid infusion further excerbates ion imbalance that occurs under hypoxic environments such as blood loss, and the ion imbalance activates a Ca protease, which depletes Ca and causes cardiomyocyte death.[10]

We propose a study to track the ionized calcium level over 24 hours and adjusted outcomes based on supplementation provided. Ionized calcium (iCa) has long been measured post-operatively as a predictor of hypocalcemia. Adams et al chart reviewed 197 patients, assessed the ionized calcium at 2 time points within 24-hours and found patients with a decrease in iCa experience hypocalcemia.[15] However, both time points were taken post-op and do not consider iCa pre-operation. Saad et al monitored serum calcium (sCa) prior to surgery and post-operative and found it to be a useful method of identifying patients experiencing hypocalcemia; however, pre surgery sCa were measured 3 months before, and post-op sCa were only measured when patients experience other hypocalcemia symptoms.[16] This corresponds to the findings in Walsh, which states patients who developed hypocalcemia had a decline of serum calcium in the first 6 hours post-operatively. These findings demonstrate the importance of immediate monitoring of calcium levels.[17] Magnotti et al assessed the ionized calcium in 591 patients and found low calcium was associated with increased mortality; however, they assessed the iCa on admission and not based on prehospital arrival.[18] MacKay et al assessed 77 patients noting no difference in mortality since their mortality rate was low, but they did note hypocalcemic patients more frequently received supplementation and blood products.[19] While not assessing mortality, Cherry et al found hypocalcemia was associated with prehospital hypotension and a worse base deficit.[20] These findings hold the potential to change the paradigm from hypocalcemia in the setting of trauma is caused purely by transfusion during resuscitation to the concept that hypocalcemia in the trauma setting may originate from the injured state with exacerbation by transfusion. This parallels previously published findings where coagulopathy often exists before interventions are done because of the serious trauma itself.[21,22] Previously, it was proposed coagulopathy was related to the infusion of large volumes of crystalloid, which is likely a contributing factor. However, more recent data suggests coagulopathy is associated with traumatic injuries before dilutional effects occur.[23,24] Treatment of prehospital hypocalcemia may therefore represent an early intervention to reduce morbidity and mortality following traumatic injury. Similar to the manner in which the

exogenous and endogenous pathways impact coagulopathy, the same may be the case for hypocalcemia. Our study proposes to test this hypothesis. With the more widespread and accepted use of prehospital blood products, and the potential for prolonged casualty care scenarios, we need to further investigate this premise to determine the need for calcium supplementation quicker to the point-of-injury.[25,26]

Table 1. Inclusion and exclusion criteria.

Inclusion Criteria	Exclusion Criteria
Major trauma activations which include any of the following: • Penetrating trauma to the head, neck, torso, or extremities (proximal to the elbow/knee) • Traumatic arrest or CPR at any time • Glasgow Coma Scale of 9 or less or deteriorating from initial arrival • Systolic <100mmHg • Respiratory rate <10 or >29 • Intubated or requiring airway assistance (e.g. bag-valve mask, etc.) • Any blood administered prehospital • Vasopressors administered • Pulseless, degloved, crushed, or mangled extremity proximal to the wrist • Suspected flail chest • Evidence of arterial bleeding with or without tourniquet application • Amputations proximal to the wrist/ankle • Evidence of spinal cord injury such as paralysis or loss of sensation • Unstable pelvic fractures with or without hypotension • Falls >3 feet with obvious injury • More than two long-bone fractures	Age <16

We are rapidly moving into operational planning for future conflicts in which we may not have ready access to surgical teams or locations with laboratory testing capabilities.[26,27] As such, the Department of Defense (DoD) needs to identify effective methods for early life-saving interventions feasible for the prehospital combat setting. Calcium administration can be easily accomplished through an intraosseous or intravenous line.[28,29] Furthermore, ionized calcium levels may be assessed even in far-forward role 2 environments without full laboratory capacity due to portable hand-held cartridges allowing iCa level testing. We are seeking to determine the incidence of hypocalcemia in the setting of trauma before and during blood product administration. If our hypothesis is supported, this potentially represents a target for a low-cost, easy-to-administer invention in the prehospital combat setting.[30] The findings of our study will potentially inform a future interventional clinical trial to study the association of early calcium replacement on survival in trauma patients.

Methods

We propose a prospective, observational study at 3 trauma centers. We will perform regular scheduled blood draws to ensure adequate capture of calcium data along with routine clinical care including interventions, medications, and outcomes. The use of 3 major trauma centers will ensure we get adequate data capture.

Setting: Our study will take place at three major trauma centers: the Brooke Army Medical Center (BAMC), University Hospital[31] at the University of Texas Health San Antonio (UTHSA), and the University of Colorado Anschutz Medical Campus (UCAMC), all of which are regional receiving, level 1 trauma centers. All have a strong history of military-relevant research and represent a rich source of data for optimizing combat casualty care.

BAMC is the same location many medical personnel work and train for combat deployments including the Strategic Trauma Readiness Center of San Antonio (STaRC), which provides crucial training to surgical teams just prior to deployment. This serves as an optimal opportunity to rapidly implement our scientific findings into clinical practice in the deployed, combat setting. The primary site will be BAMC, the DoD's only level 1 trauma center and largest hospital in the DoD which had nearly 4,900 trauma activations in the past 12 months. BAMC is physically adjacent to the US Army Institute of Surgical Research (USAISR) and is where the principal investigator (PI) has clinical privileges and practices emergency medicine. BAMC has approximately 87,000 visits per year to the emergency department (ED) including trauma activations where they receive approximately 1/3 of the trauma within the region. The University Hospital[31] at the University of Texas Health San Antonio (UHTSA) receives about 2/3 of the volume within the region with approximately 5,500 injured patients admitted per year. Both hospitals serve the Southwest Texas Regional Advisory Council (STRAC), which coordinates trauma care for the southwest region of Texas (22 counties) and spans more than 26,000 square miles. STRAC is a model, nationally recognized system for trauma patient triage, coordination, transport and care, disaster response and readiness and includes 74 general and specialty hospitals, 70 emergency medical services (EMS) agencies, all of which feed into 2 level 1 trauma centers in San Antonio. Both centers make frequent use of whole blood products for resuscitation. The University of Colorado Hospital (UCH) receives approximately 1,800-2,000 trauma encounters a year (with

360-390 ISS>16 patients/year), and the emergency department is the busiest in Colorado with over 100,000 patients per year. The UCHealth System is the largest health system in Colorado and the Rocky Mountain region of the US consisting of 3 high volume trauma centers. The CU COMBAT Center is based at CU Anschutz Medical Campus and coordinates DoD funded studies across campus with focus in the Department of Emergency Medicine, Department of Surgery, and Department of Anesthesiology at UCHealth and Denver Health. Neither Denver nor Aurora EMS systems currently use whole blood or any other blood product in the prehospital setting (although occasional aeromedical transport patients have access to prehospital component blood product therapy) which will serve as an excellent control site for that confounder. Of note, we have existing relationships with both centers including currently funded DoD efforts. We will leverage the existing infrastructures, regulatory pathways, and Cooperative Research and Development Agreements (CRADA) in place with both institutions to ensure rapid implementation and execution.

Study Procedures: Trauma patients for enrollment in the study will be identified using site-specific trauma activation protocols in the emergency department or trauma department (Table 1). The trauma activation criteria at Brooke Army Medical Center (BAMC) is provided as an example. Each site will have slight variations of this, which will be outlined in the site-specific documents. The decision to use trauma team activations will be solely at the discretion of the clinical team. All trauma patients coming in the emergency department who meet criteria for trauma activation will have routine laboratory tests as part of the standardized order set. We will modify the existing order set to include the calcium studies as outlined in this protocol. We will enroll a continuous sample as part of routine trauma care operations via the modified order set. We will promote capture by way of staff education, staff reminders, staff-facing signage, and dissemination via routine department communications. Specific to this study, we will collect samples at 0, 3, 6, 12, 18, and 24 hours after trauma center arrival, striving to have draws occur within +/- 1 hour of the goal times. Data will be extracted from the medical records by dedicated study personnel at each site (Table 2). Methods to improve adherence to the order set will be implemented at each site including near-real-time feedback to the clinical staff, staff-facing signage/reminders, and regular feedback with clinical staff.

Ethics: We will adhere to institutional requirements for all institutions in addition to all DOD-specific regulations. We will utilize a single-center institutional review

Table 2. Variables to be captured.

Demographics
- Age
- Sex
- Military status
- Height/weight/body mass index
- Admission diagnoses
- Discharge diagnoses
- Past medical and surgical history

Timing
- Time of injury
- Time of EMS arrival
- Time of air/MEDEVAC team arrival (if used)
- Time of hospital arrival
- Time of blood products transfused within the first 4 hours
- Time of vital signs, labs, medications, and procedures listed below

Vital signs prehospital
- Heart rate
- Blood pressure (systolic, diastolic, calculated shock indices)
- Temperature
- Oxygen saturation
- Respiratory rate
- Prehospital duration

Vital signs within the first 24 hours of admission
- Heart rate
- Blood pressure (systolic, diastolic, calculated shock indices)
- Temperature
- Oxygen saturation
- Respiratory rate

Scheduled laboratory studies at 0, 3, 6, 12, 18, 24 hours
- Electrolytes
- Ionized calcium
- Total serum calcium

Routine laboratory studies within the first 24 hours of admission
- Hemoglobin/hematocrit
- Platelets
- Coagulation studies (prothrombin time, international normalized ratio, partial thromboplastic time)
- Metabolic studies (electrolytes, calcium, blood urea nitrogen, creatinine, liver function tests)
- Blood gas values (base excess, pH, O2, CO2, iCa)
- Lactate
- Haptoglobin
- Thromboelastography (TEG)

Prehospital medications
- Analgesics
- Sedatives
- Paralytics
- Vasopressors
- Calcium (all forms)
- IV fluids
- Tranexamic acid

Hospital medications within the first 24 hours of admission
- Analgesics
- Sedatives
- Paralytics
- Vasopressors
- Calcium (all forms)
- IV fluids
- Tranexamic acid

Major procedures within the first 24 hours of admission
- Hemorrhage control interventions
- Chest needle decompression
- Chest tube
- Thoracotomy
- Intubation
- Resuscitative endovascular balloon occlusion of aorta (REBOA)
- Central line placement
- Interventional radiology procedures (e.g. coiling, etc.)

Imaging studies within the first 24 hours
- Computer tomography (CT) scan results
- X-ray studies
- Ultrasound including focused assessment of sonography with trauma (FAST)

Blood products for entire hospital stay with first 4 hours to include time of transfusion
- Whole blood
- Packed red cells
- Plasma
- Platelets
- Cryoprecipitate

Outcome data
- Discharge status
- Time to death (if applicable)
- Ventilator days
- Intensive care unit days
- Hospital days
- Discharge location (if alive, e.g. home, rehabilitation facility, etc.)
- Total blood products received in first 4 hours and first 24 hours after injury

board (IRB) as we have done with other studies. Since we are only collecting small blood draws (less than are usually drawn for routine clinical care labs), we anticipate this study will be deemed minimal risk. Given the nature of critically injured trauma patients, we will seek a waiver of informed consent as we have done with previous minimal risk trauma studies.[32,33]

Data Acquisition: This study will utilize a data collection and management strategy piloted in a similar multisite inpatient critical care trial funded by the DoD.[34] Data will be handled in Research Electronic Data Capture (REDCap), which is an online electronic case report form system widely used in clinical research, available at no cost to non-profit, academic, and government agencies.[35] The data coordinating center at Vanderbilt University Medical Center (VUMC) will distribute a standardized study data dictionary which sites will import into their REDCap systems. Sites will enter study data for local participants in these standardized case report forms (CRF) in their respective instances of REDCap. These data will be automatically de-identified (identifiers removed and dates shifted) and transferred to VUMC using a REDCap External Module called API Sync.[36] Study statisticians will have access to the aggregated and de-identified data for all sites in VUMC's REDCap system. Sites with an enabled connection between their electronic health record and REDCap system can also have fields automatically filled for certain types of study data such as demographics, vital signs, laboratory results, and medications.[37]

Statistical Analysis: We will primarily use descriptive and inferential statistics along with regression modeling. Significance for results will be established when p-values are less than 0.05. Categorical data will be summarized using percentages and Chi-Squared tests or Fisher's exact test, whichever is most appropriate. Means and standard deviations or medians and interquartile ranges will be used as summary statistics for continuous variables, and they will be analyzed using Student's t-test and ANOVA or Wilcoxon's Test, whichever is most appropriate. Data may be log-transformed for normalization. We will use either Discrete-Time (eg. Complementary Log-Log) or Cox Proportional Hazards to assess associations between baseline and time-dependent covariates with time-to-hypocalcemia. Treatment variables, such as blood product transfusion, will be measured at time-dependent covariates. Cox Proportional Hazards models will be used to assess associations between baseline covariates, time-dependent covariates (treatments and hypocalcemia), and mortality. We will analyze data using relevant, commercially available statistical software.

Sample Size Estimates: Based on prior estimates of hypocalcemia in trauma patients, the percentage of patients exposed can range between 50% to 55%.[3,13] Based on this estimate of exposure to hypocalcemia, with an alpha of 0.05, and power of 80%, we estimate a total sample size requirement of 391 trauma patients would need to be enrolled in the study.

Conclusions

Through a multicenter, prospective, observational study, ionized calcium levels and its association with trauma will be assessed. Our findings will inform clinical practice guidelines.

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Occam's Razor and Prehospital Documentation: When the Simpler Solution Resulted in Better Documentation

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Abstract

Introduction: The Tactical Combat Casualty Care (TCCC) card has undergone several changes since its first introduction in 1996. In 2013, updates to the card included more data points to increase prehospital documentation quality and enable performance improvement. This study reviews the proportions of data collected before and after the implementation of the new TCCC card.

Methods: This is a secondary analysis of a previously described dataset from the Department of Defense Trauma Registry (DODTR) focused on prehospital medical care. In this sub-analysis, we defined the pre-implementation period as 2009-2013 followed by a 1-year run-in with the post-implementation period as 2015-2019. Our primary outcome was documentation of a pulse rate and our secondary outcomes included documentation of other vital signs. We used multivariable logistic regression models to adjust for confounders.

Results: There were 18,182 encounters that met inclusion for this analysis—14,711 before and 3,471 after the update. Across all vital signs, there was a peak around 2012-2013 with a drop noted in 2015. Comparing the pre-implementation and post-implementation groups, there were higher proportions with documentation of a pulse rate (62% versus 49%), respirations (51% versus 45%), systolic pressure (53% versus 46%), diastolic pressure (49% versus 41%), oxygen saturation (55% versus 46%), and pain score (27% versus 19%, all $p<0.001$) in the pre-implementation group. When adjusting for injury severity score (ISS), casualty category, and year of injury, the odds ratio of documentation of a pulse after implementation was 0.01 (95% CI: 0.00-0.01). When adjusting for ISS and casualty category, the odds ratio was 0.64 (95% CI: 0.60-0.70). When adjusting for ISS only, the odds ratio was 0.58 (95% CI: 0.54-0.63).

Conclusions: Implementation of the new TCCC card resulted in overall lower documentation proportions which persisted after adjusting for measurable confounders.

Keywords: tactical; combat; casualty; card; documentation; prehospital; military

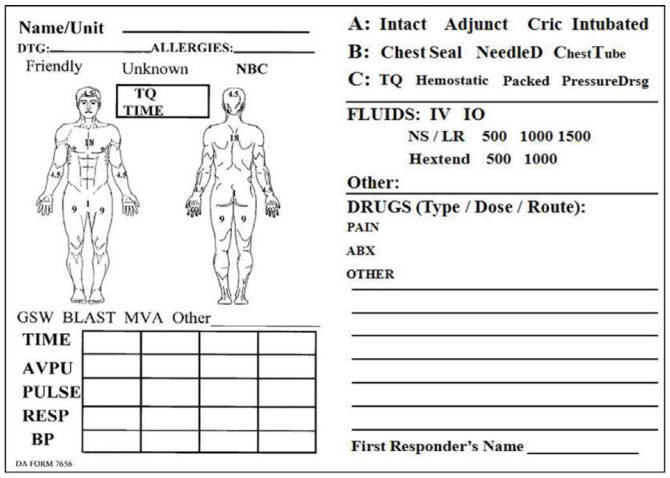
Introduction

Background: In 1996, military leaders reviewed the unique challenges of prehospital trauma care in the military and, subsequently, introduced the tenants of Tactical Combat Casualty Care (TCCC) in its original form.[1] In the following years, operational units within the Navy first incorporated TCCC into their clinical practices. All services in the US military shortly followed suit.[2] In 2001, the Committee on TCCC (CoTCCC) was founded with the goal of quality review and process improvement for subsequent iterations of TCCC.[3] In 2006, the Joint Trauma System (JTS) designed a database for the collection and analysis of combat-associated care data.[4]

In 2007, more than 30,000 new casualties (civilians and military personnel) were sustained during conflicts in Afghanistan and Iraq, yet only 10% had been recorded prior to arrival at a medical treatment facility (MTF).[5] Within this same period, existing data showed about

90% of wartime related deaths happened in the prehospital setting and up to 25% of these deaths were from potentially survivable etiologies.[6] The disparity in prehospital versus MTF recorded data highlighted the need for improvements in documentation occurring in the prehospital setting.

Figure 1. Tactical Combat Casualty Care (TCCC) Card, original 2007 version.[5]

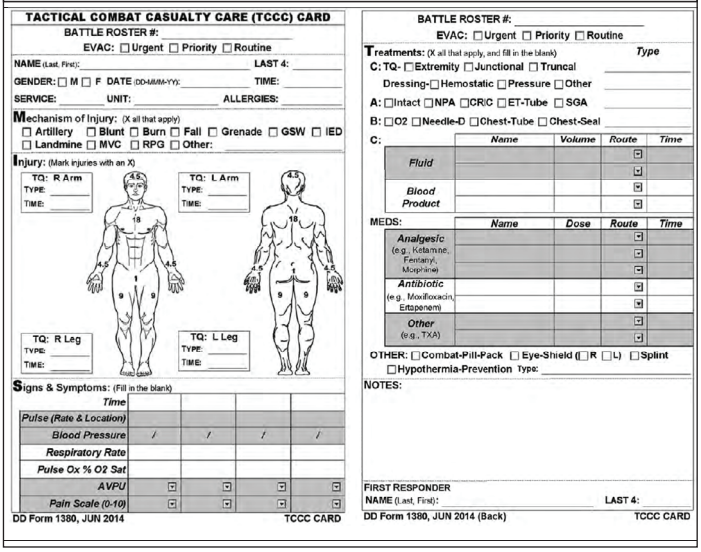


Owing to the obvious deficiencies in data collection, in 2007, the CoTCCC incorporated the casualty card used by the 75th Ranger Regiment (Figure 1).[6] This card, developed largely by Ranger medics, had proven easy to use and was well accepted by the Rangers and other special operations groups. This card had successfully captured all 450 casualties sustained by the Ranger Regiment since the onset of the conflicts in Iraq and Afghanistan.[5]

In 2013, the Department of Defense (DoD) finalized the latest change to combat care documentation. With data pulled from the TCCC After Action Report (AAR) and the Prehospital Registry (PHTR), the DoD implemented a new TCCC Card (Figure 2).[7] This card was created to address the shortcomings of previous iterations with additions to data parameters intended to improve data acquisition; it was made mandatory for prehospital use throughout US Central Command.[4] It remains unclear what effect the implementation of the new card has had on the availability of prehospital data within the Department of Defense Trauma Registry.

Goal of Study: We conducted an interrupted time series (ITS) analysis to assess the proportion of casualties with vital signs and pain scores documented before and after implementation of the new TCCC card.

Figure 2. Tactical Combat Casualty Care (TCCC) Card, 2013 version.[4]



Methods

Data Acquisition: This is a secondary analysis of a previously described dataset.[8] The original dataset was based on a data request for any casualty with documentation of prehospital activity, such as a procedure, medication administration, prehospital vital sign, or other prehospital documentation. The US Army Institute of Surgical Research (USAISR) regulatory office reviewed protocol H-20-015nh and determined it was exempt from Institutional Review Board oversight. We obtained and used only de-identified data.

Department of Defense Trauma Registry (DODTR): The DODTR, formerly known as the Joint Theater Trauma Registry (JTTR), is the data repository for DoD trauma-related injuries.[9,10] The DODTR includes documentation regarding demographics, injury-producing incidents, diagnoses, treatments, and outcomes of injuries sustained by US/non-US military and US/non-US civilian personnel in wartime and peacetime (including host nation civilians) from the point of injury to final disposition. Short-term outcome data are available for non-US casualties.

The DODTR comprises all patients admitted to a Role 3 (fixed-facility) or forward resuscitative surgical detachment (FRSD) with an injury diagnosis using the International Classification of Disease 9th Edition (ICD-9) between 800-959.9, near-drowning/drowning with associated injury (ICD-9 994.1) or inhalational injury (ICD-9 987.9) and trauma occurring within 72 hours from presentation. The registry defines the prehospital setting as any location prior to reaching

surgical capabilities at an FRSD or field hospital (FH) to include the Role 1 (point of injury, casualty collection point, battalion aid station) and Role 2 without surgical capabilities (temporary limited-capability forward-positioned hospital inside combat zone).

Data Analysis: We performed all statistical analysis using commercially available software. For univariate analyses, we presented continuous variables as means with 95% confidence intervals, non-parametric continuous variables and ordinal variables as medians with interquartile ranges, and nominal variables as counts and percentages. For respective bivariate analyses, we used t-test comparison, Wilcoxon rank sum comparison, and chi square comparison. Abbreviated injury scale measurements by body region were converted into binary variables using a serious (≥3) versus not serious (<3) as we have done with previous studies.[11]

For our multivariate analyses, we conducted an interrupted time series to compare recording of vital signs and pain scores pre- versus post-implementation of the revised TCCC card. We defined the pre-implementation period as 2009-2013. Since TCCC card implementation occurred at the end of 2013, we used a 1-year wash-out period (2014) and defined the after period as 2015-2019. We used multivariable logistic regression (MVLR) analyses to adjust for known confounders.

Given pulse rate had the highest proportions of documentation, we opted to use this as our primary outcome for the MVLR analyses. We adjusted for the ISS, patient category, and the year of injury to account for various background factors such as injury severity, changes in command priorities, operational tempo, and overall health of the casualty (e.g. host nation versus US military). We performed sensitivity analyses with and without year of injury in view of the potential interaction of this variable with our defined time periods. Results of the MVLR were presented as odds ratios comparing post card update odds of documentation divided by pre-card update odds.

Table 1. Casualty demographics and characteristics.

		Before n=14711	After n=3471	p-value
Demographics	Age* (years)	24 (21-29)	27 (21-31)	<0.001
	Male	98% (14423)	98% (3400)	0.738
Affiliation	US Military	45% (6582)	18% (627)	<0.001
	Coalition	12% (1767)	3% (98)	
	Partner force	26% (3755)	31% (1059)	
	Humanitarian	18% (2607)	49% (1687)	
Mechanism of injury	Explosive	56% (8258)	49% (1695)	<0.001
	Firearm	26% (3770)	35% (1239)	
	Motor vehicle	7% (1078)	5% (171)	
	Other	11% (1605)	10% (366)	
Injury Severity Score*		8 (3-14)	8 (2-14)	0.001
Serious injuries by body region	Head/neck	13% (1998)	11% (369)	<0.001
	Facial	<1% (59)	<1% (15)	0.795
	Thorax	11% (1568)	12% (402)	0.115
	Abdomen	7% (1048)	9% (298)	0.003
	Extremities	25% (3691)	25% (867)	0.891
	Skin	2% (239)	3% (102)	<0.001
Outcome	Survival	96% (14107)	97% (3362)	0.007

Results

The original dataset comprised 25,897 casualties, of which 18,182 met inclusion for this analysis—14,711 before and 3,471 after. Results of univariate and bivariate analysis can be seen in Table 1. Most casualties were male with US military comprising the largest proportion of casualties. Explosives represented the most frequent mechanism of injury. There were higher proportions of serious injuries to the head in the before group (13% versus 11%, p<0.001), with lower proportions for serious skin injuries (2% versus 3%, p<0.001) (Table 1).

When comparing the overall documentation proportions from the totality of the dataset, there was a peak around 2012-2013 with a drop noted in 2015, followed by a steady increase (Figure 3) with similar, yet not as pronounced of findings for the US military sub-analysis (Figure 4). There were higher proportions with

Figure 3. Overall documentation proportions across entire dataset.

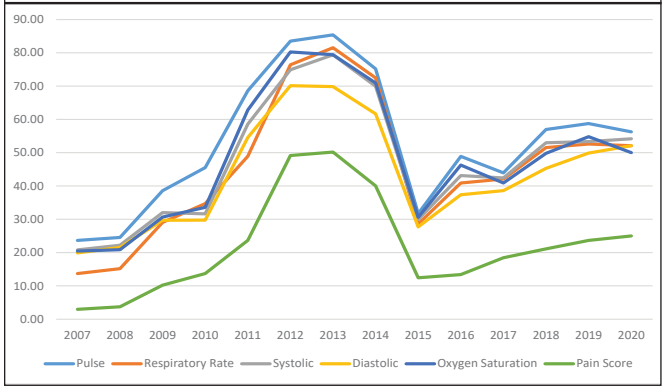
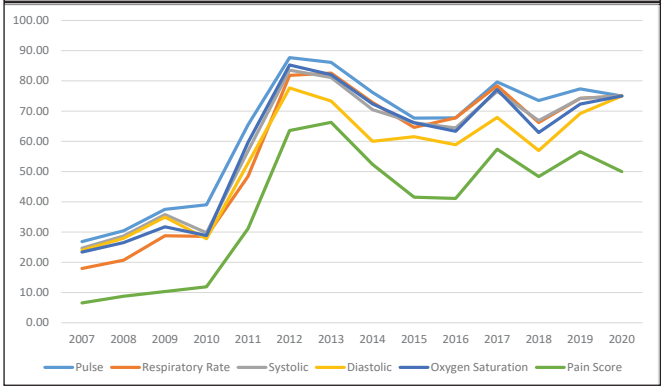


Figure 4. Documentation proportions among US military across entire dataset.



documentation of a pulse rate (62% versus 49%), respirations (51% versus 45%), systolic pressure (53% versus 46%), diastolic pressure (49% versus 41%), oxygen saturation (55% versus 46%), and pain score (27% versus 19%, all p<0.001) (Table 2).

Table 2. Comparison of vital sign documentation proportions before and after.

Intervention	Odds ratio (95% confidence interval)
Prehospital/MTF	0.34 (0.23-0.50)
Injury severity score	0.95 (0.94-0.96)
Whole blood	0.97 (0.96-0.99)
Packed red cells	0.99 (0.96-1.02)
Fresh frozen plasma	0.98 (0.95-1.01)
Platelets	1.07 (1.00-1.14)
Explosive/Other	0.81 (0.31-2.09)
Firearm/Other	0.28 (0.11-0.75)
MVC/Other	1.06 (0.19-5.97)

When adjusting for ISS, casualty category, and year of injury the odds ratio of documentation of a pulse after implementation was 0.01 (95% CI: 0.00-0.01). When adjusting for ISS and casualty category, the odds ratio was 0.64 (95% CI: 0.60-0.70). When adjusting for ISS only, the odds ratio was 0.58 (95% CI: 0.54-0.63). All variables within the models had a p-value of <0.05.

Discussion

In an effort to improve the granularity of prehospital data, the DOD updated the TCCC card in 2013; the revisions included more data points with specific attention given to medications, vital signs, and procedures performed.[2,3] Our focus on documentation of vital signs reflects the important correlation between these measurements and casualty survival in both domestic and battlefield settings.[12-16] Despite the best efforts of those involved in the 2013 changes, the results of this study show a decrease in recorded vital sign and pain score data following the implementation of the revised reporting measures. We find a decrease in annual documentation rates in the unadjusted ITS which persisted after adjusting for confounders. Our findings suggest the new card did not improve data capture, and, as evidenced by the graph, caused a substantial drop during the initial rollout period. The reasons for this relative decrease in reported values are likely multifactorial, and our retrospective study design precludes a definitive determination of causation. The decrease in documentation may reflect the greater complexity of the newer tool.

When compared with the 2013 card, the 2007 version is simpler and more concise. The 2013 card appears more complicated with an almost overwhelming level of detail that may ultimately discourage completion of desired documentation. In a study from 1993, Wilcox et al concluded manual documentation of field medical data is a labor intensive and time-consuming task.[17] As combat intensity escalates or the number of casualties increases, combat medics may choose not to initiate documentation to focus on casualty treatment.[17] Even though there are studies demonstrating card completion is possible in a reasonable timeframe (greater than 90% accuracy in less than 1 minute) in the classroom setting,[18] significant research exists demonstrating acute stress can greatly impact performance particularly for those in the medical field.[19] Some of these challenges could be negated through implementation of other methods for data collection. To start, the combat units could train other non-medical personnel to serve as documentation scribes in the way they cross-train other personnel to receive other radio reports. Other methods would include the use of better technologies for data capture outside of the TCCC card, such as the use of voice recorders, body cameras, and other biomedical sensors from which we can later extrapolate data for performance improvement purposes.

In their review of the PHTR from 2013 and 2014, Schauer et al noted of 705 patient encounters, only 3.3% had prehospital documentation recorded from a TCCC card, but 94.8% had data from TCCC AARs.[7] Although this shows the relative value of the TCCC AAR, it serves to demonstrate a paucity of data collected on the TCCC card. Quite possibly, given the complexity of the updated card, combat medics chose to document their prehospital care one time during the TCCC AAR, forgoing filling out the more cumbersome card entirely. This would completely negate the purpose of the TCCC card as a communication tool during transitions of casualty care. The 2013 card was associated with less documentation compared to the 2007 version even though it was made mandatory in the prehospital setting by commander of US Forces-Afghanistan in 2013.[4] The need for simplicity in documentation has been seen in other settings.[20-22]

In a 2007 review of the previous decade of battlefield trauma care, Butler et al commented prehospital trauma care as performed on the battlefield differs markedly from that performed in the civilian sector.[2] They state, "Simplicity is key. Equipment required to execute the plan must also be simple, light, and rugged."[2] Documentation is no different. The complexity of casualty care on the battlefield is undeniable and represents a fundamental challenge of military medicine.[23] Nevertheless, future iterations of the TCCC card must strike a balance between sufficient sophistication to capture data necessary to continue advancing the scientific frontiers of combat casualty medicine while simultaneously remaining sufficiently simple to achieve documentation compliance.

Our study has numerous limitations. This is a retrospective study and relies on the accuracy of the DOD trauma registry. Although this registry is an invaluable tool to

study the care of wounded on the battlefield, it remains inherently limited by the quality of inputted data. Also, it is unclear when the updated TCCC card was implemented in all units reporting to the PHTR/DODTR; the 1-year wash-in period used by our study may have been inadequate as certain units could have continued using the outdated card, especially if they were already deployed during the time. Another shortcoming of this study is the TCCC card is not the only source of prehospital data in the trauma registry. While we do have some information about the proportion of data entered coming from TCCC AARs versus TCCC cards, we do not have a direct count on the number of TCCC cards filled out per casualty. Additionally, there were significant changes in operational tempo during the years included in this study; these years also saw significant changes in the proportions of US military casualties as compared to those of foreign militaries and civilians. However, our post-implementation period has significantly less casualties, which curiously was inversely proportional to our documentation quality.

Moving forward, further research should explore what changes to the current TCCC card would truly yield the improvements in documentation its creators desired. A more agile method for implementation of new DOD forms would enable more rapid changes to adapt to the feedback from the end-users rather than the cumbersome bureaucracy currently requiring a prolonged period to update DOD forms. One central source, such as the Joint Trauma System, could retain command and control of the documentation forms to ensure rapid agility.

Conclusions

Implementation of the new TCCC card resulted in overall lower documentation proportions which persisted after adjusting for measurable confounders.

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Lessons from the Fallen: An After-Action Review of Prehospital Casualty Data during the Global War on Terror

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Abstract

Background: The US military's recent involvement in long standing conflict has caused the pioneering of many lifesaving medical advances, often made possible by data-driven research. However, future advances in battlefield medicine will likely require greater data fidelity than is currently attainable. Continuing to improve survival rates will require data which establishes the relative contributions to preventable mortality and guides future interventions. Prehospital data, particularly that from Tactical Combat Casualty Care (TCCC) Cards and TCCC After Action Reports (TCCC AARs), are notoriously inconsistent in reaching searchable databases for formal evaluation. While the military has begun incorporating more modern technology in advanced data capture over the past few years like the Air Force's Battlefield Assisted Trauma Distributed Observation Kit (BATDOK) and the Army's Medical Hands-free Unified Broadcast system (MEDHUB), more analysis weighing the advantages and disadvantages of substituting analog solutions is needed.

Discussion: We propose 3 changes which may aid prehospital data capture and facilitate analysis: reexamine the current format of TCCC Cards and consider reducing the number of available datapoints to streamline completion, implement a military-wide mandate for all Role 1 providers to complete a TCCC AAR within 24 hours of a casualty event, and formalize the process of requesting de-identified data from the Armed Forces Medical Examiner System (AFMES) database.

Conclusion: Reflecting on the state of US military medicine after 20 years of war, an important focus is improving the way prehospital data is gathered and analyzed by the military. There are steps we can take now to enhance our capabilities.

Keywords: prehospital; tactical; combat; casualty; battlefield; prolonged field care

Introduction

The US military's involvement in long standing conflict in Iraq, Afghanistan, and Syria has changed the way in which prehospital medicine is practiced.[1-4] It has brought the idea of tourniquet use to the forefront of combat casualty care, significantly reduced medical evacuation times, and reintroduced live donor blood transfusions to the battlefield.[5-7]

These recent lifesaving advances were made possible by data-driven research. For example, battlefield tourniquet use was introduced in the original 1996 Tactical Combat Casualty Care (TCCC) guidelines after 3 years of retrospective research on battlefield mortality conducted by the Naval Special Warfare Biomedical Research Program and Uniformed Services University of the Health Sciences. Prior to these guidelines, battlefield tourniquet use was discouraged out of concern for limb ischemia

(despite extremity hemorrhage causing 7.4% of combat deaths in Vietnam). Ultimately, limb ischemia concerns were not founded in evidence, demonstrating here and in other key areas how implementing lifesaving measures can be hindered by inadequate data.[8-11]

Future advances in battlefield medicine will likely require greater data fidelity than is currently attainable. Recent work from Mazuchowski et al and Kotwal et al suggests preventable battlefield deaths from hemorrhage alone may no longer represent the majority, supplanted by more complex injuries requiring integrated interventions for bleeding, airway and breathing.[12,13] This is likely a result of isolated compressible extremity hemorrhage no longer representing a primary cause of death as tourniquets and the use of whole blood have largely mitigated this harm. Continuing to improve survival rates will require data establishing the relative contributions to preventable mortality and guides future interventions. Any future medical research focus should include airway, breathing, and noncompressible hemorrhage as part of a comprehensive resuscitation.

Current State of Prehospital Data

TCCC Cards are physical cards and contribute to prehospital data by recording injuries sustained by, and medical interventions performed on, prehospital patients. However, one study showed only 7% of 363 US casualties from July 2013 to March 2014 who qualified for TCCC Cards were appropriately accompanied by a one when they reached the next higher level of medical care.[9] Such low compliance limits the ability to draw meaningful conclusions for performance improvement. The same study found TCCC After Action Reports (AARs)—a more robust form of TCCC Cards completed retrospectively by senior medical providers—similarly fell short. TCCC AARs were recorded in only 50% of 186 possible casualties.[9]

In the US Army Infantry, AARs are conducted after missions or training exercises to informally evaluate team performance. A team leader, squad leader, platoon leader, or platoon sergeant gathers their group of soldiers and asks them to identify elements of the operation to sustain—what went well—and elements to improve—what went poorly. High-functioning units use these AARs as an opportunity to facilitate discussion and evaluation to increase unit effectiveness in the future. Similar systems exist for capturing such data, but entry of the lessons learned into the databases is generally optional and recent experience shows contribution is rare.[14-16]

The military has also incorporated more modern technology in advanced data capture over the past few years. The Air Force's Battlefield Assisted Trauma Distributed Observation Kit (BATDOK) relies on a handheld device and utilizes software allowing medical personnel to document and monitor multiple trauma patients simultansously.[17] Similarly, the Army's Medical Hands-free Unified Broadcast system (MEDHUB) allows medical personnel to communicate between themselves and medical facilities during MEDEVAC operations.[18] Although these technologies and others like them continue to influence the course of prehospital data collection, hopefully for the better, more analysis weighing the advantages and disadvantages of substituting analog solutions is needed. Close examination of these systems awaits future study and commentary.

The Way Forward

With the US leaving Afghanistan in 2021 and Russian aggression now threatening the eastern flank of the North Atlantic Treaty Organization (NATO), now is the time for the US military to conduct robust AARs while we still have institutional memory from the Global War on Terror (GWOT) readily available. In other words, capture the lessons learned from experienced providers and senior military leaders before they transition out of the military to prevent the loss of first-hand experience that occurs after major conflict periods. These lessons are important to capture immediately following a major conflict given the cyclical nature of medical advancement during wartime.[19,20] Many have given the US military's medical community its rightful credence as a continuously evolving and progress-producing system with particularly significant prehospital advances which benefit both the military and civilian community.[2,21,23] This represents medical aspects of the GWOT to sustain. However, patients could greatly benefit from an institutional lessons learned modelby similarly identifying aspects to improve.

Given the fact TCCC Cards are so rarely filled out and follow casualties along the chain of care, it is important to revisit their application. This has been done periodically throughout the lifespan of TCCC.[24] One solution is to reduce the amount of information requested by TCCC Cards. TCCC Cards are currently designed to capture over 100 data points. This information would be great for future analysis, but not if only a small portion of cards are even completed in the prehospital setting. Reducing the number of fields may increase compliance and streamline data points needed for continuity of patient care. The recent transition of the US healthcare system from paper charts into the electronic medical record system has demonstrated more data entry points do not translate to more data entry, let alone better data. In

fact, it may lead to the exact opposite.[25-27] We contend there is room for improving TCCC Cards. This should be done with the goal of capturing only the most crucial data points needed to assure effective continuum of care and future analysis. This will have the benefit of reduced time and cognitive load spent filling out these cards with competing priorities in high-stress environments. We believe, however, the greatest opportunity for improvement lies in TCCC AAR policy reform.

In some studies, TCCC AAR data comprises up to 95% of prehospital data.[10] Thus, improving the collection and analysis of TCCC AARs may also help address the issue of insufficient prehospital military data. Adherence in completing TCCC AARs was found to be directly related to staff efforts and policies by the provider's chain of command.[9] However, there is currently no military-wide mandate requiring Role 1 providers, those who render treatment at or near the initial point of injury, to complete TCCC AARs. US Special Operations Command (USSOCOM) noticed this deficiency in 2020 and instituted a new requirement to complete TCCC AARs within 24 hours of a casualty event, but the rest of the US military has yet to follow suit.[28] Implementing a new requirement for all military Role 1 providers to complete a formal TCCC AAR within 24 hours of a casualty incident and holding unit commanders accountable would go far in improving the quality of prehospital data. This could remedy many of the shortcomings of TCCC Cards, which can be filled out in haste or lost in transit. Furthermore, technology to enable better or automatic capture of data could be beneficial. Examples include body-worn cameras, wearables, or other devices allowing data to be extracted after-the-fact or transmitted forward.

An important additional source of prehospital data is the Armed Forces Medical Examiner System (AFMES) database, which records all patients who die from their wounds. Unfortunately, this autopsy data does not directly link to the military's Prehospital Trauma Registry (PHTR). As a result, casualties who expire prior to reaching a higher level of care are generally not included in queries of the PHTR. These are arguably the most important casualties to include in studies of battlefield medicine, as success or failure of medical interventions is often measured by mortality. Due to confidentiality issues, all requests for such data—even if the request is explicitly limited to de-identified data—are considered on a case-by-case basis with few requests being granted. Aggregate level data captured in the DoDTR effectively anonymizes the data. Simply put, future deaths may be preventable if policy changes allow past deaths to be better analyzed using de-identified data via a formalized AFMES request process to mirror the way Department of Defense Trauma Registry (DoDTR) data is requested.

Conclusions

Reflecting on the state of US military medicine after 20 years of war, an important focus is improving the way prehospital data is gathered and analyzed by the military. There are steps we can take now to enhance our capabilities in this regard, namely in the realm of TCCC Cards, TCCC AARs, and AFMES data collection and analysis. We cannot improve what we do not measure.

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A Comparison of Combat Casualty Outcomes after Prehospital Versus Military Treatment Facility Airway Management

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Abstract

Background: Airway obstruction is the second leading cause of potentially survivable death on the battlefield. Previous studies demonstrate casualties undergoing airway interventions have worse outcomes when the procedure occurs in the prehospital setting versus the military treatment facility (MTF) setting. We compare outcomes between casualties undergoing airway management in these 2 settings using the Department of Defense Trauma Registry (DODTR).

Methods: This is a secondary analysis of a previously described dataset from the DODTR. We included US military casualties with at least 24 hours on the ventilator. We compared casualties who underwent intubation in the prehospital setting versus hospital setting. Multivariable logistic regression models were constructed to adjust for available confounders.

Results: There were 2,124 that met inclusion for this analysis—278 in the prehospital cohort and 1,846 in the MTF cohort. Median injury severity scores were higher in the prehospital cohort (25 versus 22, $p<0.001$). The survival to discharge was lower in the prehospital cohort (80% versus 93%, $p<0.001$). On multivariable logistic regression model, when adjusting for injury severity score, mechanism of injury, and first 24-hour blood products, the odds of survival were 0.34 (95% CI 0.23-0.50) for those intubated prehospital versus MTF.

Conclusions: We found worse survival for those with prehospital airway intervention versus those in the MTF-setting. These findings persisted after adjustment for measurable confounders. Our findings suggest prehospital-focused improvements in airway interventions are needed and/or robust methods for rapid evacuation to an MTF for airway intervention.

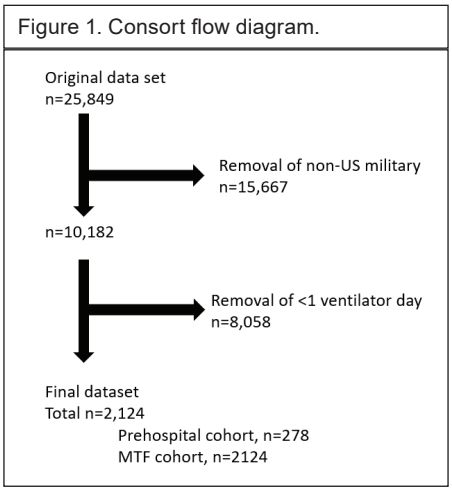
Keywords: airway; combat; prehospital; military; intubation

Introduction

Background: Airway obstruction is the second leading cause of potentially survivable death on the battlefield.[1] Multiple previous studies have demonstrated intubation is the most common prehospital airway intervention in the combat setting.[2-5] Other analyses from combat zones focused on comparing outcomes after prehospital versus hospital-based intubation demonstrate better outcomes following intubation in the hospital setting.[6,7] A combat-based study comparing intubation versus a bag-valve-mask (BVM) found no benefit to intubation and also found prolonged prehospital time for casualties undergoing prehospital intubation.[8] However, these data sets spanned only a limited number of years and included host nation casualties such as partner force and humanitarian mission casualties which introduce many confounders. Data sets focused on the US military personnel would provide useful additional information. Maddry et al found similar outcomes for those casualties who underwent a cricothyrotomy versus BVM; this study also found similar outcomes for casualties receiving a supraglottic airway versus BVM.[9] Maddry's findings suggest noninvasive airway intervention yield similar outcomes to more invasive definitive management techniques.

A major limitation to studies in combat settings is they are retrospective and, hence, carry limitations for inferring causal relationships. There are high quality studies from the civilian prehospital setting with similar findings. In a systematic review with meta-analysis by

Fevang et al, the median mortality for those intubated prehospital was 48% versus 29% in the emergency department.[10] The adjusted odds ratio also favored emergency department intubation (OR 2.59, 1.97-3.39). A pediatric- based study found no benefit to intubation over BVM in the prehospital setting.[11]



The US military is preparing for conflict with a near-peer adversary. Such a conflict will contrast significantly with the recent asymmetric, counterinsurgency operations in Iraq, Afghanistan, and Syria.[12] In future large-scale combat operations (LSCO), the US will likely not enjoy the uncontested airspace movement which characterized these conflicts.[13] As such, the US military health system may experience prolonged casualty care (PCC) events in which casualties will remain in forward casualty collection points (CCP).[14] However, the effects of PCC on survival are not clear currently. More data is necessary to inform commanders of the risks associated with medical care delivery in these scenarios.

Goal of this Study: We compare outcomes among US military combat casualties undergoing prehospital versus military treatment facility (MTF) airway management.

Methods

Data Acquisition: This is a secondary analysis of a previously described dataset.[15] The US Army Institute of Surgical Research (USAISR) regulatory office reviewed protocol H-20-015nh and determined it was exempt from Institutional Review Board oversight. We obtained and used only de-identified data.

We analyzed US military casualties with at least 1 day on the ventilator. We excluded casualties who were non-US military due to challenges associated with follow up and varying levels of care for the host nation population.[16]

Department of Defense Trauma Registry (DODTR): The DODTR, formerly known as the Joint Theater Trauma Registry (JTTR), is the data repository for DoD trauma-related injuries.[17,18] The DODTR includes documentation regarding demographics, injury-producing incidents, diagnoses, treatments, and outcomes of injuries sustained by US/non-US military and US/non-US civilian personnel in wartime and peacetime (including host nation civilians) from the point of injury to final disposition using standardized data capture forms. Data is extracted and entered into the registry by trained registrars. Short-term outcome data are available for non-US casualties. The DODTR comprises all patients admitted to a Role 3 (fixed-facility) or forward resuscitative surgical detachment (FRSD) with an injury diagnosis using the International Classification of Disease 9th Edition (ICD-9) between 800-959.9, near-drowning/drowning with associated injury (ICD-9 994.1) or inhalational injury (ICD-9 987.9) and trauma occurring within 72 hours from presentation. The registry defines the prehospital setting as any location prior to reaching surgical capabilities at an FRSD, field hospital (FH), or a combat support hospital (CSH) to include the Role 1 (point of injury, casualty collection point, battalion aid station) and Role 2 without surgical capabilities (temporary limited-capability forward-positioned hospital inside combat zone).

Data Analysis: We performed all statistical analysis using commercially available software. We present continuous variables as means with 95% confidence intervals compared using t-test. We present non-parametric continuous variables and ordinal variables as medians with interquartile ranges compared using Wilcoxon rank sum test. We present nominal variables as percentages with numbers compared using chi square test and Fisher's exact test when the expected cell count was less than 5. We analyzed the data under the assumption of accurate documentation of all care rendered. We present p-values for the reader to assess the strength of differences and associations. We constructed multivariable logistic regression and linear regression models to assess for associations with outcomes while adjusting for relevant confounders.

Results

Within the DODTR from January 2007 to December 2019, there were 25,849 adult encounters within our original dataset. After removal of all non-US military casualties and those with <1 ventilator day, we had 2,124 available for analysis—278 in the prehospital cohort and 1,846 in the MTF cohort (Figure 1).

The median age of both cohorts was 24 and overwhelmingly male. Explosives were the most frequent mechanism of injury for both cohorts for prehospital versus MTF (71% versus 71%, p=0.616). Median ISS scores were higher in the prehospital cohort (25 versus 22, p<0.001). Head injuries were more frequent in the

prehospital cohort (38% versus 25%, p<0.001); otherwise, the rest were generally similar. The prehospital cohort had more median ventilator days (5 versus 4, p=0.005) and total hospital days (5 versus 17, p<0.001). The survival to discharge was lower in the prehospital cohort (80% versus 93%, p<0.001) (Table 1).

Table 1. Combat data.

		Prehospital cohort	MTF cohort	p-value
Demographics	Age	24 (21-27)	24 (21-28)	0.268
	Male	98% (273)	98% (1818)	0.611
Mechanism of Injury	Explosive	71% (198)	71% (1317)	0.616
	Firearm	22% (60)	21% (381)	
	Motor vehicle	1% (3)	2% (42)	
	Other	6% (17)	6% (106)	
Injury Severity Score		25 (17-34)	22 (14-30)	<0.001
Serious injuries by body region	Head/neck	38% (105)	25% (462)	<0.001
	Facial	2% (5)	1% (23)	0.410
	Thorax	28% (523)	26% (71)	0.333
	Abdomen	19% (52)	23% (423)	0.116
	Extremities	56% (155)	57% (1056)	0.649
	Skin	9% (24)	9% (167)	0.822
Outcome	Ventilator days	5 (2-8)	4 (2-7)	0.005
	ICU days	7 (4-10)	7 (4-12)	0.531
	Hospital days	5(3-21)	17 (5-39)	<0.001
	Discharge Alive	80% (222)	93% (1714)	<0.001

On multivariable logistic regression model, when adjusting for injury severity score, mechanism of injury, and first 24-hour blood products, the odds of survival were 0.34 (95% CI 0.23-0.50) for those intubated prehospital versus MTF (Table 2).

Discussion

We analyzed casualties who had an airway intervention prehospital versus the MTF setting and found casualties consistently experience worse survival with airway placement in the prehospital setting. These findings persisted even when adjusting for measurable confounders. The findings of this study had similar findings to our previous studies comparing patients with airway interventions in this settings.[6,7] This study further supports improvements with airway interventions in the prehospital setting have not occurred since this dataset includes more recent casualties than our previous analyses.[6,7]

The underlying cause for these findings is likely related to the relative lack of resources and time to optimize conditions in the prehospital setting. Pre-intubation resuscitation is undoubtedly more challenging in these circumstances. This may contribute to worse outcomes in the prehospital setting given the incidence of peri-intubation hypotension and its association with peri-intubation cardiac arrest.[19,20] Furthermore, the prehospital setting is less likely to benefit from advanced technology such as video laryngoscopy which is associated with improved first pass intubation success.[21-23]

Since the publication of our previous studies, there has been substantial change in the combat landscape. The US has begun a transition from counterinsurgency operations as part of the Global War on Terrorism (GWOT), to that of potential LSCO with near-peer adversaries which may require prolonged casualty case (PCC). In LSCO settings, substantially more casualties are likely which overwhelm our medical capabilities. The findings of the study highlighted worse outcomes after intervention in the prehospital setting suggest in future LSCO operations it will be necessary to either bring more airway capabilities further forward, or more likely, substantially enhance capability to rapidly evacuate casualties while delaying airway interventions.

Our study has several limitations. As a retrospective analysis of registry data, the conclusions are limited to associations and not causation, and the study shares the same biases previously described with using data from the DODTR. Inclusion into the DODTR requires arrival at a deployed military treatment facility with surgical capabilities as an entry point for capture into the registry. As such, the registry does not capture those who died prehospital before reaching a facility with surgical capabilities without signs of life or ongoing interventions.

However, given we specifically excluded patients who died within the first 24 hours to avoid a survival bias on the inclusion, this likely would have little material impact on our findings. Data in the trauma registry is dependent upon documentation in austere combat conditions and have demonstrated suboptimal compliance with documentation requirements.[24,25]

Table 2. Multivariable logistic regression model for survival.

Intervention	Odds ratio (95% confidence interval)
Prehospital/MTF	0.34 (0.23-0.50)
Injury severity score	0.95 (0.94-0.96)
Whole blood	0.97 (0.96-0.99)
Packed red cells	0.99 (0.96-1.02)
Fresh frozen plasma	0.98 (0.95-1.01)
Platelets	1.07 (1.00-1.14)
Explosive/Other	0.81 (0.31-2.09)
Firearm/Other	0.28 (0.11-0.75)
MVC/Other	1.06 (0.19-5.97)

Military treatment facility: MTF; R^2 0.153: Area under the receiver operating characteristic (AUROC) 0.788; Akaike information criterion (AICc) 1095.6; Bayesian information criterion (BIC) 1152.11.

Conclusions

We found worse survival for those with prehospital airway intervention versus those in the MTF-setting. These findings persisted after adjustment for measurable confounders. Our findings suggest prehospital-focused improvements in airway interventions are needed and/or robust methods for rapid evacuation to an MTF for airway intervention.

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Expert Consensus Panel Recommendations for Selection of the Optimal Supraglottic Airway Device for Inclusion to the Medic's Aid Bag

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Abstract

Introduction: Airway obstruction is the second leading cause of potentially survivable death on the battlefield. The Committee on Tactical Combat Casualty Care (CoTCCC) has evolving recommendations for the optimal supraglottic airway (SGA) device for inclusion to the medics' aid bag.

Methods: We convened an expert consensus panel consisting of a mix of 8 prehospital specialists, emergency medicine experts, and experienced combat medics, with the intent to offer recommendations for optimal SGA selection. Prior to meeting, we independently reviewed previously published studies conducted by our study team, conducted a virtual meeting, and summarized the findings to the panel. The studies included an analysis of end-user after action reviews, a market analysis, engineering testing, and prospective feedback from combat medics. The panel members then made recommendations regarding their top 3 choices of devices including the options of military custom design. Simple descriptive statistics were used to analyze panel recommendations.

Results: The preponderance (7/8, 88%) of panel members recommended the gel-cuffed SGA, followed by the self-inflating-cuff SGA (5/8, 62%) and laryngeal tube SGA (5/8, 62%). Panel members expressed concerns primarily related to the (1) devices' tolerance for the military environment, and (2) ability to effectively secure the gel-cuffed SGA and the self-inflating-cuff SGA during transport.

Conclusions: A preponderance of panel members selected the gel-cuff SGA with substantial feedback highlighting the need for military-specific customizations to support the combat environment needs.

Keywords: combat; medic; airway; supraglottic; extraglottic; panel

Introduction

Background: Eastridge et al found airway obstruction is the second leading cause of potentially preventable deaths on the battlefield during the recent conflicts involving the US.[1] In a more recently published study focused on deaths in special operations forces, Mazuchowski et al found nearly 1 in 6 potentially survivable deaths resulted from airway obstruction or airway obstruction was a major factor.[2] These 2 studies establish the increasing importance of airway management for mortality reduction in the prehospital combat setting. Recent data demonstrates high mortality associated with the need for airway interventions in this setting.[3,4] Optimized airway management is among the top 5 battlefield research and development priorities identified by the Committee on Tactical Combat Casualty Care (CoTCCC), yet the challenge of airway management has evolved little during the recent conflicts.[5,6]

We sought to assess feedback from relevant subject matter experts to make recommendations for the ideal supra-glottic airway (SGA) device for fielding into the medic's aid bag. As part of the expert consensus panel, we summarized our findings from previous phases of this project and provided the full manuscripts to panel members. We summarize below the findings of the relevant studies with excerpts from the abstracts and references to the full manuscripts.[6-11]

Summary of Airway Management in the Prehospital, Combat Environment—Analysis of After Action Reviews and Lessons Learned: We queried the Center for Army Lessons Learned (CALL), the Army Medical Department Lessons Learned (AMEDDLL) and the Joint Lessons Learned Information System (JLLIS).[7] Our queries comprised a series of search terms with a focus on airway management. Eight experts performed reviews. The varied nature of the sources lent itself to an unstructured qualitative approach with results tabulated into thematic categories. The panel of 8 experts reviewed retrieved results including 74 available after-action reviews (AARs): 70 deployment-based lessons learned, and 4 training-based lessons learned. We categorized 37 AARs as equipment challenges/malfunctions, 28 as training/education challenges, and 9 as other. Several lessons learned specifically stated units failed to prioritize medic training; multiple comments suggested units should consider sending their medics to civilian training centers. Other comments highlighted equipment shortages and equipment malfunctions specific to certain mission types (e.g. pediatric casualties, extreme weather). Most of the feedback referenced equipment malfunctions and gaps in initial and maintenance training.

Summary of An Analysis of Prehospital Trauma Registry After Action Reviews on Airway Interventions in Afghanistan: The Prehospital Trauma Registry (PHTR) AARs allow for unique perspectives and an enhanced analysis of interventions performed.[6] We analyzed all AAR comments included for airway interventions. We applied unstructured qualitative methods to analyze themes within these reports and generated descriptive statistics to summarize findings related to airway management.

Out of 705 total casualty encounters in our dataset, 17 had accompanying AAR comments for review. AAR comments focused primarily on cricothyroidotomy, endotracheal intubation, and ventilation management, citing needs for improvement in technique and anatomy identification. There were no reviews specific to SGA devices.

Summary of An Inventory of the Combat Medics' Aid Bag: We sought combat medics (Army military occupational specialty 68W) organic to combat arms units stationed at Joint Base Lewis McChord.[8] Medics volunteered to complete a demographic worksheet and have the contents of their aid bag photographed and inventoried. We spoke with each combat medic's respective unit leadership prior to their participation and asked the medics to bring their aid bags in the way they would pack for a combat mission. We categorized medic aid bag contents in the following manner: (1) hemorrhage control; (2) airway management; (3) pneumothorax treatment, or (4) volume resuscitation. We compared the items found in the aid bags against the contemporary TCCC guidelines. We prospectively inventoried 44 combat medic aid bags. Overall, 93% carried a nasopharyngeal airway 93%, 31% a SGA, and 64% a cricothyrotomy setup/kit.

Summary of Review of Commercially Available Supraglottic Airway Devices for Prehospital Combat Casualty Care: We conducted a market review of 25 SGA devices which may meet possible inclusion into the medics' aid bag.[9] The companies' official "Instructions for Use" document, Google Scholar, and FDA reports were reviewed to obtain information for each SGA device. Twenty-five commercially available SGA devices were explored by the study team members and presented from manufacturer online sources. The totality of the list of the devices discovered are available within the full publication. Of note, many were either (1) no longer in production, (2) non-procurable by the DoD due to their lack of a physical presence in the US (e.g. foreign sales only), or (3) cost prohibitive.

Summary of Military Standard Testing of Commercially Available Supraglottic Airway Devices for Use in a Military Combat Setting: The harsh conditions of the military combat setting requires devices be able to withstand extreme conditions.(unpublished data) Military standards (MILSTD) testing is required prior to device fielding. We tested 10 SGA models according to 9 MIL-STD-810H test methods, Department of Defense Test Method Standard, Environmental Engineering Considerations and Laboratory Tests, US Defense Logistics Agency, 2022. We selected these tests by polling 5 military and civilian emergency medicine subject matter experts who weighed the relevance of each test. We performed tests on 3 devices for each model, with operational and visual examinations to assign a score (1-10) for each device after each test. We calculated each SGA model's final score by averaging each device's score and multiplying it by the weight for each test for a possible final score of 2.6-26.3. Lower scoring models may not be optimal for military field use.

Summary of An Assessment of Combat Medic Supraglottic Airway Device Design Needs Using a Qualitative

Methods Approach—A Preliminary Analysis: We performed prospective, qualitative-designed studies in serial to discover emerging themes on interview.[10] A physician with airway expertise presented medics with 2-3 airway devices in the same session with formal training to include practice application and troubleshooting. We used semi-structured interviews after the training to obtain end-user feedback with a focus on emerging themes. Of the 77 medics surveyed and interviewed, we noted 5 emerging themes: (1) insertion, which pertains to the ease or complexity of using the device; (2) material, which pertains to the tactile features of the device; (3) versatility, which pertains to the conditions in which the device can be used as well as with which other devices it can be used; (4) portability, which refers to how and where the device is stored and carried; and (5) training, which refers to the ease and frequency of initial and ongoing training to sustain medics' technical capability when using the device.

Table 1. Select qualitative feedback from panel members.

"The reasoning is that the majority of medics felt comfortable using those devices [gel-cuffed SGA] and [laryngeal tube SGA] and they have been previously taught in 68W Advance Individual Training."
The [laryngeal tube SGA] comes in a smaller package and is more agile in an aid bag compared to the [gel-cuffed SGA] with it being more rigid and bulky.
"…with OJT, the medic could be taught how to administer sedatives, paralytics, and other drugs to help with the securing of the airway."
"The gel material of the [gel-cuffed SGA] did appear to hold onto sand/dust particulates which could prove significant in the prehospital military environment. Perhaps for the military, the device could be modified to be built of plastic except for the oropharyngeal mask. This would likely improve the compliance during cold testing and reduce the sand attraction."
"[The gel-cuffed SGA] was already determined to be the device by two panels of combat medics and providers in 2021 and recommended by CoTCCC in 2017."
"Recommend seeking a securing device that is effective. Early use in SOF, we noticed it ([the gel-cuffed SGA]) was easily dislodged during movement."
"Recommend that a requirement be written for a compact packaging solution. The MES Combat Medic cube space and weight has exceeded the maximum standard during the 2021 MES Panel Review."

Summary of A Mixed Methods End-User Assessment to Determine the Ideal Supraglottic Airway Device for Inclusion to the Medic's Aid Bag: We used a mixed methods approach to investigate the properties of an ideal device for inclusion to the medic's aid bag.[11] We performed prospective, serial qualitative studies to uncover and articulate themes relative to airway device usability with 68W, combat medics. Physicians with airway expertise demonstrated the use of each device and provided formal training on all the presented devices. We then administered performed focus groups to solicit end-user feedback along with survey data. We enrolled 250 medics during the study. When reporting on usability, the gel-cuffed SGA had the highest median score, ease of manipulation, grip comfort, and ease of insertion while also scoring the best regarding requiring minimal training. The other compared devices had no clear highest score. Qualitative data saturated around a strong preference for the self-inflating-cuff SGA and/or the gel-cuffed SGA airway device, with the least favorite being the more malleable devices and the intubating rigid supraglottic device. There was a strong qualitative alignment in how both the self-inflating-cuff SGA and/or the gel-cuffed provided ease of use and simplicity of training. The overall data suggests medics would prefer a device engineered with features from several devices.

Methods

We convened an expert consensus panel to review the aforementioned literature supported and funded by this project. We selected panel members based on engagement with the study project and the recommendations of the project portfolio manager. We sent out invitations to participate in the virtual discussion and sent all the supporting manuscripts and key findings to all panel members prior to the meeting. Selected study investigators presented a summary of the work. After conclusion of the presentations of the previous work, the panel then had an opportunity to ask the investigators questions to obtain clarification and other relevant details. The principal investigator (PI) moderated the discussion until all the panel members were satisfied with the discussion and able to share key points from their interpretation of the studies. At the closure of the discussion, the panel provided rank order preference for 3 devices as recommendations to the medical logistics leadership based on the devices previously described.[9] They were also advised to make recommendations whether the commercial off-the-shelf (COTS) solution was sufficient or whether specific military customizations are necessary. The PI solicited additional information from each panel member as required. Appendix 1 includes relevant details of the panel numbers.

Tradename Information: DoD and Army regulations require specific authorizations when publishing intellectual property, copyright, and/or trademark items and information. Several companies were not responsive to our requests for permission or had other agreement requirements which were not feasible. Specific tradename information is available in the reviewed publications cited or by request to the corresponding author.[9-11]

Panel Recommendations: The preponderance (7/8, 88%) of the panel members recommended the gel-cuffed SGA, followed by the self-inflating-cuff SGA (5/8, 62%) and laryngeal tube SGA (5/8, 62%). Panel members expressed concerns (Table 1) primarily related to (1) the devices' tolerance for the military environment, and (2) the ability to effectively secure the gel-cuffed SGA and the self-inflating-cuff SGA during transport. The panel numbers concluded the gel-cuffed SGA and the laryngeal tube SGA devices were optimal for use. However,

they did find concerns with the gel-cuffed SGA being able to withstand the military combat environment, specifically the temperature and dust. There are also concerns regarding the packaging and the ability to secure the devices.

Discussion

In this expert consensus panel, we found the preponderance of recommendations supported the use of the gel-cuffed SGA, followed by the self-inflating-cuff SGA, followed by the laryngeal tube SGA. As previously stated, they also noted concerns whether the devices can tolerate the military environment and securing the devices during transport. Our findings generally mirror the TCCC guidelines in that they had preferences for the laryngeal tube SGA which was the first SGA recommended by TCCC. They also previously expressed preference toward the gel-cuffed SGA; although the most recent iteration of the guidelines only lists a generic SGA recommendation as part of the airway algorithm.

The primary purpose of this expert consensus panel was to provide recommendations for medical logistics and acquisitions for purchasing of devices and including them in deployed sets, kits, and outfits (SKOs). Given panel members primarily recommended the gel-cuffed SGA device (which is already in the military inventory), this likely will serve to reinforce in the short-term the acquisitions process. However, given the expressed concerns about this device's ability to tolerate the military environment, the military should explore a custom designed military specification (MILSPEC) version of this device. This could occur by way of modification of an existing market device if the manufacturer cooperates. Alternatively, the military could seek a new custom-made device from alternative manufacturers.

Beyond the recommendations made by the expert consensus panel, we highlight additional recommendations for the US military to consider for future acquisitions namely with our methods for obtaining preliminary data followed by the inclusion of the intended end-users (68W combat medics) into the data acquisition process. We designed this project in a stepwise fashion starting with feedback from the field using sources of lessons learned and after-action reviews not previously implemented into other acquisition recommendation-based projects. This first allowed us to highlight needs from the field in the recent conflicts.[6,7] This is especially important given the conflict activity of the recent wars is rapidly declining, thus we are entering a period of limited conflict before the next war happens. These databases allow us to get actionable information from the field to inform project decisions. Next, we performed a market analysis to determine what devices were available on the market. This allowed us to assess whether there is adequate availability of devices on the market to proceed with the project.[9] We then went on to perform engineering testing of these devices to determine which ones could withstand the military operational environment.(unpublished data) We took the devices to the intended end-users enrolling 250 combat medics into our study.[11] To the best of our knowledge, this is the largest combat medic-based study published, and the first time such a substantial number of end-users were included in the development process. Lastly, we took this information to the expert consensus panel which is presented herein. This panel included a variety of prehospital and emergency medicine specialists, as well as several end-users to ensure the panel was well rounded and provided recommendations grounded in both science and experience. Our project highlights the ability to incorporate the end-user into the project development processes.

There are several limitations to this project. The expert panel was selected based on expertise and included a variety of credentials and experiences; however, they were not randomly selected nor was the panel qualifications distributed using *a priori* criteria. The panel discussion and deliberation was moderated by the PI, but a formal consensus structure was not used. While it is possible a different panel could arrive at contrasting conclusions, this limitation is tempered by the objective results of the reviewed studies and the convergence of the panel's opinions with existing guidelines. Alternatively, confirmation bias may contribute to the panel convergence. In any event, it is important to recognize the panel's recommendations were limited to existing SGAs and did not consider alternative devices or procedural categories (e.g., tracheal intubation), nor the efficacy of SGA use in the first place.

Conclusions

A preponderance of panel members selected the gel-cuffed SGA with substantial feedback highlighting the need for admission military-specific customizations to support combat environment needs.

APPENDIX

Appendix 1. Panel members.

Name	Affiliation	Background
Michael April	40th Forward Resuscitative Surgical Detachment	LTC April is a board-certified Emergency Physician. He has 9 years' experience as an emergency physician including one Role 2 combat deployment to Afghanistan. He currently serves as commander of the 40th Forward Resuscitative Surgical Detachment at Fort Carson, CO.
Hunter Black	US Army Medical Materiel Development Activity	SFC Hunter P. Black, NRP, Combat Medic Specialist, is the Senior Enlisted Leader for US Army Medical Materiel Development Activity. He has three deployments, one conventional and two special operations tours. Prior to his current assignment, he served as the 68W Enlisted Subject Matter Expert for Office of the Commandant, MEDCoE/OTSG and the Senior Training Developer for TCCC and MOS 68W.
Tyler Davis	59th Medical Wing	Maj Tyler Davis, MD, MPH is an emergency medicine physician at Brooke Army Medical Center. He has one combat deployment performing en route critical care. He is currently in a research fellowship with the En Route Care Research Center in San Antonio.
Robert De Lorenzo	University of Texas Health San Antonio	COL (US Army, Retired) Robert De Lorenzo, MD, MSM, MSCI, FACEP is a Professor of Emergency Medicine, Vice Chair of Research in the Department of Emergency Medicine at UT Health San Antonio, and Adjoint Faculty, Joint Graduate Program in Biomedical Engineering, University of Texas at San Antonio, and UT Health San Antonio. A retired Army combat veteran with more than 25 years' military experience, he is board certified in emergency medicine and an active clinician-scientist.
Romeo Fairley	University of Texas Health San Antonio	Dr. Romeo Fairley is a board-certified emergency medicine physician, who specializes in disaster medicine preparedness and response. He is currently an associate professor at UT Health, San Antonio serving as the Director of Disaster Preparedness and Response as well as the Director of the Disaster Medicine Fellowship. He maintains deployable readiness with the Texas Emergency Medical Task Force 8 Mobile Medical Unit, as well as the Texas Infectious Disease Response Unit.
Robert Gerhardt	Medical Capability Development Integration Directorate	Colonel (US Army, Retired) Bob Gerhardt currently serves as a senior consultant for the Clinical Support Branch, Requirements Division, Medical Capability Development Integration Directorate, Futures and Concepts Center, U.S. Army Futures Command. He has served as a prehospital provider in combat and other deployed settings with conventional and special operations forces. He is also an adjunct teaching staff physician with the Department of Emergency Medicine, Brooke Army Medical Center, Fort Sam Houston, TX. He is board certified in Emergency Medicine and Emergency Medical Services.
Austin Langdon	US Army Medical Materiel Development Activity	Mr. Austin S. Langdon, Deputy of Medical Modernization under Warfighter Deployed Medical Systems of USAMMDA. Prior to being in acquisitions he was a combat medic first and then went on to be a flight medic. He completed a tour in Helmand province Afghanistan in 2012 and was one of the first to do blood transfusions for the vampire program.
Peter Stednick	Joint Multinational Readiness Center	MSG Peter Stednick Jr., BS, NREMT-B, is a combat medic Observer, Coach, and Trainer (OC/T) at the Joint Multinational Readiness Center and is currently in MEDCoE's Project Warrior program. He has two combat deployments both with light Infantry units. Prior to his current assignment, he served as the Brigade Medical Operations NCOIC for 2/4 ID. He has also served as an instructor for both the Center for Pre Hospital Medicine (CPHM) and the Department of Combat Medic Training (DCMT).

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Placement of Antibiotic Powder in Open Fracture Wounds during the Emergency Room (POWDER): Design and Rationale for an Investigation of the Acute Application of Topical Antibiotic Powder in Open Fracture Wounds for Infection Prophylaxis

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Abstract

Background: Open fractures are at high risk for complications both in the military and civilian setting. Treatments to prevent fractures are limited in the Role 1 (prehospital, battalion aid station) setting. The goal of this study is to assess the efficacy of topical vancomycin powder, administered within 24 hours of an open fracture injury, in the prevention of infection and infection-related complications.

Methods: The POWDER study is a multicenter, prospective, randomized controlled clinical trial using a pragmatic open-label design. We will recruit 200 long bone open fracture patients from University Hospital at University of Texas Health at San Antonio (UTHSA) and the Brooke Army Medical Center (BAMC). We will screen and randomize patients in a 1:1 ratio to receive either usual care plus 2g topical vancomycin or usual care only. The primary objective of this study is to compare the proportion of infection and infection-related complications which occur in the 2 arms. An additional objective is to develop a risk-prediction model for open fracture wound complications.

Conclusions: The infection rates seen in open fractures remain alarmingly high in both combat and civilian settings. Several orthopedic surgery studies suggest vancomycin powder is effective in reducing surgical site infections when applied topically at the time of wound closure. We expect to see a reduction in infections in open fracture injuries treated acutely with vancomycin powder. This study may provide important information regarding the use of local vancomycin powder during the acute treatment of open fractures. If shown to be efficacious, vancomycin powder could provide a simple, time- and cost-effective infection prophylaxis strategy for these injuries.

Trial Registration: This trial is registered at ClinicalTrials.gov (NCT03765567)

Background

Open fracture wounds are highly susceptible to infections and infection-related complications. Open fractures sustained in combat environments are especially prone to infection due to immediate exposure of the wound to external debris such as dirt, weapon fragments, and shrapnel.[1,2] Infections following combat open fracture are associated with longer recovery time, poor bone healing, and complications leading to poor function and even amputation.[3-5] Reducing infection rates has thus become a primary goal in combat care.[6] In civilian settings, open fractures account for an estimated 250,000 fractures in North America annually.[7] Infections can occur in up to 50% of severe or grossly contaminated open fractures.[8,9] Complications caused

by infection of these injuries include wound healing problems and failure of fracture healing, both of which often necessitate re-operation and can lead to increased health care costs and additional negative impact on patients' quality of life.[10]

The current standard of care for infection prevention in open fracture injuries is intravenous (IV) antibiotics, ideally provided early, within 3 hours of injury.[6,11-13] However, IV antibiotic administration is limited by the time it takes to establish IV access and blood flow to the injury site, which is often compromised in open fracture patients.[14-16] Additionally, increasing the IV antibiotic dose to overcome these limitations elevates the risk of injury to non-target organs such as the kidney and liver.

Local antibiotics offer several advantages for infection prophylaxis in open fracture injuries. Topical antibiotics can be applied directly to the injury site more quickly and in higher therapeutic concentrations compared to the intravenous route, with minimal systemic antibiotic exposure.[17,18] Early application of a topical antibiotic may reduce the risk of infection in these injuries.[16,19,20] Such an intervention can be easily forward-staged as an effective intervention when surgical intervention is delayed during future large-scale combat operations (LSCO) when delays in evacuation occur.[21]

We selected vancomycin as the study drug because of its established efficacy against the pathogens most commonly seen in orthopedic trauma patients, particularly methicillin-resistant *Staphylococcus aureus* and other gram-positive bacteria.[22-24] Vancomycin powder has also been extensively studied in the spine literature for surgical site infection prophylaxis, with several studies reporting a benefit without an apparent increased risk of adverse events. While these studies are limited by their retrospective nature, the results demonstrate a reduced incidence of infection in patients treated with vancomycin powder, a reduction in cost of care, and rare complications or side effects associated with vancomycin use.[17,25-31] A high quality, multicenter, clinical study is currently assessing the efficacy of this treatment in reducing surgical site infections after definitive fixation surgeries for lower extremity fractures.[32] The POWDER clinical trial aims to assess the efficacy of vancomycin powder in reducing open fracture infections when applied prior to surgery in the acute emergency department (ED) setting.

The rationale behind earlier application of a topical prophylactic antibiotic to open fractures, before surgical intervention, is informed by preclinical studies on biofilm development in open fracture injury models. Upon entering a wound, bacteria can rapidly form a biofilm, composed of extracellular matrix which protects against phagocytosis by host immune cells. While bacteria in this biofilm phenotype are quiescent and seemingly non-threatening, they are essentially resistant to antibiotics and, after surviving antibiotic therapy, can transition back into actively replicating bacteria thereby causing an active infection in an apparently healing wound. Studies show without wound debridement, biofilm formation is robust at 3 hours following inoculation and nearly impenetrable to IV antibiotics within 6 hours.[33,34] In a preclinical study using a rat femur open fracture model contaminated with *Staphylococcus aureus*, vancomycin powder applied directly to the fracture wound at 6 hours resulted in a significant infection reduction while no effect was seen in the wounds treated 24 hours after inoculation.[35] Another study using an open fracture animal model demonstrated locally administered vancomycin powder delivered greater drug doses into the wound than IV vancomycin.[18] These preclinical studies suggest applying topical vancomycin to open fractures as early as possible will reduce the risk of infection when used as an adjunctive therapy with standard care systemic antibiotics.

Although a shorter period between injury and intervention is expected to result in better outcomes, a 24-hour window was chosen for this study for the pragmatic purpose of including all eligible patients, including those possibly delayed because of inter-facility transfers. A gradual decline in efficacy over time is expected and while animal models show biofilm formation by 6 hours,[33,34] human data is lacking and may be longer owing to variable circumstances. Additionally, limited preclinical data suggest there may be some residual efficacy of vancomycin powder as far out as 24 hours.[35] By including the time interval between time of injury and study intervention, subgroups within the 24 hours can potentially be identified as receiving greater benefit from the topical vancomycin.

The selected dose is also supported by a preliminary study which showed a minimum effective dose of 0.02g vancomycin per cm^2 for consistent eradication of target bacteria. A dose of 2 grams therefore allows for adequate coverage of wounds with a surface area up to 100 cm^2. A smaller dose would introduce an unacceptable risk of under-dosing and reduced efficacy, while a larger dose is outside the range (up to 2g) routinely used in clinical practice. For pragmatic purposes, this dose will be used for every study injury regardless of wound size. The long term, military application of this is to have these small, heat-stable, inexpensive vials, provided to the medics to apply at or near the point-of-injury as part of the wound prophylaxis.

This study will compare the efficacy of vancomycin powder plus usual care versus usual care alone in the treatment of open long bone fractures in the acute setting of the ED, prior to surgery, to improve post-surgical infection outcomes.

Methods & Design

Study Design Overview: This study is a multi-center, randomized, controlled, open-label clinical trial to assess the efficacy of the acute topical administration of vancomycin powder for infection prevention in open fracture injuries. Patients who arrive at either study center within 24 hours of sustaining an open fracture injury are randomized to 1 of 2 treatment arms: 1) usual treatment including irrigation and debridement and prophylactic IV antibiotics, and 2) usual treatment plus 2g of vancomycin powder administered topically on the wound. The primary goal of the POWDER study is to compare the proportion of deep-space infections in patients treated with topical vancomycin powder with those treated without topical vancomycin powder within 1 year.

Table 1. Eligibility criteria.

Inclusion Criteria	Exclusion Criteria
• Patients aged 18-89 years old • Subject or LAR is willing and able to provide written informed consent • Open fracture of the humerus, radiu, ulna, femur, tibia, and/or fibula • 24 hours or less has elapsed from the estimated time of injury to study intervention	• Time from injury is > 24 hours • Patients have received acute operative care of the open fracture at an outside facility • High-potency antibiotic powder or solution applied to the wound prior to enrollment • Subject or LAR speaks neither English nor Spanish. (Subjects unable to consent will be enrolled in the Observational Arm) • Patients who are currently pregnant • Patients who are incarcerated • Patients with documented allergies or serious reactions to vancomycin

Legally authorized representative (LAR)

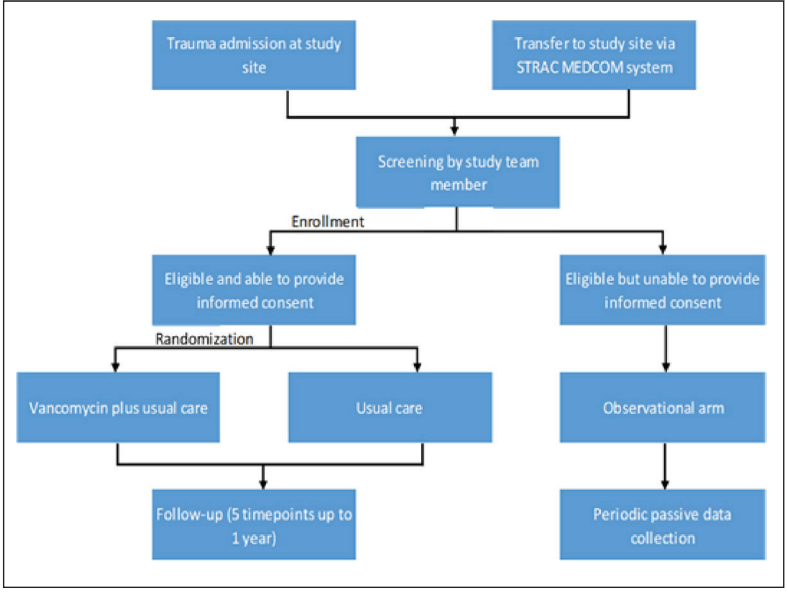
Although vancomycin is a Food and Drug Administration (FDA) approved drug, the method used to administer the drug for this study (applying the powder directly to the open fracture wound) is considered an off-label use. Approval of an investigational new drug (IND) from the FDA (IND # 141453 received 1 November 2018) is thus mandatory for this study.

The POWDER study is a collaborative effort between the 2 Level-1 trauma centers in San Antonio, the Brooke Army Medical Center (BAMC) and the University Hospital at the University of Texas Health Science Center San Antonio. The study protocol, including written informed consent, was approved by the Investigational Review Board (IRB) at University of Texas Health San Antonio (UTHSA, study sponsor), the Department of Defense Human Research Protection Office (DoD HRPO), the IRB at BAMC, and the US Army Institute of Surgical Research (USAISR). Both sites will obtain DoD HRPO approval of local IRB documents and certification to ensure proper training on study procedures and data collection prior to initiation of the study.

Randomization: Following informed consent from either the patients or their legally authorized representative, enrolled study subjects will undergo randomization in a 1:1 ratio to receive either vancomycin powder plus usual care or usual care alone. Patients will undergo block-randomization by study site, using randomizer.org or similar sites using permuted blocks of 10. A study team member not involved in enrollment will generate the randomization list and deliver it to the principal investigator for implementation at each study site.

Patient Selection: The study population consists of patients aged 18 to 89 years who present or undergo transfer to BAMC or UTHSA with an open fracture to a long bone (humerus, radius, ulna, femur, tibia, or fibula) sustained less than 24 hours prior to arrival. We will include only 1 fracture per patient for inclusion in the study. For patients with multiple eligible open fractures, we will designate the single fracture determined to be the most severe by the treating physician as the study fracture. Eligibility criteria are per Table 1.

Figure 1. Patient identification and screening procedures.



Patient Recruitment & Screening: Figure 1 summarizes patient identification and screening procedures. We will recruit subjects into the study by 1 of 2 mechanisms. First, directly through patient admittance to the ED of either of the level-I trauma study centers. Second, through trauma transfers from facilities throughout the

region. We will obtain informed consent from all eligible patients. We will consider patients who meet all the inclusion criteria but fail to meet the standards set within the exclusion criteria, including being unable to provide informed consent, as screening failures not eligible to enroll in the randomization-arm. Patients who meet all criteria but are unable to provide informed consent may undergo placement into the observation-arm. Study team members will perform screening upon arrival of open fracture patients to the study center through either of the mechanisms described.

Figure 2. Depiction of application of vancomycin powder to open facture injury.

Study Interventions—Treatment Arm: The application technique is topical application of 2g of sterile vancomycin powder directly to the open fracture site to uniformly cover all visible surfaces of the wound completely and uniformly, including bone edges (Figure 2). If possible and clinically safe, the patient or extremity will undergo repositioning by the clinical staff so all aspects of the wound receive an even coating of vancomycin powder. The entire contents of two-1g vancomycin vials will be applied to the wound by the clinical staff.

The study intervention will take place in the emergency department immediately following participant consent and randomization and after irrigation and debridement. As this study strives for a pragmatic treatment strategy, all patients randomized into the study treatment group will receive a topical dose of 2g of vancomycin powder applied topically, regardless of wound size or severity. We will photograph the injury before and after application of the vancomycin powder and store to facilitate an objective description of the wound and validate study interventions. We will draw peripheral blood samples, 8ml per subject, at approximately 0 (before), 4, and 24 hours (±30 minutes) after topical vancomycin administration for analysis of plasma vancomycin levels.

All subjects will receive usual care, which will vary slightly by site and treating physician, but we expect will include removal of gross contamination, application of loose and dry wound dressing, fracture splinting, and IV antibiotics.

Control Arm: Study participants who undergo randomization to the control group will receive the usual treatment only, which includes prophylactic IV antibiotics. They will not receive local vancomycin or any other antibiotic powder at any time during treatment of the study injury. This study team will not administer any placebo as any attempts to provide a placebo treatment to the wound may unnecessarily increase the risk of infection, complicate surgical debridement and irrigation, and increase risk of adhesion. Subjects enrolled and randomized into this arm will receive only the usual care deemed appropriate by the subject's treating physician.

Observational Arm: Given the polytrauma nature associated with many acute open fractures, we anticipate some potential subjects will be unable to participate in the consent process. Open fracture patients presenting to either study center who are otherwise eligible for the study but are unable to provide consent and do not have a legally authorized representative (LAR) will be enrolled in the observational arm. Patients in this arm will receive no study treatment, only the usual care determined by the institution and treating physician. We will collect only observational data from this group as part of a comparator arm.

Study Endpoints—Primary Study Endpoints: The primary study endpoint is development of deep-space infection at the prophylaxis site within 1 year of the injury. For the purposes of this study, we define deep infections as those requiring operative treatment by the attending orthopedic surgeon.[32] We will determine the degree of infection by documentation through reliable diagnostic means (e.g., wound cultures or tissue culture) and patient care interventions through documentation of procedure and operative notes. If these are not obtained or available, then we will use the determination of tthe attending orthopedic surgeon. If this opinion is not available, then we will utilize the consensus of blinded key study personnel with adjudication by a third reviewer.

Secondary Study Endpoints: The secondary study endpoints include post-operative medical intervention rate, repeat visit rate, readmission rate, and death rate for open fracture infection over a 1-year follow-up. Another

secondary endpoint for this study is the development of local or systemic complications within 1 year of injury. For this study, superficial infections are those not requiring operative treatment.[32] Non-surgical medical interventions include addition or change of antibiotic, bedside application of incision and drainage, needle aspiration, and bedside application of a drain. Repeat visit and readmission rates included in assessment are those unscheduled and related to open fracture-site infection or local site complication. An additional objective of this study is the development of a risk-prediction model for open fracture wound complications.

Study Follow-Up: We will follow up subjects at 5 time points following enrollment. At each follow-up, we will evaluate and record patient conditions and outcomes using medical records review and case report forms. We will assess patients for bone and wound healing and any sign of infection or other complication. We will record any adverse events, infections, complications, antibiotic use relating to the fracture, and protocol deviations. We will also document any missed follow-up or early withdrawal.

We will consider participants as lost to follow-up if no follow-up visits occur at either enrollment sites after the initial discharge from the hospital, if the study team is unable to make contact, and a search of the 2 sites' medical records indicates no follow-up. Participants may also withdraw consent for participation, at which time no further information will be recorded. We will document the reasons for patient withdrawal from the trial.

Protecting Against Sources of Bias: The study team felt the use of a placebo application unnecessarily increased risk of bias and will not be used. Thus, it is not ethically possible to allow blinding for either the patient or the provider. We will block-randomize patients by study site. We will prepare randomization lists using randomizer.org or a similar site using permuted blocks of 10. To minimize risk of bias, a study team member not involved in enrollment will deliver the randomization lists to the principal investigator for implementation at each study site. Following enrollment, we will randomize consented study subjects in a 1:1 ratio to receive either vancomycin powder plus usual care or usual care alone.

Statistical Plan—Sample Size Determination: Data from the surgical literature on lower extremity fractures have shown rates of surgical site infection and osteomyelitis ranging from 14.3%-60.0% in both military and high-energy civilian settings.[36] Infection rates for low-energy civilian open fractures are likely somewhat lower and based on the literature, we anticipate a rate of 20% in the untreated arm. For this expected infection rate, a relative reduction of 50% (absolute reduction of 10%) yields a sample size of 199 per arm. Less substantial absolute reductions would still be clinically significant given the low cost and ease of application of the intervention and the large morbidity burden of open fracture infections. Preliminary statistical power calculations based on the surgical literature and preliminary preclinical studies suggest a target enrollment of 74-107 patients per arm, considering a 25% follow-up attrition rate. Because high-quality data relevant to acute long bone open fractures in humans is not available to provide a sample size with a high degree of confidence, we will utilize an adaptive design in this study with interim data analysis after follow-up completion on the first 74 subjects to re-evaluate the number needed to enroll.

Statistical Methods—Primary Analyses: We will compare the intervention and control groups' background regarding age, race, and sex, using t-tests, Wilcoxon tests, Pearson's chi-square, or Fisher's exact test as appropriate. We will assess the significance of the association between treatment group and the need for surgical intervention for open fracture infection with a repeated measures logistic regression model, with baseline demographic, injury and treatment covariates, as well as indicators for study site (UTHSA, BAMC), time (baseline, 10-21 days, 5-7 weeks, 11-13 weeks, 5-7 months, and 11-13 months), and the treatment by time interaction. We will structure the model as a mixed-effects generalized linear mixed model, and we will test both fixed and random effects using the Durbin-Wu-Hausman test.[37] The aforementioned time frames reference the time of subject follow-up and not necessarily the timing of the event recorded by the study team.

We will handle missing data as per the intent-to-treat analysis. We will assess missing data for patterns of missingness (e.g., Missing completely at random versus missing at random), and we will impute data based on the extent of missingness and degree of randomness. We will remove the treatment by time interaction from the model if found to be not significant and we will summarize the main effect for treatment; otherwise, we will describe the interaction. We will explore interactions between treatment and study site area of interest. Within the treated group, we will assess the significance between the primary outcome and time to drug application with a logistic model. We will analyze all data in the per-protocol cohort of subjects who complete the trial without a protocol violation or loss to follow-up and in the intent-to-treat cohort of all randomized subjects.

Secondary Analyses: We will analyze secondary endpoints including the need for medical treatment for open fracture infection, repeat visit for infection-related

complications, readmission for infection-related complications, and local site complications. We will also analyze the relationship between each of the secondary outcomes and time to drug application with a logistic model, as described above for the primary outcome. Specifically, we will use the Holm step-down procedure to conduct hierarchical significance testing of secondary outcomes to control family-wise type 1 error. We will also compare secondary study aims regarding classifications of open fracture wounds, surgical treatments of the open fractures, standard care antibiotics chosen for care of the injury, and treatment of open fracture infection.

Subgroup Analyses: We will perform secondary analyses *a priori* by fracture classification using the Orthopaedic Trauma Association (OTA) open fracture classification and Gustilo-Anderson open fracture classification.[38] We will also perform a series of exploratory regression analyses seeking significant factors related to outcome complications.

Interim Analyses: The study biostatistician will conduct an interim and safety analysis. At the time of interim analysis, time=0.5, we will conduct a safety analysis using the primary and secondary endpoints. If the analysis shows the potential for safety problems with the intervention, we will inform the study monitor as part of the data safety monitoring plan.

We will use the O-Brien-Fleming procedure[39] to conduct an interim analysis for efficacy on the primary outcome at information-time=0.5 and 1.0 with an overall significance level of 0.05. At the time of interim analysis, we will conduct a futility test. If the statistical test does not exceed the cut point at the interim analysis and if the trial is deemed futile, then the study may be stopped. If the test statistic exceeds the cut point at the interim analysis, then a statistical basis for stopping the study due to efficacy will have been obtained.

Ethical Considerations: We will conduct this trial in accordance with International Conference on Harmonization Good Clinical Practice (ICH GCP), applicable US Code of Federal Regulations, and the CDRMP Terms and Conditions of Award. The principal investigator will ensure no deviations from or changes to the protocol will take place without prior agreement with the Investigational New Drug, funding agency, and documented approval from the IRB. The informed consent documents given to all patients for this study provide sufficient information for patients to make an informed decision about their participation. These documents have been submitted to and approved by the IRB for each clinical study site. We will obtain formal consent from each patient or a legally authorized representative before the patient undergoes any study procedure.

Discussion

Previous studies have evaluated the use of topical vancomycin powder in reducing orthopedic infection in the surgical setting with promising results. These studies are largely retrospective and observational and are primarily focused on reducing post-operative infection in spine surgery rather than infection following orthopedic trauma. The POWDER study is the first clinical trial assessing the efficacy of topical vancomycin powder in reducing infection in open fracture injuries in the acute, emergency room setting. This trial will test whether vancomycin powder applied topically within 24 hours will reduce the risk of deep-space infection in open fracture injuries. This strategy is easily applicable and associated with minimal costs, and may even reduce the overall cost of treatment for open fracture injuries.[25]

There are several strengths of this study. The randomized design of the study ensures definitive answers will be provided to address the scientific questions within the study objectives. Also, as the study uses patients treated at Level-I trauma centers, the results should be strongly generalizable given the represented patient population and the facilities. Another major advantage of this study is the pragmatic and simple nature of the treatment strategy. Patient enrollment criteria are simple and minimal, and most clinical care is provided under the discretion of the treating physician for treatment of these injuries. In addition, vancomycin powder is very inexpensive (approximately US $14 per dose) and easily storable compared with the expenses associated with other new infection prevention medications and treatments. Furthermore, vancomycin is already regularly used by physicians and hospital personnel, so there would be little resistance to regular clinical use if this treatment strategy is proven effective. Moreover, this low cost, field stable intervention is ready for inclusion into the medics' aid bag, the Role 1, the Role 2, and the field hospital settings.

Some potential limitations of this study are associated with the open-label design. First, blinding is not possible; thus, there is a potential for bias. We arrived to this conclusion through clinical knowledge and experience and discussion with subject matter experts. It was impractical to use a placebo powder containing no antibiotics, as this would introduce a foreign body into the wound thereby increasing the infection rate for the control group. We will minimize the potential for bias of individuals assessing for primary and secondary outcome

measurements using standardized and descriptive case report forms and medical records review.

This study should provide valuable and clinically convincing information concerning the use of vancomycin powder during the acute treatment of open fracture injuries. Vancomycin powder, already familiar to emergency and trauma care teams, provides a low-cost and readily available infection prevention strategy. If proven efficacious, vancomycin powder could significantly reduce the incidence of infection after open fracture injury through instituting a minor change in clinical practice. Our results, whether positive or negative, will inform clinical practices during the Role 1 phase of care during future LSCO.

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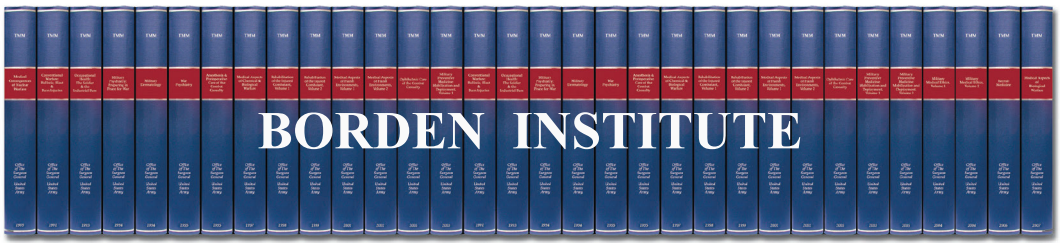

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