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Note from the Editor...

The 2023 summer quarterly is dedicated to all things related to military Physician Assistants (PA). A few of the articles offer some history about the PA's role in the military, as well as the profession's growth. As a whole, the issue demonstrates the broad medical spectrum in which PAs serve and operate.

Is your agency or team involved in noteworthy research? Perhaps your unit has made some exciting or groundbreaking discoveries. Please consider sharing it with the military medical community in a special topic issue. Contact us for more information and planning strategies.

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Physician Assistant/Associate Profession: The Future Is Bright!

COL Bill A. Soliz, DMS, MBA, PA-C

I have great pride in being a US Army physician assistant (PA) and am honored to be part of a growing profession which has experienced tremendous change and modernization since its existence. I vividly recall my first experience with a PA in 1988 when I was a medic in the infantry. I had just arrived to my unit as a new medic and was immediately put on duty to conduct sick call. There was a long line of waiting soldiers, and the platoon medics were signing them in, taking vital signs, performing exams and procedures, writing prescriptions and profiles, and taking directions from this "older soldier" everyone was either calling Doc, Chief, or Sir. My assumption was he was a physician.

I later found out he was a warrant officer and held the title of physician assistant. I was amazed as he went from exam room to exam room to see the patients, and each medic would brief him on what they thought was wrong with the soldiers they evaluated. After several back and forth questions and answers, the PA would then examine the soldier and confirm or deny the medic's clinical conclusion. The PA then took the opportunity to coach, teach, and mentor the medics allowing them to expand their knowledge, physical examination skills, and most of all, clinical decision-making competency. This was built upon with hands-on experience treating soldiers in an austere environment, patrolling, ambush, and raids, as well as mass casualty (MASCAL) exercises with lessons in triage. My first assignment culminated with a deployment to Operation Desert Storm, where I was able to perform due to my training. For me, my PA education started as a medic.

In this special topic issue of *The Medical Journal*, you will read professional, peer-reviewed manuscripts from authors in the US Army PA community. These articles are an example of the quality of content PAs can produce as well as the knowledge, skills, and abilities Army PAs provide for the US Army and Joint Military Force. PAs are the Army's frontline providers who are chiefly responsible for the medically ready force and ready medical force. Not only do they provide direct medical care to soldiers and their families, they are also responsible for the training of their medics, ensuring they are competent to treat disease and save lives on the battlefield to conserve the fighting strength.

The PA profession has come a long way since October 1967, when the first class graduated at Duke University as a certificate program. The 2-year intensive education program was modeled after the fast-track training of physicians during WWII to support the draft. Our country has a long and growing history of a physician shortage (especially in primary care), and it is thanks to this shortage which prompted the genesis of our profession and continues to grow.

The education, training, and scope of practice have evolved over the years since its beginning as a certificate, transitioning to an associate's, a baccalaureate's, then a master's degree as the base qualifying education across the country. There are now many doctorate level PAs in clinical specialties, administration, research, education, and public health. The scope of practice today is not what it was in 1973, when the Army first graduated 400 PAs from its own program. PAs quickly became the battalion primary care providers for all the battalions in the Army. This increase of responsibility and autonomy assisted in the growth and experience in clinical decision making and management of the health and readiness of the Army active force. The profession also evolved in the civilian sector with state laws increasing PA scope of practice throughout the country and increase in the number of PA education and post graduate fellowship programs.

Just like physicians, the PA scope of practice is determined by education and experience, state law, and the polices of employers and facilities. Today, the PA profession and scope of practice has evolved even further. PA professional organizations and advocates have adopted "Optimal Team Practice," which occurs when PAs, physicians, and other healthcare professionals work together

to provide quality care without burdensome administrative constraints.

> *To support Optimal Team Practice, states should: eliminate the legal requirement for a specific relationship between a PA, physician or any other healthcare provider in order for a PA to practice to the full extent of their education, training and experience; create a separate majority-PA board to regulate PAs or add PAs and physicians who work with PAs to medical or healing arts boards; and authorize PAs to be eligible for direct payment by all public and private insurers.*
>
> *Like every clinical provider, PAs are responsible for the care they provide. Nothing in the law should require or imply that a physician is responsible or liable for care provided by a PA, unless the PA is acting on the specific instructions of the physician.*
>
> *American Academy of Physician Associates: https://www.aapa.org/advocacy-central/optimal-team-practice/*

On March 21, 2021, Governor Spencer Cox of Utah signed into law major PA modernization legislation, enacting a number of improvements to PA practice: removing the requirement for physician supervision and delegation of services agreement, repealing the prohibition of PAs independently billing a patient—now allowing for direct pay, which makes the PAs responsible for the care they provide. Utah has essentially adopted Optimal Team Practice. Utah has joined North Dakota and Wyoming, becoming the third state to remove onerous supervision restrictions on PA practice.

On May 24, 2021, the House of Delegates from the American Academy of Physician Associates (AAPA) passed a resolution affirming "physician associate" as the official title of the PA profession. As the organization representing the PA profession, American Academy of Physician Associates (AAPA) is implementing the title change. Full implementation will take some time as the process is complex and involves state and federal governments, regulators, employers, as well as a host of national organizations and PA programs. The title change directly addresses the common misperception PAs merely "assist" physicians, causing the patient and community confusion thinking PAs are medical assistants or technicians. It is in the best interest of patients and the healthcare system for PAs to hold a professional title to ensure clarity about the work of PAs.

The future of the Army PA is bright. The profession has proven its value on the battlefield after the recent 2 decades at war being one of the most deployed AMEDD AOCs. War has an enduring nature demonstrating political and human dimensions, uncertainty, and a contest of wills. However, the character of warfare is ever-changing. The future battlefield will be different as we understand how growing technology adds to the multi-domain complexity and fighting a near-peer competitor. On the conflict continuum, we anticipate our future fight to be large-scale combat operations which will present the greatest challenge for Army forces. With conditions of great complexity, chaos, fear, violence, and uncertainty, operations for certain will be intense, lethal, and brutal. WWII casualties are the closest comparison our nation has experienced.

This creates challenges and capability gaps for Army medicine to resolve. I can assure you Army PAs are on this task. Army PAs have been heavily involved in the innovation and experimentation of future battlefield capabilities. Finding unique solutions to continue to evacuate the wounded, clearing the battlefield in a contested environment, designing novel capabilities to push far-forward to support the tactical maneuver mission, and return soldiers to duty. For the first time in Army medicine history there is a PA serving as the Army Futures Command's Director of Medical Capability Development Integration Directorate (MED CDID) and a PA as Medical Center of Excellence's Director of Fielded Force Integration Directorate (FFID). The majority of Army PAs have prior Army service as an enlisted solider or officer, some medical and some not. Their prior service and experiences define our Army PA motto well, "From the Line, For the Line."

If you are interested in becoming an Army PA and contributing to our Army mission, you can find the details on how to apply at https://recruiting.army.mil/armypa/.

Army Medicine is Army Strong!

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The Continued Misadventures of Intentional C4 Ingestion: A Case Cluster

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Abstract

Several published case reports describe the intentional ingestion of cyclotrimethylenetrinitramine, more commonly referred to as Composite-4 (C4), by military personnel. This putty-like explosive material, used for breaching operations, can produce euphoric effects through polyisobutylene; however, the additional ingredient of Research Department Explosive (RDX), or "Cyclonite," can cause significant central nervous system disruption resulting in seizures. We report a unique case cluster of active-duty personnel with intentional C4 ingestion and wide-ranging symptoms, including seizures. Unit personnel discovered this cluster after progressive patient presentations. This report illustrates the spectrum of C4 ingestion effects, as well as the need for investigation to ensure prompt medical evaluation and management of those suspected of consumption.

Keywords: toxic ingestion; toxicology; explosives

Introduction

Cyclotrimethylenetrinitramine, commonly referred to as Composite-4 (C4), is a putty-like explosive material used for breaching in military operations. The addition of polyisobutylene, which constitutes 2.1% of C4, has traditionally been studied for its euphoric properties soldiers sought for recreational use, with Vietnam-era reports of intentional C4 ingestion seeking a euphoric "high" similar to ethanol.[1-4] However, approximately 91% of C4 is made from Research Department Explosive (RDX), or "Cyclonite," which gives C4 both its explosive and malleable properties but can cause central nervous system (CNS) disruption.[2,3] Modern reports of intentional C4 ingestion illustrates prior recreational use replaced by a perceived "rite of passage" for professional advancement in professions using explosive materials.[2,4] Here, we report a unique case cluster of active duty personnel with intentional C4 ingestion and wide-ranging symptoms.

Case 1

A 19-year-old, otherwise healthy, active duty male presented to a civilian emergency department (ED) for a witnessed, unprovoked seizure described as tonic-clonic convulsions lasting approximately 5 minutes, which started while waiting for a live-fire exercise. On initial evaluation at a field aid station, his initial Glasgow coma scale (GCS) score was 9 (eye: 2, motor: 4, verbal: 3), then given 1L intravenous (IV) bolus of 0.9% saline, with additional 5% dextrose in normal saline, administered during rotary wing evacuation to the ED. On arrival, vital signs reported blood pressure 113/55 mm Hg, heart rate 60 beats per minute, 16 respirations per minute, oxygen saturation 100% on room air, and an oral temperature of 96.6 °F. Repeat GCS showed improvement to 14 (eye: 4, motor: 6, verbal: 4) and exam was otherwise unremarkable. Laboratory testing was notable for an anion gap acidosis of 21, glucose of 212 mg/dL, and CO2 of 16, with additional findings of proteinuria, glucosuria, and trace

ketonuria. Non-contrast computed tomography of the head showed no intracranial hemorrhage or significant masses, and an electrocardiogram (ECG) showed a normal sinus rhythm without conduction delays or ischemia. After several hours of observation, the patient was released. Approximately 7 hours after initial field presentation, the patient suffered a second witnessed tonic-clonic seizure lasting approximately 5 minutes, and was flown back to the same ED. Vital signs were within normal limits and largely unchanged from the previous visit, and repeat laboratory and ECG evaluation found no significant additional findings. After being given an IV bolus of levetiracetam 1,500 mg, 4mg of IV ondansetron, 30mg of IV ketorolac, and 500 mL of IV 0.9% saline, the ED discharged the soldier again with an additional prescription for levetiracetam.

Figure 1. Images depicting sizes of intentional ingestion involving Case 1 (right), and Case 2 (left) relative to a common quarter and dime coins, respectively.

The following day, a unit inquiry found multiple witnesses stating they saw the soldier and others intentionally ingest various amounts of C4 as part of a dare. The soldier admitted to ingesting a "quarter-sized" amount (approximately 2.5 centimeters diameter), or an estimated 3.5g of RDX, a few hours prior to his initial seizure (Figure 1). Upon discovery, the unit medical team contacted a nearby military treatment facility (MTF) toxicologist and ED, and the soldier was voluntarily evacuated by helicopter for direct intensive care unit (ICU) admission and neurologic observation. His work-up continued to be unremarkable. He received no pharmacologic interventions and was discharged after 48 hours of observation.

Case 2

Approximately 8 hours after the initial presentation of the Case 1 patient, a 25-year-old, otherwise healthy, male presented to the same field aid station complaining of ongoing nausea, vomiting, and abdominal cramping over a 12-hour period. He endorsed approximately 12 episodes of non-bloody, non-bilious emesis. Initial vital signs were within normal limits, and aside from a single episode of non-bloody, non-bilious emesis during evaluation, a focused evaluation found no tenderness, distention, rigidity, or abnormal bowel sounds of the abdomen. After being given a 1L bolus of IV Lactated Ringer's and 4mg of IV ondansetron, his nausea improved. He tolerated oral ingestions, and he was discharged to his unit with recommendations for 24-hours of quarters. Approximately 12 hours after discharge, Case 1 identified the soldier as also intentionally ingesting C4. The soldier admitted to eating a "pea-sized amount" (5-8mm diameter) and was immediately evacuated to the same MTF for ICU admission and monitoring. He was discharged after 48 hours of observation without pharmacologic intervention.

Cases 3 & 4

During the course of the unit inquiry, 2 additional young males, ages 23 and 24 years-old, were identified by the initial patient as intentionally ingesting small amounts of C4. On initial evaluation, over 24 hours after the first patient presented, both individuals stated they intentionally ingested sparse amounts, described as "flakes off of the fingertips" at the same time as the first cases. Although both were asymptomatic and had an unremarkable prehospital evaluation, they were evacuated to the same MTF for comprehensive evaluation in the ED to include metabolic and toxicology testing, ECG, and neurology and toxicology assessment. After repeat evaluation proved unremarkable, and consideration for the small amounts ingested and proximity to presentation, ED clinicians discharged both individuals in consultation with neurology and internal medicine.

Discussion

Modern reports of intentional C4 ingestion exist, but are mostly from foreign countries, while only 2 domestic cases are cited since the Vietnam War era, each from a single military installation in Texas.[2-6] Both reports occurred within the last 5 years, and detail intentional C4 ingestion due to perceived social or professional indicators, completely separate from previously described recreational euphoria-seeking behavior.[2,4] Therefore, this impulse appears to be a modern phenomenon. This case cluster is unique in supporting a new perceived professional motivation for ingestion, but also illustrates indication for epidemiological-style investigation of witnesses and nearby persons, as unit inquiry revealed other individuals with varying symptoms proximate to a common intentional C4 ingestion event, furthering concerns for a modern evolution in toxic ingestion motivation.

Concerns about C4 ingestion center on its CNS pathology through non-competitive inhibition of gamma-aminobutyric acid A (GABAA) chloride channels by cyclonite.[2-4,7] Toxic cyclonite effects on GABAA result in seizures, the most common symptom documented in C4 ingestion literature, while other noted symptoms and evaluation findings involve the CNS as well gastrointestinal, renal, and cardiovascular systems (Table 1).[2-5,7] Multiple authors advocate in military patients with

new seizure onset, C4 toxicity should be suspected, and if proximal exposure is found, require admission.[2-4] Weight-based exposure for C4 toxicity has been hypothesized, but no definitive threshold exists and should not be cited for reassurance on initial evaluation.[5,6] Patients may exhibit diverse symptoms; however, the primary case in this cluster underlines a falsely reassuring initial evaluation (despite recent history), which led to initial discharge. Other modern cases illustrate status epilepticus occurring sometimes as long as 16 hours after an initial unremarkable evaluation, necessitating multiple anticonvulsive interventions and even protective intubation.[2,4-6]

Table 1. Symptoms and evaluation findings of C4 ingestion.[1-7]

Symptoms	Exam Findings	Laboratory Findings
General: fever, lethargy, weakness	**General:** fever, lethargy	**Hematologic:** leukocytosis
Gastrointestinal: Nausea, vomiting	**Cardiovascular:** Sinus bradycardia, hypotension, sinus tachycardia	**Chemistry:** Metabolic acidosis, elevated BUN, CK, lactate
Neurologic: Seizures, headache, confusion, hyperirritability, dizziness	**Neurologic:** Seizures, confusion, hyperreflexia, clonus	**Urinary:** Hematuria, myoglobinuria, proteinuria
Urinary: hematuria	**Gastrointestinal:** Abdominal tenderness	

BUN: blood urea nitrogen; CK: creatinine kinase

Treatment of C4 ingestion is largely supportive and primarily focused on seizure control. Previous literature focuses on the use of benzodiazepines including as-needed dosing of diazepam 5-10mg IV and lorazepam 1-2mg IV, with additional considerations for phenytoin or fosphenytoin.[2-4,6] A loading dose of levetiracetam 1,500mg IV or orally with continued 500-1,000mg twice daily dosing can additionally be considered.[4] In refractory cases, a propofol infusion should be considered.[2,4] Authors note C4 exhibits slow gastrointestinal transit, and therefore activated charcoal and gastric lavage can be considered if patients are not at risk for aspiration, as well as bowel clearance with polyethylene glycol for further decontamination.[2,6] Fluid resuscitation and urine output monitoring are emphasized for possible acute renal injury, especially given soldiers coming from a field environment where dehydration may already be present.[2,3,6] While the patient may be stabilized in the prehospital or ED setting, progression to ICU is ultimately warranted in all acute symptomatic patients for neurologic monitoring given the risk for seizure.[2-4] Other dispositions should be done in consultation with a multidisciplinary team.

Conclusion

An evolution in C4 ingestion trends to garner some sort of perceived professional rite warrants further emphasis, especially in the setting of falsely reassuring initial evaluation and ultimate risk for seizure. This case cluster uniquely highlights multiple modern aspects of intentional C4 ingestion, including the medical indication for admission and monitoring in all patients with new onset seizure and potential exposure to C4, as well as both a medical and professional responsibility to probe close contacts of the patient for possible other consumers to prevent poor outcomes.

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From Assistant to Associate: A PA Professional Evolution

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Fifty years after the US Army initiated its first class of physician assistants (PA), the American Academy of Physician Assistants voted to officially change the professional title to physician associate. The name transition aims to codify a continued evolution in both civilian and military practice. Although the organization passed the resolution on 24 May 2021, and subsequently changed its name to the American Academy of Physician Associates (AAPA), state licensures and federal systems have yet to pass resolutions or laws adopting similar title updates. Regardless of the historical context of "assistant" or contemporary change to "associate," the Army PA continues to provide critical prehospital care and frontline medical readiness.

Understanding the impact of physician shortages in the mid-twentieth century, the Army sought to capitalize on the newly-formed PA to further extend medical care, leveraging experienced medics into its own PA school in 1971. Initially, the "assistant" aspect of PA attempted to simplify the practical relationship between a small group of experienced medical professionals and their supervising physicians. However, over the last 50 years the civilian and Army PA professions grew substantially in both sheer size as well as credibily earning increased scope of practice. The responsibilities of Army PAs grew far beyond routine primary care, including medic training and advanced prehospital trauma management. During this time, the training and commensurate academic credit evolved as well, from an associate degree to the current master's degree awarded at the Interservice Physician Assistant Program since 2003. In the Army, this education is enhanced by a vast array of advanced training opportunities from tactical care to trauma to special operations.

Reciprocally, Army PAs are no longer simply medical extenders. The Army PA profession mission includes serving as the premier proponent and leader of advanced medical care and military medicine in the most remote environments around the world. While a name change to physician associate acknowledges the increased autonomy of modern Army PA, we continue to function and demand a medical hierarchy closely with the collegial leadership of specialty physicians as part of an optimal team practice. As the military pivots towards multi-domain and large-scale combat operations, Army PAs are sought to extend medical care farther into the battlefield environment for immediate stabilization and prolonged casualty care, but this still remains a team environment.

Fifteen years ago, the progression of specialty certificate programs to first-of-their-kind doctoral residencies in emergency medicine, orthopedics, and general surgery, signaled an Army PA professional evolution. In addition to advanced specialty training, these programs demonstrate the Army PA's unique combination of experience with a research focus to advance military medicine forward, from hemorrhage control to surgical practice. These programs serve as an example for civilian institutions, while continuing to progress the PA profession.

While Army PAs strive for professional advancement and recognition on par with our experience and skill, we continue to work in collaboration with our physician colleagues. As the AAPA pushes our professional recognition forward, Army PAs remain vital partners by continuing to demonstrate their indispensable contributions to military medicine. Ultimately, a title can only reflect what the profession offers. Above all, Army PAs must ensure we persist in our evolution to serve the Army Medical Department motto of *Experientia et Progressus* (Experience and Progress) for the betterment of those in our care.

Authors

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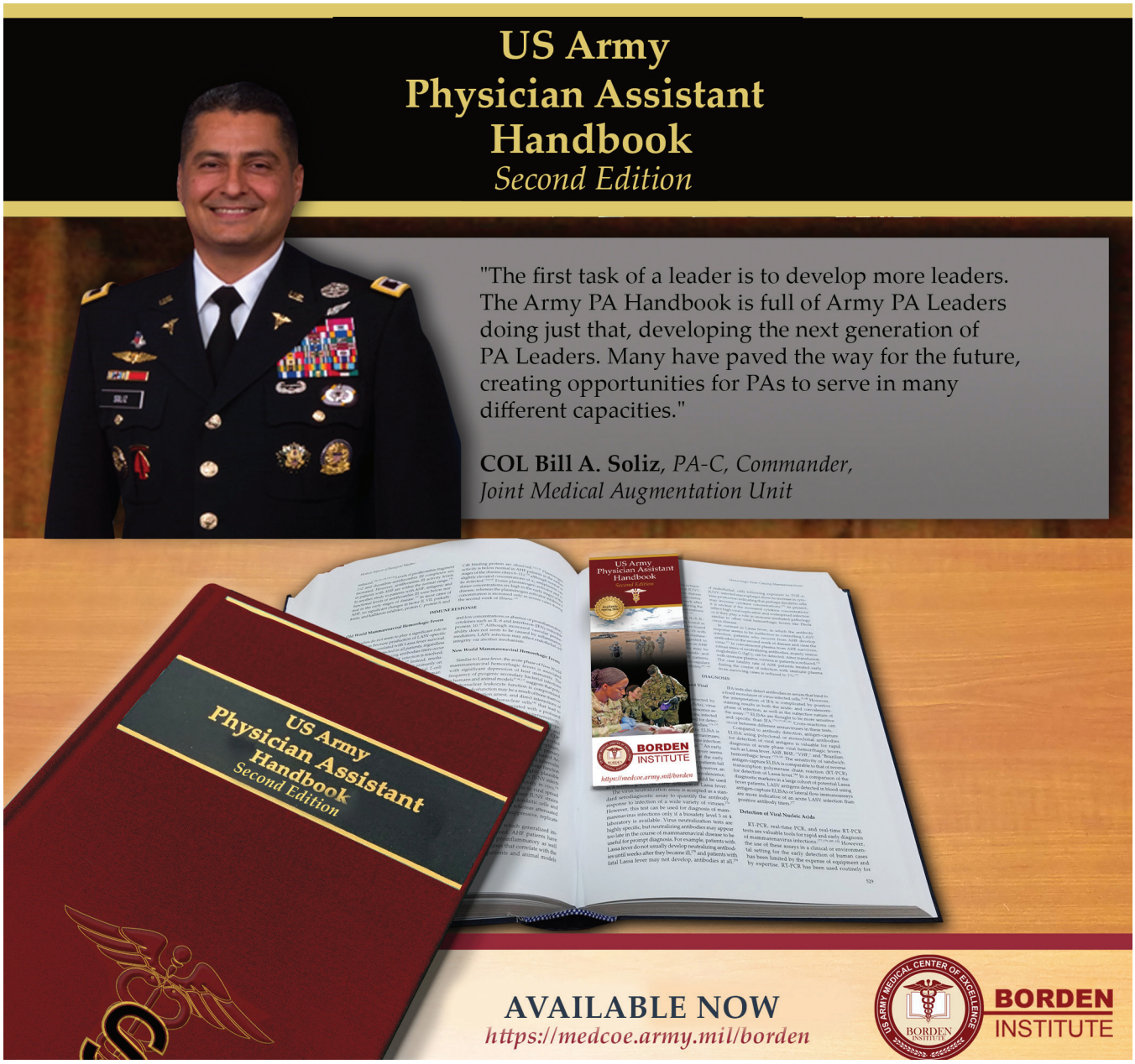
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MRI Predictive Model's Utility in a Recruit Training Environment for Tibia Stress Fractures

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Abstract

Objective: The purpose of the study was to assess the utility of Fredricson Magnetic Resonance Imaging Grading model in predicting return to duty in Marine recruits who sustain tibia stress fractures at Marine Corps Recruit Depot San Diego (MCRDSD).

Materials and Methods: A retrospective review of 106 tibia stress fractures in 82 Marine recruits was performed. A baseline Fredricson grade was assigned, based on magnetic resonance imaging (MRI) evaluation. The electronic health record was reviewed for return to full duty. Non-parametric testing and descriptive statistics were used to evaluate the study population, varying subgroups, and the utility of this model in predicting the return to full duty in the recruit population and any differences based on stress fracture location or training platoon.

Results: The mean return to full duty (RTFD) was 11.8 weeks. The study participants sustained a greater percentage of middle tibia stress fractures (51.2%) and grade IV stress fractures (37.8 %) than other tibia sites and severities. There was a difference in RTFD amongst the Fredricson grades (p=0.001). The median RTFD for grade I stress fracture was 8.5 weeks, the median RTFD for grade II stress fracture was 10.00 weeks, the median RTFD for Grade III stress fracture was 10.00 weeks, and the median RTFD for grade IV stress fractures was 13.00 weeks. As Fredricson grade increased, RTFD increased (p=0.00) although no median RTFD met the Bonferroni correction for statistical significance.

Conclusion: The analysis suggested the Fredricson MRI grade was associated with RTFD in the recruit population. As Fredricson grade increased, median RTFD increased; however, mid-grade stress fractures (i.e., II-III) had similar median RTFD.

Background

General conditioning of recruits consists of running, calisthenics, obstacle courses, and weight training.[1] Military specific training includes 5- to 10-mile load-bearing conditioning hikes, physical fitness testing, and combat fitness testing.[1] This vigorous physical training can vary from less than 2 hours to 21 hours of training daily. The above training tempo has been associated with stress injuries, with injury patterns and the location of stress fractures being associated with the volume and type of training.[1] The etiology of bone stress injuries results from high impact repetitive training and can range from stress reaction to cortical fractures.[2] The highest injury rates tend to be clustered around weeks 1-10 of training, when the vigorous activity levels rise most dramatically.[1] Despite a growing body of evidence to etiology, overuse injuries of the lower extremities continue to have a high incidence rate, long recovery time, and large impact in military training.[3] At a cost of approximately $187.00 per day, per recruit, and attrition rates between 14%-21% for these injuries, the loss in training time and money to the military can be significant.[4]

Health care providers in military sports medicine clinics see high volumes of overuse musculoskeletal injuries, and of these, most overuse injuries fall into the category of lower extremity stress fractures. Stress fractures are

well recognized in military training, with incidences as high as 12% of recruits sustaining these injuries.[5] Tibia stress fractures are a common overuse injury and one of the largest causes of musculoskeletal morbidity in military recruit populations.[5] One challenge with tibia stress fractures, when recruit care is a shared responsibility among health care providers, is developing a standardized and evidence-based approach for the care of recruits. This is especially important, as return to recruit training and graduation rates are highly visible metrics among Navy Medicine and Marine Corps leadership.

Table 1. Fredricson Magnetic ResonanceImaging (MRI) Grading based on MRI findings.

Grade of Stress Injury	MRI Findings
0	No abnormality
1	Periosteal edema with no bone marrow signal abnormalities
2	Periosteal edema with bone marrow edema visible on T2-weighted images
3	Periosteal edema with bone marrow edema visible on T-1 and T-2 weighted images
4a	Multiple focal areas of intracortical signal abnormality and bone marrow edema on both T-1 and T-2 weighted images
4b	Linear area of intracortical signal abnormality and bone marrow edema on both T-1 weighted and T-2 weighted images

Adapted from Validation of MRI classification systems for tibial stress injuries, Kijowski et al., 2012, Am J Roentgenology, 198(4), 878-884.

Prior Theoretical & Empirical Work: Evidence-based clinical approaches are developed to improve patient safety and quality of care.[6] Evidenced-based practice is used on a regular basis within the US Marine Corp (USMC) recruit treatment environment to ensure standardized care among recruits and to improve patient outcomes. For example, in the evaluation of upper respiratory symptoms a standardized sepsis algorithm based on vital signs and time of symptoms will prompt blood work and chest radiographs to ensure high-risk infections are not missed. The utilization of similar evidence-based approaches in the clinical management of lower extremity stress fracture follows other treatment approaches in the military recruit environment. Due to the increase in sensitivity and specificity of magnetic resonance imaging (MRI) over other imaging modalities, MRI models now exist in the literature aimed at rating the severity of stress fractures and providing a prognostic tool in stress fracture healing and return to sport or activity. Additionally, many clinicians now designate it the gold standard for evaluating stress fractures over conventional radiographs and even bone scintigraphy.[7]

Fredricson et al[8] developed an MRI model which notes specific findings on T1 weighted and T2 weighted imaging, as well as short tau inversion recovery (STIR) sequences, which correlate to a stress fracture severity grade (Table 1). Identification and grading can assist in deciding treatment, including time of protected weight bearing, rehabilitation needs, and finally return to sport activity in stress fracture management. Time to return to training for Grade I-IV stress fractures can vary from 4-16 weeks on average.[9] Currently there has been little research about the use of these imaging models in assessing length of time required to rehabilitate military recruits from stress fractures and return them to pre-injury states, as most studies using imaging models have been applied to collegiate athletes.[10] In military population, estimates of return to training often rely on epidemiologic data, clinical exam, and symptom severity.[5] Few prognostic tools have been used to assist in estimating time to return to training for these injuries. Standardized and evidence-based approaches to treatment using validated MRI predictive models for tibia stress injuries could be similarly useful if applied to military recruit populations.[10]

Relevant Literature & Current Views: MRI predictive models have been used outside of the military as prognostic tools in stress fracture management, with the Fredricson MRI model as one such model.[8] MRIs can be highly sensitive and specific for the diagnosis of stress fractures.[11] Additionally, studies have shown the prognostic value of MRI imaging-based grading scales for stress fracture management. MRI is not only more sensitive in demonstrating early stress changes to bone than conventional radiographs and bone scans, but also more specific than bone scans.[12] This sensitivity and specificity in early identification of injury and subsequent grading can assist in deciding treatment, rehabilitation needs, and return to activity.[9] More importantly, these models have been validated for predictive value and reliability in civilian athletic populations.[10] Dobrindt et al[13] found this prognostic value is especially true for stress fractures at low-risk sites and for high-grade versus low-grade lesions. Although of useful prognostic value as described, Kijowski et al[10] felt the mid-Fredricson grades could be combined. Their feeling was RTFD in the grade II-III regions could be similar, allowing for an abbreviated Fredricson grading classification system.

One paradigm shift is using a validated MRI predictive model and standardizing a clinical approach with this model could lead to more uniformed treatment and be predictive for return to training time among military recruits. As Nye et al[14] concluded, bone stress injuries in military training environments are common and MRI should be the imaging study of choice after conventional radiographs in working up this common recruit condition. Fredricson approach to grading stress injuries and predicting return to training in other stress fracture sites, such as tibia stress fractures, has not been extensively researched outside of the civilian or collegiate athlete population. As such, utilizing the Fredricson model in a military recruit population to see if the model provides an evidence-based approach to stress fracture

management would expand the current literature.

Using validated MRI predictive models, and standardizing the clinical approach with these models, may lead to a more evidence-based approach, uniformed treatment, and return to training among military recruits who sustain stress fracture injuries. Therefore, the objective of this study was to apply the Fredricson MRI grading model to tibia stress fractures in a military recruit population, in the setting of a standardized rehabilitation program, to see if the model was an accurate predictor of time to return to full duty (RTFD).

Table 2. Participant descriptive statistics and platoon classification.

Participant Characteristics			
Age	Mean	Median	SD
	19.5	19.0	1.72
	Percent	Frequency	
Ethnicity			
White	65.9	54.0	
Black	2.4	2.0	
Hispanic	3.7	3.0	
AI or AN	2.4	2.0	
Not Reported	25.6	21	
Platoon Class			
MRP	65.9	54	
BMP	34.1	28	

SD: Standard Deviation, AI: American Indian, AN: Alaskan Native, MRP: Medical Rehab Platoon, BMP: Basic Marine Platoon, BRP: Basic Rehab Platoon.

Methods

After institutional review board approval was obtained from A.T. Still University and Navy Medical Readiness and Training Center San Diego, a retrospective review was performed on the electronic health record (EHR) of patients diagnosed with a tibia stress fracture, at a single sports medicine clinic at MCRDSD from July 2019 to December 2019 and dropped for rehabilitation. In the recruit-training environment, this rehabilitation drop occurs to the Medical Rehabilitation Platoon (MRP) or the Basic Marine Platoon (BMP) depending on where a recruit is in their training cycle. In reviewing the EHR, a dataset was created containing demographic data such as age and ethnicity, training platoon classification (MRP or BMP), tibia stress fracture location, concurrent injuries, RTFD, and whether the individual ultimately completed training or was separated from the military following a standardized and phased rehabilitation process.

Participants: Patients included in the study were those with a documented tibia stress fracture with a baseline MRI (n=82). There were 58 participants with unilateral tibia stress fractures and 24 participants with bilateral tibia stress fracture, which results in 106 total stress fractures among the 82 participants. Patients were excluded if they did not have tibia stress fractures or a baseline MRI. The MRI was used to assign a Fredricson Grade based on findings on short tau inversion (STIR) and T1 and T2 weighted images. A fellowship trained musculoskeletal radiologist evaluated the MRIs. The Fredricson grade was assigned by 3 fellowship trained military musculoskeletal providers including the first author, using Fredricson criteria, and with grading agreed upon by consensus. All musculoskeletal providers, except the first author, were blinded to demographic data and only reviewed the MRI for grading.

Study Measures: The independent variable being investigated was the Fredricson MRI grade and the dependent variable being investigated was the RTFD, measured in weeks. Each participant's Fredricson grade was retrospectively reviewed and recorded via the Picture Archiving and Communication System (PACS) from their injury baseline. Each participant's RTFD was retrospectively reviewed and recorded from the Electronic Medical Record (EMR). The time to return to training was easily extracted from the EMR, as each recruit has an encounter documented RTFD, which signifies the day they pass their physical fitness assessment, post injury, and return to an active training status.

Additional information collected included the participant's age, self-reported race and ethnicity, whether they had waivers for service limiting conditions prior to recruit training, and tibia stress fracture location. Tibia stress fracture location was recorded as the proximal tibia (plateau and meta-diaphysis), mid-tibia diaphysis, and distal tibia. Finally, concomitant injuries or stress fractures other than the tibia, lack of return to duty, and the platoon classification were recorded.

Platoon classification is important as it relates to graduation status. If the individual is still in a recruit status, they are earlier in their training pipeline, and are dropped to the medical rehabilitation platoon (MRP). Conversely, if the individual graduated, they have completed their training pipeline, and they are dropped to the basic marine platoon (BMP).

Data Analysis: All statistical analysis was performed using commercially available software, and the first author manually entered all data. Frequencies and means were performed for age, ethnicity, training platoon, and stress fracture location. Tests of normality were performed for RTFD including the Kolmogorov-Smirnov test as the number of participants supported this as the statistical test of choice.[15] The data analyzed met the criteria for non-normal distribution; therefore, the statistical analysis was nonparametric in nature.[15] Kruska-Wallis test was used to determine any significant difference in RTFD amongst the Fredricson grades. As the Kruska-Wallis test was significant (p=0.001), a Mann-Whitney

U test was used post-hoc to compare the median RTFD amongst the Fredricson grades and see which grades differed. A Bonferroni correction was completed to avoid a type I error (p=0.008) and control for potential alpha inflation in multiple tests.[15] The main outcome measurement was RTFD, with the goal of seeing how closely the initial assigned Fredricson Grade correlated to the RTFD. All tests were 2-sided and a p value of 0.05 was considered statistically significant.[15]

Table 3. Tibia stress fracture characteristics.

Tibia Stress Fracture Characteristics		
Fracture Location		
Proximal	33	40.2 %
Middle	42	51.2%
Distal	7	7.0%
Fredricson Grade		
Grade I	20	24.4%
Grade II	16	19.5%
Grade III	15	18.3%
Grade IV	31	37.8%

	Fredricson Grade at Fracture Location			
	Grade I	Grade II	Grade III	Grade IV
Proximal	1	2	8	22
Middle	16	12	7	7
Distal	3	2	0	2

Results

Sample Characteristics: MCRDSD is exclusively male aged 17-28 years, as MCRDSD currently only accepts male recruit applicants from the western two-thirds of the US. A small percentage of recruits, who have obtained age waivers, may be greater than 28 years old; however, no participant in this study fit this criterion. Table 2 summarizes the participant descriptive statistics, including platoon classification. Patients included in the study were those with a documented tibia stress fracture with a baseline MRI (n=82). The majority of participants were between the ages of 18 and 20 years with 32.9% 18 years of age, 26.8% 19 years of age, and 16% 20 years of age. Participants between 22-26 years represented 17% of the sample. Patients were excluded if they did not have tibia stress fractures or lacked a baseline MRI. The participant ethnicity as listed by electronic health record demographics section included 54 White, 2 Black, 2 Hispanic, 3 American Indian or Alaska Native, and 21 not reporting an ethnicity. The mean age of the population was 19.54 years with a minimum age of 18 years and a maximum age of 26 years. Of the 82 participants who met inclusion criteria, 54 recruits were in the Marine Rehabilitation Platoon (MRP), and 28 participants were in the Basic Marine Platoon (BMP).

Stress Fracture Characteristics: There were 58 participants with unilateral tibia stress fractures and 24 participants with bilateral tibia stress fracture, which resulted in 106 total stress fractures among the 82 participants. Table 3 summarizes the overall tibia stress fracture characteristics of the study participants. There were 33 proximal tibia stress fractures, 42 middle tibia stress fractures, and 7 distal tibia stress fractures. In reviewing Fredricson grades, there were 20 Grade I fractures, 16 Grade II fractures, 15 Grade III fractures, and 31 Grade IV fractures. Of the 82 total participants, Fredricson Grade I-III stress fractures were almost evenly distributed among the participant sample (24.4%, 19.5%, 18.3%, respectively). Higher Grade IV stress fractures represented almost 37.8% of the sample participants stress injury.

Comparison of Median RTFD amongst Fredricson Grade: The mean time to RTFD was 11.80 weeks (range, 2 weeks to 49 weeks), and the standard deviation was 6.93. The Kruska-Wallis test was 15.87 (p=0.001), which means there was a difference in RTFD amongst the Fredricson grades. Post Hoc testing utilizing Mann-Whitney U revealed the median RTFD for grade I stress fracture of 8.5, a median RTFD for grade II stress fracture of 10.00, a median RTFD for Grade III stress fracture of 10.00, and a median RTFD for grade IV stress fractures of 13.00. There were differences in median RTFD between Fredricson grades, the most significant being between lower as compared to higher-grade stress fractures and higher-grade stress fractures as compared to each other. Mid-grade stress fractures had similar median RTFD. However, as outlined in Table 4, the differences did not meet the Bonferroni correction for statistical significance.

Table 4. Mann Whitney U values.

	Median RTFD	MWU	*P - value*
Comparison Grade I to II	8.5 v/s 10.0	120.500	.207
Comparison Grade II to III	10.0 v/s 10.0	97.5	.379
Comparison Grade III to IV	10.0 v/s 13.0	146.500	.042
Comparison Grade I to IV	8.5 v/s 13.0	133.00	.011
Comparison Grade II to IV	10.0 v/s 13.0	138.00	.013
Comparison Grade I to III	8.5 v/s 10.0	87.00	.035

MWU: Mann Whitney U

Discussion

Tibia stress fractures are common overuse injuries in the military. Developing a standardized and evidence-based approach to the care of recruits who sustain stress fractures is essential as return to recruit training and graduation rates are highly visible metrics. MRI predictive models have been used outside of the military as prognostic tools in stress fracture management, and the Fredrickson MRI model is one such model. This study retrospectively reviewed the use of the Fredricson grading model for tibia stress fractures in a military recruit population and tried to assess if the model was a good predictor of the severity of the injury and a prognostic tool for RTFD.

Findings: This study built upon previous research supporting the idea the higher the Fredricson MRI grade, the longer the RTFD for tibia stress fractures. Statistical analysis suggested in this study sample, as Fredricson Grade increased so did RTFD in a positive linear manner. There also appeared to

be a difference in the median RTFD between Fredricson groupings, as the higher the Fredricson grade the larger the difference in median RTFD. Therefore, the recruit population seems to be consistent with their civilian athlete counterparts. Although there appeared to be a correlation of Fredricson grade to RTFD, RTFD within the participant sample was not normally distributed. This non-normal distribution may be secondary to the population sample being exclusively male and primarily Caucasian descent. This study was also consistent with the literature, as on average the RTFD for Grades III and IV stress fractures matched Fredricson estimation of return to activity based on graded severity. For example, Fredricson Grade III stress fractures in recruits had a mean RTFD of 11.8 weeks, and Fredricson model estimates return to activity for this grade at approximately 12. Similarly, Arendt et al[12] compared RTFD based on fracture severity and site, and found high-risk and high-grade fractures had a longer RTFD than low-risk and low-grade fractures.

Unexpected Findings: RTFD for Grade I and II fractures did not match Fredricson predictive model, as with these lower-grade injuries, the study sample nearly doubled Fredricson estimated RTFD. This is counter to conclusions in the previous studies by Dobrindt et al,[13] Kijowski et al,[10] and Ramey et al[11] as they reported MRI models seem more predictive in stress fractures of lower grade and in lower risk regions. Additionally, mid-grade stress fractures, such as grade Fredricson grade II and III seem to have similar median RTFD. This result may reinforce the findings by Kijowski et al,[10] which suggest the Fredricson mid-grade stress fracture may be combined into a single abbreviated Fredricson classification system. Although mid-tibia stress fractures were common and represent lower risk stress fractures in comparison to their proximal counterpart, the mid-tibia stress fractures in our participants were of a surprisingly higher severity stress fractures grade (III and IV) and represented a large number of the overall stress fractures in the participants.

Comparison to Prior Research: Fredricson et al[8] MRI model notes specific findings to grade stress fracture severity, hoping that grading can assist in deciding treatment and return to activity in stress fracture management. Models by Arendt, Nattiv, and Kaeding, use similar approaches regarding T1, T2, and STIR sequence findings to provide a stress fracture grade, which then correlates to the severity and potential time to healing.[12,16] More importantly, these models have been validated for predictive value and reliability in civilian athletic populations.[10] The RTFD findings for military recruits in this study were consistent with Fredricson grading models; however, it appeared the model showed greater predictability for mid-tibia stress fractures and higher-grade stress fractures in the recruit population.

Theoretical & Practical Application/Recommendations: First, a clinician must be able to give recruits a reasonable time estimate of their expected recovery. The time estimate is important as recruits can feel a sense of decreased motivation when they sustain stress fracture injuries and must delay their training. Providing them with a timeline and a goal can address that decrease in motivation. Second, providers meet weekly with Marine leadership to update them on these injured recruits' rehabilitation progression. This model allows providers to give leadership more accurate estimates of return to training for injured recruits, contributing to planning and resource management. Finally, if we see changes (increases or decreases) in the amount or severity of tibia stress fractures from historical averages, especially in the setting of changes in Marine training regimens, we may be able to work with Marine leadership to make changes in training for safety and preventive measures.

Limitations: This study contributes to the research which validated MRI predictive models for tibia stress injuries may be useful if applied to military recruit populations.[10] Additionally, knowledge of the severity of stress fracture via validated grading models may assist military leadership in predicting time to return to training, monetary cost, and redirect resource to this area to increase prevention strategies for tibia stress fractures. A few limitations of this research must be mentioned.

First, the large majority of the participants were white males; therefore, many other demographics and females were under-represented in this study. As females and non-white males were under-represented or not represented in this study, the result may not be as generalizable to these populations. Second, anecdotal evidence suggests there are varying motivational factors among the MRP versus BMP training categories. This motivational variation may change length of RTFD, independent of Fredricson grade, thereby skewing RTFD in these sub-groups. Pope et al,[4] in evaluating attrition in Basic Military Training for example, found injury in training was greatly associated with attrition risk. Although some recruits were discharged as a direct result of their injuries, many were discharge for difficulty coping, reduced motivation to continue after an injury, or concomitant injury.[4] This trend seems to persist among military recruits over the years. Third, the Fredricson grade was applied by fellowship trained sports medicine providers, based on musculoskeletal (MSK) radiologist MRI description and fitting this into Fredricson grading criteria. Grading applied directly by MSK radiologist

may increase the accuracy of the Fredricson grading process. Fourth, as the first author was not blinded to patient information upon initial data collection, this could introduce selection bias; however, the author tried to combat this through grading by consensus as discussed in the methods section.

Important to note is MRIs may not always be in all clinical settings to apply as discussed above, making it difficult to apply this evidence-based practice in all environments.

Future Research: As the Marine Corps Recruit Depot San Diego will be integrating female recruits by February 2021, future providers may consider a similar study in female recruits. Future research projects could also consider greater integration of musculoskeletal radiologist to apply Fredricson grading for a more accurate assessment of Fredricson grade. In taking into account motivation as a confounding variable, future research may include a qualitative study of the effect of motivation on RTFD, controlling for stress fracture grade and location. As stress fracture location and platoon classification could be additional predictors of RTFD; each of these variables could be evaluated to see if there was a statistically significant difference in RTFD amongst these 2 groupings. The importance of comparing tibia stress fracture locations is the bone matrixes in these locations are different (Trabecular versus Cortical bone) and can have an effect on the healing outcomes.[8] The importance of comparing platoon classification is the further a recruit is in the training pipeline, often the greater the severity of their stress fracture and subsequent Fredricson grade. Therefore, further evaluation including regression may control for categorical difference in BMP versus MRP or biomechanical differences in stress fracture location to better assess predictive value of Fredricson grading to RTFD.

Conclusions

As discussed, tibia stress fractures are significant sources of morbidity in the recruit-training environment. Concurrently, this results in a significant cost in loss of training time and money, and, therefore, is a highly visible metric for military leadership. In this environment standardized and evidence-based approaches to treatment are essential. MRIs can be highly sensitive, specific standardized approaches for the diagnosis of tibia stress fractures and have shown prognostic value in stress fracture management. As a validated model, the Fredricson model may be used for the clinical management of tibia stress fractures. Although the Fredricson model has been applied to civilian populations, very few studies use this model as a prognostic tool in the military environment. This study demonstrated as Fredricson grade increased, median RTFD concurrently increased. Additionally it demonstrated the Fredricson MRI classification system provided a positive linear correlation to RTFD in the recruit population, and may lead to a more evidence-based predictor of return to training among military recruits who sustain stress fracture. In addition to prognostic value, the clinical benefit of utilizing MRI predictive models in the recruit population could include goal setting, motivation, communication with Marine leadership, and training safety.

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Platelet-Rich Plasma Improves Strength and Speed of Recovery in an Active-Duty Soldier with Isolated Injury to the Lateral Collateral Ligament of the Knee: A Case Report

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Abstract

Ligamentous injuries of the knee occur in the military, but constitute an overwhelmingly disproportionate number of medical discharges, which can be due to prolonged recovery through traditional use of physical therapy (PT) and other non-operative modalities. The use of platelet-rich plasma (PRP) may substantially increase the speed of recovery and patient outcomes but is little explored for less common isolated ligamentous injuries, such as the lateral collateral ligament, especially in active-duty populations. We describe the use of PRP in a young, otherwise healthy active-duty male to treat an isolated LCL injury with significant positive outcomes. These findings support consideration for early use of PRP in similar cases to improve recovery timelines and aid in return to duty.

Keywords: knee sprain; prolotherapy; injury

Introduction

Military occupations are physically demanding, creating high risk for injury with subsequent loss of work hours and overall personnel readiness.[1-3] While knee injuries such as ligament sprains are common throughout military populations, their rates peak at only about 3%, yet disproportionately result in more than half of medical discharges due to overly-slow or otherwise insufficient recovery.[1,3-5] Traditionally, rehabilitation for knee injuries involves prolonged use of physical therapy (PT) and a home exercise program (HEP) as initial management, followed with specialized orthopaedic involvement only if the service member fails to adequately progress over time. With specialty consultation, platelet-rich plasma (PRP) is an increasingly popular treatment consideration for soft tissue injuries, using bioactive proteins and growth factors to aid the healing and tissue regeneration.[6,7] While PRP demonstrates growing popularity for musculoskeletal injuries, there is a lack of literature evaluating potential benefits in some ligaments, as well as in active duty populations. We describe the case of an active-duty service member with a less-common isolated lateral collateral ligament (LCL) injury, minimally improving after traditional PT and HEP, with expedited recovery after PRP therapy.

Case

A 33-year-old active-duty male suffered significant pain and swelling of his left lateral knee after stepping in a hole while trail running with a described varus stress and

palpable popping sensation. He reported sporadic giving out in the knee joint and severe pain with lateral movements. He started physical therapy 2 days after initial injury with an initial lower extremity functional scale (LEFS) of 51/80 (Table 1), prompting concern for ligamentous injury, with orders for magnetic resonance imaging (MRI) and HEP. The MRI revealed a partial tear of the LCL extending near the femoral insertion (Figure 1). At 4-week PT follow-up, continued limitations with range of motion (ROM), muscle weakness, and pain were noted. A repeat LEFS noted minimal improvement.

Table 1. Progression of knee scores on evaluation.

Time since injury	2 days	4 weeks	9 weeks	PRP injection	11 weeks	15 weeks
LEFS	51/80	63/80			71/80	
KOOS			58%		84%	90%

LEFS: lower extremity functional scale; KOOS: knee injury & osteoarthritis outcome score

Subsequent evaluation by an orthopaedic physician assistant at 7 weeks post-injury demonstrated tenderness over the LCL and pain with varus stress; although, varus stress radiographs were negative for instability. An initial 42-point knee injury and osteoarthritis outcome score (KOOS) of 58% indicated significant knee-related lifestyle problems, far below expected values of 90-100% seen in healthy military populations.[8] Shared decision-making established a treatment plan of PRP, and the patient received an ultrasound-guided 3-milliliter PRP injection into the LCL at 9 weeks post-injury with continued PT follow-up.

After 2 weeks (11 weeks from initial injury), the patient denied significant knee pain or instability, and stated he could perform heavy-weighted squats and other physical activities without limitations. His KOOS score improved substantially, and he continued PT and follow up in 4 weeks. Subsequent PT encountered noted substantial LEFS score improvement. At final orthopaedic follow-up, 6 weeks from PRP therapy (15 weeks from initial injury), the patient demonstrated full pain-free active range of motion without LCL tenderness or pain with varus stress. His KOOS score demonstrated continued improvement to ranges comparable to healthy individuals.

Discussion

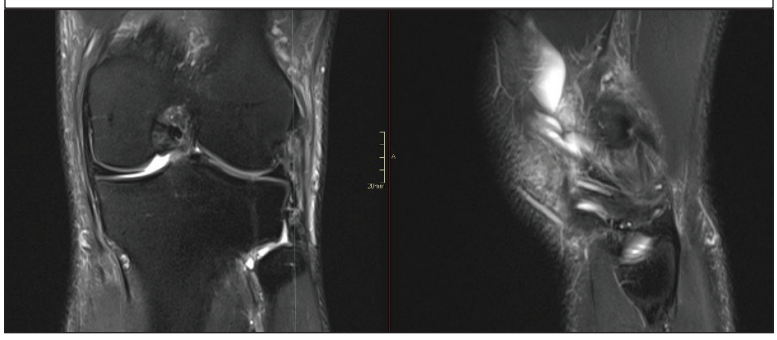
Although the LCL is one of the less common knee ligaments torn, nevertheless significant injury can hinder return to sports (RTS) and the demanding physicality of the military profession.[9] Like other ligamentous injuries of the knee, management largely centers on physical therapy and step-wise progression to RTS. However, especially in active-duty populations, reliance on tempered advancement through standard rehabilitation can pose issues for service members eager to return to full duty, affect unit readiness, and prompt medical discharge. While surgery may be required in some instances, the use of non-operative adjunct therapies, including PRP, are of interest to speed recovery.

Several systematic reviews and meta-analyses describe PRP in non-operative knee injury management with rates of success up to 70-84%; however, these largely focus on anterior cruciate ligament (ACL) injury, as these are most common.[10,11] A 2014 Cochrane systematic review found insufficient evidence to support PRP in any ligamentous injury; however, this included only 7 trials regarding knee injury, 6 from ACL reconstruction and 1 for patellar tendinopathy.[12] While PRP is generally defined as autologous blood with higher platelet concentrations than donor plasma baselines after being placed in centrifuge, heterogenous compositions of PRP injections used in research, some of which are not defined at all, make direct comparisons of treatment for knee injuries difficult.[9,10,13,14] Case reports and small studies show promise for non-operative PRP management in isolated medial collateral ligament (MCL) injuries, with some RTS as soon as 18-31 days.[15,16] At the time of this writing, there are no significant cases or trials detailing the use of PRP in isolated LCL injuries, including in active duty populations.

Conclusion

Although limited in its generalizability, the substantial non-operative expedited improvement demonstrated in an active-duty service member with isolated LCL injury prompts interest in the use of this treatment as an adjunct to traditional PT-based routines. Further research should seek to evaluate other cases and look towards possible trials, given the potential decreased interval for return to duty. he role of PRP use in ligamentous

Figure 1. Magnetic resonance imaging of the left knee demonstrates a partial tear of the lateral collateral ligament extending to near its femoral insertion.



injuries, especially in the knee, remains in relatively early stages, but nevertheless should be considered early in the treatment course rather than after other options are exhausted. The desire for individuals to return to preinjury levels of function, and the ongoing need for optimal military medical readiness, supports continued inquiry into the use of PRP for treating ligamentous injuries.

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Closing the Trauma and Critical Care Gap: A Paradigm Shift through Virtual Reality and Augmented Reality

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Abstract

A nationwide surgeon shortage, particularly with general surgeons and trauma surgeons, continues to plague the civilian and military systems readiness. To fill this shortcoming, we provide a narrative review describing current and potential uses of augmented reality and virtual reality (AR/VR) for synthetic training environments which could significantly improve the Army's wartime medical readiness through improved skills of surgeons and non-surgeon providers. Multiple studies demonstrate the potential benefits of AR/VR in cost, time, and critical medical skills for enhanced care delivery. While encouraging, the novelty and relative youth of AR/VR platforms requires further prospective validation as the data for its use as a training adjunct is limited. Nevertheless, state of the art simulated training platforms like AR/VR which mimic surgical trauma cases and review critical surgical skills could help enable a transformation of non-surgeon providers to quickly augment current surgeon personnel shortages.

Keywords: augmented reality; virtual reality; hololens; COSCCC; ARSC; MHS

Introduction

Skilled surgeons and trauma specialists are essential for high quality, wartime medical care. While military medicine has enjoyed some well deserved fame for the unprecedented survival rates in our nation's recent conflicts, it belies the reality casualty estimates for any future near peer war will be catastrophic and will require an unprecedented scaling of highly skilled surgical professionals; professionals who are increasingly difficult to produce and train.[1] A paradigm shift to how military medicine recruits, resources, and trains surgical personnel is needed if we are to meet the demands. A materiel solution which integrates virtual reality and augmented reality (AR/VR) to create a synthetic training environment could significantly improve the Army's war time readiness by increasing fine motor surgical skills at scale, enabling task shifting of select surgical procedures to non-surgeon providers with potential cost savings to shorten this surgical capability gap. By enabling the diffusion of surgical and critical care skills, synthetic training platforms increase readiness while facilitating sustainment of these skills, ultimately resulting in a highly prepared military medical enterprise.

Capability Gap

Today, the nation's ability to respond to a precipitous increased wartime demand for damage control surgery is inadequate and at odds with the National Security Strategy's priority to support biomedical innovation.[2] According to Vice Admiral Bono, former Defense Health Agency (DHA) director, "the military's surgical shortages represent a microcosm" of a larger national problem and contribute to the military's inability to surge these precious skills through recruitment.[3] The nation as a whole is experiencing a significant shortage of surgeons. The US produces about 1,000 general surgeons a year, yet needs 1,700 to maintain the minimal ideal surgeon to patient ratio of 7.[4] The military surgical training pipeline experiences similar shortages, yet the demand for such professionals in the near future is significantly higher. In 2016, the National Trauma Data Bank accounted for approximately 860,000 civilian trauma admissions with an overall mortality rate of 4.3% with most cases considered to have minor to moderate injury severity scores.[5] In contrast, the injury severity scores in recent armed conflict have been consistently higher resulting in mortality outcomes of about 6%.[6] At the same time, war games conducted by Pentagon officials estimate casualties in the realm of 20,000 per day with far more complex injury patterns than what was seen in recent combat operations.[7] The Army currently maintains less than 150 general surgeons, with less than 30 trained trauma surgeons.

Lengthy training timelines for surgery residents and the increasing skill demands are historically problematic and contribute to the capability shortage. The average number of years for a general surgeon to operate independently is 5, and about one-third of the nations' general surgery graduates are unable to perform operative care independently.[8] Generally speaking, a surgeon needs to perform anywhere from 50 to 100 cases of a single procedure to be considered proficient, though these requirements increase with the evolving complexity of medicine.[9] In the Army, these issues are arguably magnified. Surgical readiness in the Army is decaying primarily as a result of disproportionately low operative case volume within the military health system (MHS).[10,11] For instance, a civilian trauma surgeon may average upwards of 500 cases a year to stay proficient, while military surgeons do about one-fifth of the volume.[3]

Meanwhile, the skills of other trauma specialists in the military have evolved almost independently and are neither being fully leveraged to augment the surgeon nor to close the capability gap on the battlefield. Today's non-surgical physicians, physician assistants, and special operations medics are already performing most of the essential trauma care services defined by the International Association for Trauma Surgery and Intensive Care (IATSIC).[13] These include the 75th Ranger Regiment novel Ranger O Low Titer (ROLO) whole blood program, successfully executed in late 2019.[14] These forward employed advanced lifesaving tasks, coupled with timely medical evacuation (MEDEVAC) are largely responsible for unprecedented survival rates within recent conflicts.[1] More importantly, it is also proof that task shifting of these critical skills is effective. Expanding the surgical scope and skills of these non-surgeon providers can extend individual surgeons' operational reach and task shed procedural and patient management burdens of a surgeon caring for daunting volumes of critical patients. Unfortunately, without a synthetic training platform, non-surgeon providers will similarly lack case volumes to justify an expansion of their scope of practice and benefit battlefield wounded. Luckily, this nascent technology is already making its way into medical industry and military medicine.

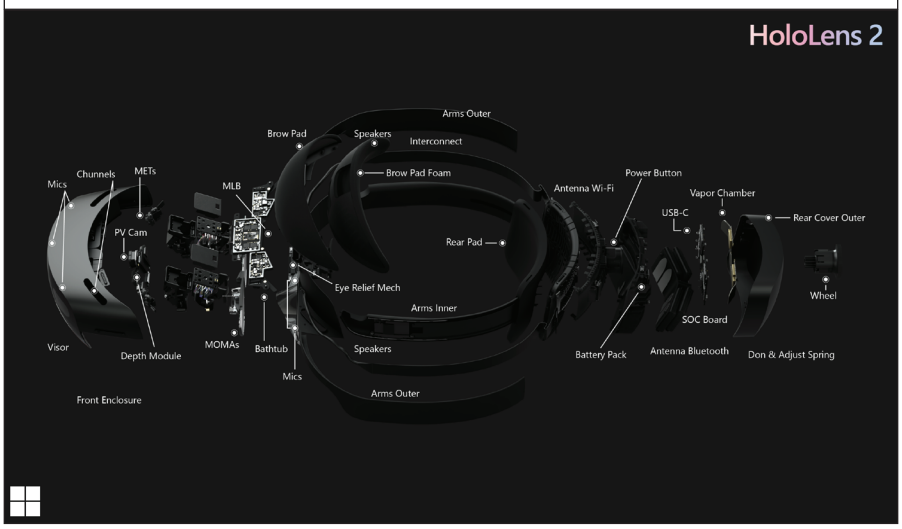
AR/VR for Surgical & Resuscitative Skills

Rapid advances in biotechnology and medical devices continually contribute to medical training programs nationwide, including laparoscopic procedures through dedicated hospital simulators for skills practice. AR/VR represent untapped potential as adjuncts which can further refine individual skills, transform medical infrastructure, and notably reduce training costs.[14] While critics cite concerns for funding, the initial investment in technology will indisputably reduce training costs dramatically. While the cost to live train a surgeon may exceed $400,000 dollars, high-fidelity AR/VR systems cost as little as $3500 dollars to train low- and medium-complexity medical tasks.[14,15] One 2020 pilot study, by Harris et al, demonstrated a non-surgeon provider using commercial AR systems could successfully perform a damage control procedure with guidance from a remotely located surgeon.[16]

Much like a flight simulator can reduce the cost of training for a pilot, AR/VR can dramatically cut the costs of surgical training with equitable training value for proficiency while potentially decreasing training timelines. This type of material solution is an opportunity for the larger military medical force to increase surgical case volumes, albeit simulated, and thus increase the pool of trained professionals. The Army must be the leader in this field for not only reasons of self preservation, but because no other organization in the world will see the type and volume of trauma cases so close to the point of injury Army clinicians will see in combat.

Current alternatives to live human surgery, such as

Figure 1. Microsoft Hololens 2 components, an untethered holographic computer (Holographic Glasses/National Stock Number: 7010-01-665-6349).



cadaver labs and live tissue models, while great training modalities, demonstrate finite use and often do not create accurate interfaces of live patient care, further burdened by social and political pressures.[17] The technology proposed to replace these must replicate, as much as possible, the tactile nature of patient care to simulate the operating room and the physiologic responses to the surgeon's interventions. AR/VR platforms are potentially far more versatile, effective and affordable than cadaveric training aids. From instrumentation to sensory tactile and visual inputs, AR/VR technology has matured over the years to the degree it could simulate numerous aspects of an operating room by immersing the clinician into a virtual environment. One 2021 study by Riley et al evaluated the learning and performance outcomes in tactical combat casualty care training across 3 AR/VR modalities demonstrating significant improvement in system efficacy, receptivity, and suitability. The application in surgery can be anything from increasing visual capacity with radiological imaging to enabling machine learning which can automate recommendations and highlight critical structures in the patient of which the surgeon must be mindful. Some AR/VR platforms are a compact mixed hologram and physical environment headset which feature world-scale positional tracking, providing substantial portability, so the surgical specialist could practice anytime, anywhere to include in contingency or deployed environments (Figures 1 and 2).

For this solution to be acceptable, research is needed to demonstrate the platform in fact improves surgical skills and reduces medical errors. If not trained properly, proficiency may not actually improve and medical errors are more likely to occur on a real patient. One World Health Organization (WHO) study which analyzed the challenges of increasing complexity in medical technology reported improper training and longer learning curves are the primary contributors to adverse events when using similar technologies. Nonetheless, in their current state, their contribution to training is compelling. Anecdotally, research demonstrated medical students given AR/VR training for orthopedic bone fracture repair completed the procedure 20% faster, with 38% more steps performed correctly than those without AR/VR training.[9] The Defense Advanced Research Programs Agency (DARPA) Accelerated Computation for Efficient Scientific Simulation (ACESS) program, while not necessarily a AR/VR surgery platform, shows promising features by leveraging advances in optics and additive manufacturing and other emerging tech to develop hybrid analog and digital approaches to create an "intrinsically parallel physical processes."[18] Successful ACESS technology development demonstrates the potential to produce foundational tech for specialized scientific computing systems such as a trauma surgery simulator.

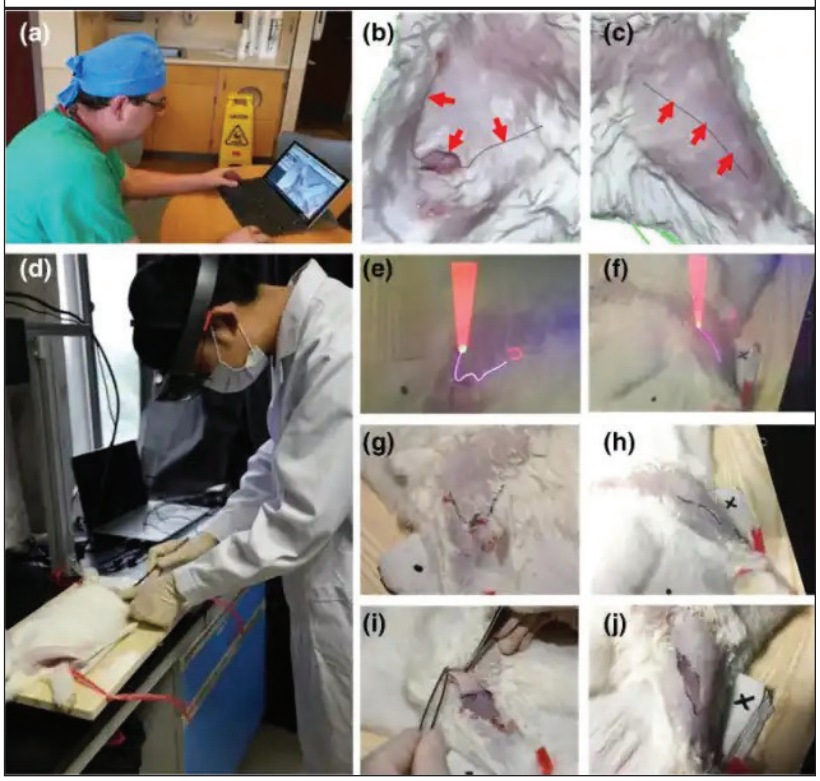
Admittingly, fully trained surgeon deficits may not be completely mitigated by AR/VR technology. We are at the crossroads in which we must consider a serious investment in the training of our non-surgeon providers. Policy and doctrinal changes which drive offloading certain aspects of trauma care to non-surgeon providers is an emerging concept to be taken seriously and considered in informing our doctrinal training tasks as the profession continues to shape individual critical task lists and training priorities. Proof of concept opportunities in safe training environments for the expansion of non-surgeon provider scopes of practice should continue to be pursued, similar to the US Army/Baylor University general surgery physician assistant (GSPA) doctoral program. These GSPAs exhibit a strong lineage of augmenting surgical teams, performing trauma and critical care tasks in both austere and hospital environments.[19] Nevertheless, the scope of training is mostly non-operative with limited primary assist roles in real time surgical care. An AR/VR adjunct to training is a logical next step in this type of program and could very well not only enable but also catalyze this paradigm shift of

scaling surgical and critical care capabilities within our military. Through this type of model, the Army over time, could train more trauma surgeons and their augmentees and consequently justify an increase in authorizations of its surgical units, making this notion a reality.

Conclusion

Army medicine is experiencing a crisis to recruit, train, retain, and effectively employ medical personnel to resource medical facilities within the DHA. Simultaneously, it is unprepared to perform its doctrinal warfighting function at scale. Meanwhile, experts such as those of the committee on surgical combat casualty care (COSCCC) submit ongoing military operations dictate the need for continued development of austere resuscitative surgical care (ARSC) capability.[20] The next combat environment will be met with contested air superiority, and our ability to move patients to definitive surgical care will be woefully inadequate.[21] This advanced care will need to be pushed far forward if we are to address potentially survivable combat deaths, deaths that could be mitigated through pervasive implementation of surgical and critical care training in the form of VR and AR programs. At this juncture, however, AR/VR requires further prospective validation through greater fielding across both surgeon and non-surgeon cohorts for study. Without prioritization of these synthetic training platforms, surgeon shortages will continue to plague medical readiness and preparations for future conflicts.

Figure 2. Hololens depictions of in-vivo skin grafting and and fasciotomy surgery carried out on the thighs of the rabbit using HoloLens based telementoring system. (a) An experienced surgeon at Ohio State University Wexner Medical Center (OSUWMC) is watching the 3D model of the thighs and drawing the optimal trajectories for skin grafting surgery and fasciotomy. (b) and (c) The 3D models of the left and right thighs and the annotation guidance by the experienced surgeon at OSWMC are transferred back to the HoloLens device at University of Science and Technology of China (USTC) for guided skin grafting surgery and fasciotomy respectively. The black curves pointed by red arrows show the optimal surgical trajectories defined by the experienced surgeon at OSUWMC. (d) An inexperienced trainee wearing the HoloLens device is carrying out the surgical operations. (e) and (h) The HoloLens device displays the actual surgical scene superimposed with the augemented reality scene for skin grafting (left) and fasciotomy (right) surgeries. (f) and (i) Following the virtual scalpel guidance, the trainee draws the predefined trajectories in black ink on the left and right thighs for grafting and fasciotomy surgeries respectively. (g) and (j) The actual dissected skin tissues for skin grafting and fasciotomy surgeries. (Holographic Glasses/National Stock Number: 7010-01-665-6349).



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Impact of a Novel Biplane User Interface on Ultrasound-Guided Vascular Access Performance: A Prospective, Randomized, Crossover Study

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Abstract

BACKGROUND: Controversy exists regarding the optimal methods of employing ultrasound to enhance vascular access. A novel user interface which dynamically displays transverse (short) and longitudinal (long) planes simultaneously was developed to optimize ultrasound-guided vascular access. This study aimed to assess the impact of this novel biplane axis technology on central venous access performance.

METHODS: Eighteen volunteer emergency medicine resident physicians and physician assistants were recruited from a single center to participate in this prospective, randomized crossover study. Following a brief instructional video, participants were randomized to perform ultrasound-guided vascular access using either short-axis or biplane axis approaches first, followed by the opposite technique following a brief washout period. Time to cannulation was the primary outcome measure. Secondary outcome measures included success rate, posterior wall and arterial puncture rates, time to scout, number of attempts, number of needle redirections, participant cannulization and visualization confidence, and interface preference.

RESULTS: Short-axis imaged approach was associated with a significantly shorter time to cannulation (34.9 seconds versus 17.6, $p<0.001$) and time to scout (30 versus 49 seconds, $p=0.008$) when compared to biplane-axis imaging approach. No significant differences were noted when comparing first pass success, number of attempts, number of redirections, and posterior wall and arterial wall puncture. Participants' cannulation/visualization confidence and axis preference both favored the short-axis imaging approach.

CONCLUSION: Further studies are needed to assess the clinical value of novel biplane axis ultrasound imaging in the performance of ultrasound-guided procedures.

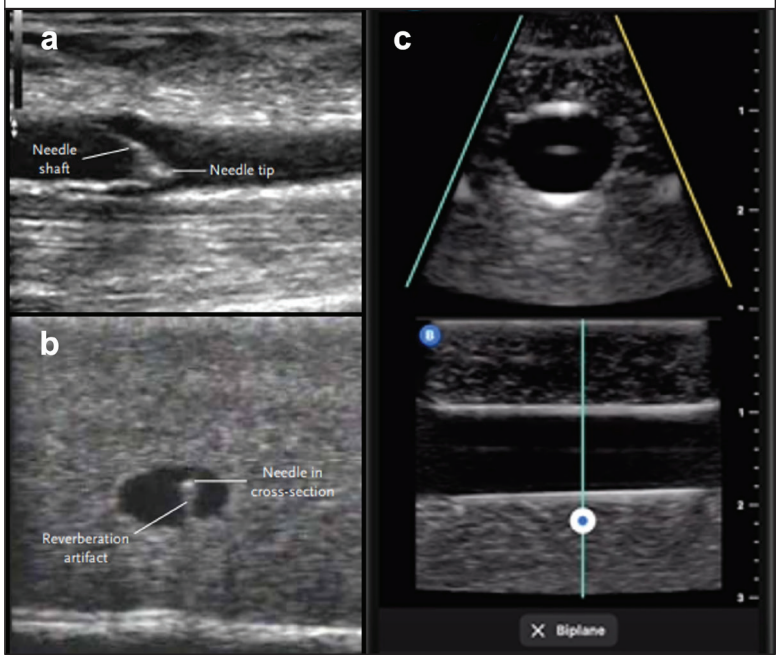
Keywords: central venous access; ultrasound; cannulation; emergency medicine; performance; POCUS; vascular access

Introduction

Critically ill patients require prompt venous access for medication administration and fluid resuscitation.[1,2] While peripheral intravenous (PIV) access is used as part of a broad safety net of patient care in the hospital and prehospital environments, emergency medicine (EM) clinicians, including physicians and physician assistants (PA), often perform central venous catheterization (CVC) in the severely ill and injured as part of critical care management. Traditionally, CVC largely relied on anatomical landmarks involving the sternocleidomastoid muscle; however, the advent of an ultrasound guided approach demonstrates improved procedural accuracy, efficiency, and safety.[2-5] With a decrease in complication rates as much as 71%, an ultrasound guided

approach for CVC is now widely accepted as the standard of care.[6-8]

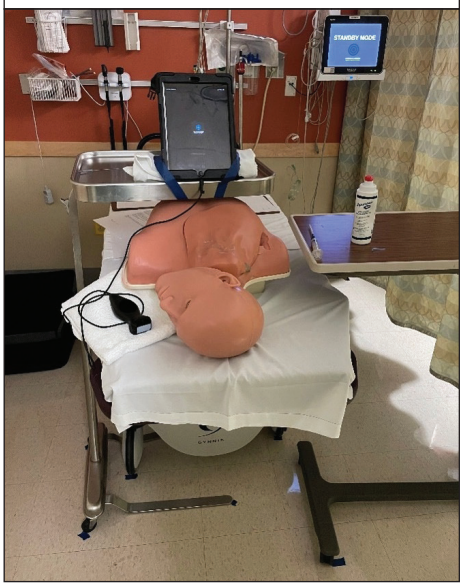
Figure 1. Ultrasound vascular phantom views with (a) long axis view, (b) short axis view, and (c) biplane axis view with short and long axis views at the top and bottom of the image, respectively.



The short-axis (SAX) and long-axis (LAX) views are the primary US transducer orientations described for CVC placement in literature. The SAX view transversely cuts across the target blood vessel with an out-of-plane view of both the vessel and approaching needle, while the LAX permits views of the vessel and needle longitudinally or in-plane (Figure 1). Both views find support as the optimal view perspective in prior studies. However, previous literature is conflicting on preference and does not demonstrate repeatable evidence to confer a significant benefit of one axis over another.[5,6,9-14] At the time of this writing, there is no clinical consensus or societal guidelines advocating for a superior US view for CVC.

A novel biplane axis (BPX) utilizes dynamic, simultaneously displayed views of both the SAX and LAX on a single screen for enhanced context when performing venous procedures like CVC. This novel feature theoretically improves speed and accuracy of vascular access by eliminating end-user need for mid-procedure graphical user interface manipulation to toggle between views if desired. Yet, despite its combination novelty and relevance to vascular access, few studies evaluate the BPX for CVC.[15,16] Previously published literature evaluating BPX compared it solely to an SAX view; however, these studies occurred in either a planned operative setting or for obtaining only PIV access, thereby limiting its applicability across other populations and settings including EM.[15,16]

Figure 2. Standardized investigation set-up.



Given CVC is most likely to be performed by EM clinicians in an emergent setting, it is therefore imperative this provider population be targeted for BPX evaluation compared to more traditionally utilized single views like SAX. We sought to conduct a prospective, randomized crossover trial of EM clinicians to evaluate for the speed, success, and safety of CVC utilizing BPX compared to SAX ultrasound views.

Methods

The Regional Health Command-Pacific Human Protections Office determined protocol #221059 exempt from Institutional Review Board review. We conducted a prospective, randomized, crossover study utilizing a convenience sample of active duty US Army EM clinicians stationed at Joint Base Lewis-McChord, Washington working at the Madigan Army Medical Center (MAMC) emergency department. Participants had previously completed or were participating in an EM training program, to include physician and PA residencies. All residents and faculty at this facility completed an ultrasound training program prior to this study and were credentialed for ultrasound procedures in accordance with the American College of Emergency Physician guidelines, including ultrasound-guided vascular access. Participants were excluded if they were clinicians rotating in the EM from other medicine services, medical students, or non-clinicians.

Participants received a brief introduction to the study, then watched a brief commercial instructional video from the BPX-capable transducer manufacturer describing the BPX view and the tablet application/user interface. Volunteers completed a brief demographic questionnaire,

then were randomized using a random number generator to decide whether they performed CVC first using the BPX or SAX view. Each volunteer completed the procedure in a fully functional vacated patient care bay within the Madigan Army Medical Center (MAMC) emergency department.

Table 1. Participant Demographics.

Characteristic	Total (%)	Median (IQR)
Gender		
Male	13 (72)	
Female	5 (28)	
Age		28 (27,29)
Medical Training Level		
PGY-1	9 (50)	
PGY-2	4 (22)	
PGY-3	2 (11)	
EMPA	1 (6)	
Attending	2 (11)	
Prior US access experience		9 (5, 46)
Total CVC		7 (5, 29)
IJ CVC		

CVC: central venous catheterization; EMPA: emergency medicine physician assistant; IJ: internal jugular; PGY: post-graduate year; US: ultrasound

Within the bay, investigators utilized a gurney with standardized set-up for simulated patient, bed height, instrumentation placement, and equipment setup. Volunteers utilized a standard 18-guage central venous needle attached to a 10-milliliter syringe with a hole drilled near the tip to prevent suction forces from distorting the manikin. All participants performed CVC on a commercially available adult central line training manikin (Figure 2.) The investigation team employed a commercially-available multifrequency transducer for all imaging in this study, connected to a standardized 10" tablet in rugged cases with integral stands, with settings (to include depth and gain) optimized for vascular access with SAX or BPX. Investigators provided participants with a 10-milliliter syringe connected to a standard central venous 18-gauge catheter overlying a 20-gauge introducer needle assembled by investigators. Researchers disabled the syringe vacuum by drilling a small hole near the tip to prevent aspiration during the procedure, as well as limited distortion of the manikin model for subsequent trials.

Volunteers were allotted 2 minutes to adjust available equipment without using the ultrasound probe on the manikin. Volunteers then began to scout the manikin with the ultrasound probe, and began cannulation immediately once they felt able to achieve access. Once complete, participants moved out of the bay while other volunteers proceeded, then returned to perform the other view.

The primary concern for this trial centered on time to cannulation, defined as the introduction of the aspiration needle into the targeted vessel. Investigators agreed on a mean clinically important difference (MCID) of 13 seconds to obtain venous cannulation based on the only published research evaluating for a difference in time between BPX and SAX for CVC.[15] Using a crossover design, a power analysis established a minimum sample size of 10 volunteers completing both views to establish significance.

Scouting time was measured as the time spent locating pertinent anatomy and location for cannulation, starting once the volunteer placed the transducer on the manikin and stopped once the needle touched the manikin skin. Time to cannulation was measured as the time from the needle touching the skin to the time the volunteer verbalized they were complete. Investigators also recorded the number of attempts, number of needle redirections, if posterior venous wall or arterial wall puncture occurred. Procedure success was defined as successful passage of a guidewire through the established catheter and observing its intraluminal location with ultrasound.

After finishing CVC with both SAX and BPX views, volunteers completed a post-participation survey, including self-assessment on confidence utilizing a 0-100 Bandura scale. They additionally answered questions utilizing Likert items to assess perceived ease of use for the SAX and BPX views.

Investigators performed statistical analysis using a commercially available statistical software program. Continuous variables are reported as means with standard deviations, ordinal variables as medians and interquartile ranges, and nominal variables as percentages and numbers. Continuous nonparametric data (time to scout, time to cannulation, number of attempts, number of redirections, and confidence on a 0-100 Bandura scale) are analyzed with a Wilcoxon-signed rank test. Binary data (user preference, success, posterior and arterial wall puncture) are analyzed using the Chi-Square test, and ordinal nonparametric data (Likert items) using a Wilcoxon-signed rank test. Statistical significance was set as $p \leq 0.05$.

Results

Over 3 non-consecutive days, a total of 18 EM clinicians completed the study, without any lost to incomplete data collection or withdrawal. The median age of volunteers was 28 years old, with most clinicians being EM resident physicians in their first year of residency, and reported experience using ultrasound for vascular access and CVC (Table 1). Participants demonstrated a significantly shorter mean time to cannulation utilizing the SAX compared to BPX view (34.9 seconds versus 17.6, $p<0.001$), as well as time to scout (30 versus

49 seconds, p=0.008) (Table 2). Other measures, including first pass success, number of attempts, number of redirections, and posterior wall and arterial wall puncture, did not demonstrate significant difference. Notably, there were no findings of significant period or sequence effects (Table 3).

Table 2. Short-axis (SAX) versus biplane axis (BPX) access comparison.

	SAX (n = 18)	BPX (n = 18)	*p*-value
Mean time to cannulation (sec)	34.9	60.6	**0.001**
Mean time to scout (sec)	30.0	49.0	**0.008**
Number of attempts	18	20	0.157
Number of needle redirections	2	6	0.461
Success (%)	83	78	0.674
Posterior wall puncture	4	2	0.371
Arterial wall puncture	0	0	1.00

Participants reported significantly greater confidence on average using SAX view for visualizing the internal jugular vein anatomy and performing cannulation compared to BPX (89.4 versus 77.8, p=0.019 and 84.7 versus 69.7, p=0.003, respectively) (Table 4). Similarly, participants reported higher overall preference for SAX view over the BPX view.

Discussion

Our study found significantly shorter times to cannulation and scouting times when EM clinicians used the SAX view compared to the BPX for CVC, without significant differences in complications or other measures of success. Additionally, EM clinicians' preference and confidence favored the SAX view over the BPX view when performing ultrasound-guided central venous axis.

Limited prior research supports the use of BPX over SAX for venous access.[15,16] However, the dearth of studies conducted previously is further limited by their respective sample populations, thus comparison to these studies as well as their generalizability overall is difficult. Prior findings of faster cannulation times with BPX compared to SAX (23.7 versus 10.4 seconds, p=0.0001) by Panidapu were notably performed by a single anesthesiologist in an operative setting, and are therefore limited given this lone population with a non-randomized methodology of alternating SAX and BPX views for CVC compared to our larger population of EM clinicians completing CVC with view randomization.[15] Our opposing results are relatively strengthened by the lack of significant period or sequence effect found in our study. Similarly, previously identified higher rates of posterior wall puncture with SAX compared to BPX (26% versus 4%, p=0.022) were not replicated in our study.

Our findings also contradict the favorability of BPX views for PIV access reported by Convissar, albeit with additional differences in methodology and population.[16] Convissar and colleagues evaluated intensive care unit nurses solely for PIV catheterization in an inpatient population rather than CVC performed in our study. Although significant, the average difference in time between BPX and SAX views (27.8 versus 36.6 seconds, p=0.003) was smaller, as was the difference in rates of posterior wall puncture (1.5% versus 0.4%, p=0.001).[16] Notably, investigators provided the sample population with training for each view, which could influence results in a naïve population. Direct comparison is difficult given these methodological factors; however, the findings of this prior study should only be translated into other populations, including the EM setting, with caution.

Clinical ultrasound employment has expanded considerably in recent years, led primarily by machine miniaturization, image quality, user interface advancements, and decreased machine cost. This expansion has resulted in a wider range of variously skilled clinicians employing ultrasound at the point of care. Emerging technologies designed and purported to enhance the clinical experience, either via improved clinical end-user performance or via patient-focused outcomes, should be carefully assessed for their value in the clinical setting. This study highlights the importance of gathering clinically-focused end-user feedback and performance data with emerging technologies prior to their widespread adoption.

This study's primary limitation is its small sample size derived from a single medical center. Similarly, while enabling investigators to efficiently evaluate multiple vascular access attempts, the use of a manikin for vascular simulation limits applicability to in vivo application.

Table 3. Period and sequence effect on time to cannulation.

Method	Median time to cannulation (sec)	*p*-value
Period 1 (SAX1 & BPX1)	51.9	0.58
Period 2 (SAX2 & BPX2)	43.6	
Sequence SAX1 (SAX1 & BPX2)	50.3	0.82
Sequence BPX1 (TM1 & DA2)	45.7	

BPX: biplane axis; BPX1: biplane axis performed first; BPX2: biplane axis performed second; sec: seconds; SAX: short axis; SAX1: short axis performed first; SAX2: short axis performed second

Table 4. Volunteer confidence and preference comparison.

Characteristic	SAX	BPX	*p*-value
Confidence			
Visualize IJ	89	78	**0.019**
Cannulate IJ	85	70	**0.004**
Preference	5	4	**0.001**

BPX – biplane axis; IJ – internal jugular (vein); SAX – short axis

The use of the BPX may be less familiar to some participants given its relative novelty compared to more traditional views like SAX; however, the utilization of instructional periods as performed in some prior literature could likewise confound results with undue influence on participants' knowledge and perception of ultrasound views and devices. Our study utilized a single ultrasound device for imaging, and results may not be generalizable to other commercial devices capable of providing a BPX view. Finally, although participants were able to adjust the equipment, initial standardizations of equipment height and user interface settings may not be optimal for all. Participants may have felt compelled to keep equipment in the initial settings for efficiency in a research focused on procedural speed, potentially confounding results.

Conclusion

Timely and uncomplicated vascular access in CVC is imperative in the EM setting and must be balanced with procedural safety to prevent complications. When employing ultrasound for visualization, EM clinicians perform CVC cannulation faster and more confidently with the SAX view compared to the BPX view, without significant differences in complication rates. This study highlights the importance of end-user performance and feedback data prior to integration of novel technologies intended to enhance patient care. Future research should expand these methods to a larger, multisite, in vivo population among more heterogeneous cohorts for validation.

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Neuroprotection and Therapeutic Implications of Creatine Supplementation for Brain Injury Complications

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Abstract

Creatine supplementation has not been researched for Traumatic Brain Injury (TBI) extensively, but studies suggest potential as a neuroprotective agent and potential treatment for brain-injury complications. Patients suffering from TBI experience mitochondrial dysfunction, neuropsychological burden, and deficits in cognitive performance due to malperformance of brain creatine levels, diminished brain Adenosine Triphosphate (ATP) levels, glutamate toxicity, and oxidative stress. In this systemic review, the current available research is reviewed to examine the effects of creatine on common sequalae of TBI within children, adolescents, and mice. Past and present data still lacks the knowledge of creatine supplementation for the adult population and military members during TBI. PubMed was searched for studies which assessed the correlation between creatine supplementation of TBI complications. The search strategy yielded 40 results, of which 15 articles were included in this systemic review. The results of the review supported an apparent understanding creatine does offer an obvious benefit to patients suffering from TBI and post-injury complications under specific guidelines. Time and dose dependent metabolic alterations seem to be only exceptionally prevalent when given as a prophylaxis or if given acutely. Results are only clinically significant after a month of supplementation. Although patients may need many therapeutic treatments to recover from TBI, especially in acute resuscitation, creatine shows superior efficacy as a neuroprotective agent in battling the chronic manifestations which lead to oxidative stress and cognitive function post brain injury.

Keywords: creatine; traumatic brain injury; mTBI; concussion; brain injury

Introduction

Creatine, a commonly used supplement in sports nutrition for performance enhancement, has shown a potential correlation in neuropathology, mild traumatic brain injury (mTBI), TBI, and post TBI complications.[1] This study's main objective is to review the currently available literature to determine the neuroprotection qualities and potential therapeutic implications of creatine supplementation in the treatment of brain injury complications. This review will provide information gathered from studies regarding creatine's cellular role and importance, evidence of creatine alterations after brain injury, and how creatine treatment affects adolescents, pediatrics, and rodents suffering from TBI sequalae. Results from a variety of previous studies have demonstrated improved prognosis for TBI patients to include the duration of post-traumatic amnesia, length of intubation within the intensive care unit, overall good recovery, cognitive function, and neurophysical behavior.[2]

Of all trauma deaths, 25% are caused by head injury and the neurophysiological recovery that ensues post-injury is a lengthy process following the resolution of acute complications.[3] Creatine supplementation has not been researched for mTBI extensively; more recent studies suggest potential as a neuroprotective treatment when administered for brain injury. However, the gain of neuroprotection may only be clinically significant if a lengthy pretreatment is administered. This hypothesis stems from measured brain creatine levels and their effect on energetic buffering needed to achieve therapeutic neuroprotection.[4] There is sufficient evidence to support the use of short- and long-term creatine supplementation as a useful option for performance enhancement, but it plays a large role in preventing and reducing the severity of post brain injury rehabilitation.[5]

Devastating short-term and long-term medical complications, behavioral, physical, and emotional disabilities may arise from post-TBI. Creatine supplementation plays a significant role in its positive impact on cognitive processing during stressful events when brain creatine levels are acutely suppressed due to initial trauma or chronically from post-TBI complications. Some research has been conducted in the form of preventative or prophylactic creatine supplementation to protect brain function during sporting events from acute hypoxia, herniation, or exhaustive exercise.[6]

Further research for prolonged field care and prophylactic treatment for service members when current treatment protocols lack significant reliability or efficacy has become an important topic due to the upscale of traumatic brain injuries across areas of operation. Committee members of the Institute of Medicine of the National Academies state there have been improvements in cognition and behavior from creatine trials in children and adolescents. In these studies, creatine treatment was initiated early after injury and may have subdued extreme disease processes during the acute phase post-injury.[7] The protection seems related to brain creatine-induced maintenance of mitochondrial levels and available bioenergetics. When these levels are diminished, primary and secondary mechanisms of TBI deficits appear more prominent.[8]

Therapeutic creatine supplementation will restore brain creatine content; this may facilitate the recovery of usual brain function. Evidence indicates increasing brain creatine levels may be useful as a neuroprotective agent to reduce or enhance the recovery from mild traumatic brain injury. Unfortunately, only limited or dated trial information in humans is available to verify this topic, representing an exciting area for further research.[9]

Methods

A systematic literature search was conducted from August through September 2020, using the following databases: PubMed, Elsevier Science Direct, Google Scholar, and Embase. This systemic review was performed in accordance with the Preferred Reporting Items for Systematic Review and Meta-Analysis guidelines to clarify the question and provide a suitable approach for comparison.

The initial search was cast to identify research articles that were randomized control trials, review articles, descriptive studies, meta-analyses, or systematic reviews. The search keywords within the PubMed database and other databases stated above were "creatine," "traumatic brain injury," "mtbi," "concussion," "brain injury." The initial search included the years 2012 to 2020 and yielded 40 articles. After the initial screening of the article, title, and abstract, 15 articles were excluded. Articles were excluded if they did not report a self or object measure of creatine's effect on a post brain injury scenario or brain injury complications.

Additionally, articles were not included if they were not peer-reviewed or not in English. Five articles out of the prescribed search dates were kept due to the strong evidence of efficacy and provide further context during the discussion section of this review; those articles were not used as significant data for this review's results section. Articles were included if they had human subjects or animal subjects, contained evidence of civilian or military personnel with no restriction on age; geriatrics and pediatrics are included. There was no restriction on gender.

An additional 5 articles were removed for being narrative studies, and supplemental articles on creatine's interaction with the brain and the central nervous system. Many of the included articles describe dual use in concussions relating to sports medicine and how creatine affects the brain or axonal injury. Lastly, 5 articles were removed for merely describing current treatment protocols using such drugs as mannitol, tranexamic acid, progesterone, and hypertonic saline with no comparison treatment data with creatine. After a full manuscript review and application of inclusion criteria, a total of 15 articles are included in this systematic review. The 15 included articles used in this review highlight the current and past research on the effectiveness of creatine supplementation and treatment for brain injury complications and neuroprotection.

Results

The reviewed literature displays recent research results

of the efficacy of creatine supplementation for brain injury complications in mice and humans from September 2012 until 2020. A total of 15 articles met inclusion criteria and were included in this systemic review. A total of 10 articles met the requirements for the 8-year time inclusion. The results section will be represented by the overall effects of prophylactic and post supplementation for brain injury complications, supplementation on brain creatine levels, cognitive performance, glutamate toxicity, and creatine biomarkers of acute brain injury stress.

Prophylactic Versus Post Creatine Supplementation for Brain Injury Complications: Riesberg et al[9] addressed a randomized control trial demonstrating the efficacy of prophylactic creatine treatment in cerebral ischemia, common sequelae of traumatic brain injury. Mice were supplemented with 2% creatine for 1 month and subsequently subjected to 2 hours of middle cerebral artery occlusion and then allowed reperfusion. Significant improvement was demonstrated by a neurological score of 24 hours post insult in the creatine-fed group in comparison to the control group (n=5; p<0.01). A comparison of brain lesion volume performed 24 hours post-reperfusion correlated with improved behavioral scores, and cerebral infarct of the creatine-fed mice was reduced by 56% in comparison to the controls (51.4 versus 22 mm^3; n=5; p<0.01).

Creatine brain levels are essential for ATP concentrations and ischemia. Riesberg et al[9] compares the hemispheres of brain tissue affected, stating mice fed non-supplemented food experienced a significant reduction in brain creatine at 30 minutes post-injury (11.2 to 9.3 mmol/gm; n=8; p<0.01); creatine-fed mice were not significantly affected (11.4 to 10.8 mmol/gm; n= 8; p< 0.18).

Post Creatine Supplementation in Children & Adolescents: Oliver et al recently readdressed the potential for neuroprotective agents and their clinical relevance to TBI using an open-labeled pilot study using creatine on a total of 39 children and adolescents, 20 with creatine and 19 controls, from the ages of 1 to 18 years old with a TBI. Four children died during the study due to the severity of their injury. Non-control patients received 0.4gr/kg PO every day for 6 months, and a Pearson's X2 test was used to show differences between the two groups.[1] When using the Gaucher Disease Outcome Survey, the authors stated the creatine group performed significantly better than the control group at 3 months post-injury (X2=21.099; df=7; p=0.004). At 6 months post-injury a "good recovery" was significantly higher in the creatine group using Gaucher Disease Outcome Survey (X2=29.231; df=5; p<0.001; 88.9% versus 5.9%). Additional improvements were seen in cognitive awareness (X2=29.262; df=4; p<0.001), personality/behavior (X2=29.262; df=4; p<0.001), self-care (X2=9.050; df=3; p<0.029), communication (X2=8.011; df=2; p<0.018), and locomotion was not statistically significant.[1]

Creatine Brain Levels & Supplementation: Turner et al[10] stated a standard loading dose of 5 grams ingested 4 times daily for 5-7 days would increase muscle creatine levels and Phosphocreatine (PCr) by 20-40%, and a continued regimen of 3-5g a day allowed maintenance of these benefits. Dolan et al[6] meta-analysis showed the effects of creatine supplementation on brain creatine and PCr. Six adults, 26 years old, were given a 20g dose which increased total brain creatine 3.1-7.7% across multiple regions of the brain. These same 6 adults were given the same dose for 28 days, resulting in a total brain creatine increase of 4.7% to 14.6% across multiple brain regions. Ten men in the creatine group, 23 years old, were administered 0.3 g/kg a day for 7 days and 0.03g/kg a day for 7 days resulting in a 3.9% increase in brain PCr levels. Twelve men in the creatine group, 23 years old, were administered 20g a day for 5 days with no change in brain levels.6 Twelve adults, 7 males, 5 females, 32 years old were administered 20g a day for 7 days with a 5.2% increase in creatine brain levels, and a 3.1% PCr increase across multiple brain regions.[6] Fifteen adults, 10 male, 5 women, 31 years old, were administered 20g a day for 7 days and experienced a 9.2% increase in brain creatine. A creatine group of 35 children, 11 years old, was administered 0.3g/kg for 7 days and this did not affect brain creatine levels.[6]

Dolan et al[6] included patients diagnosed with aliments to include major depressive disorder, amphetamine use, and selective serotonin reuptake inhibitor-resistant major depressive disorder. Five females, ages 13-18 years old, with major depressive disorder were administered 4g a day for 8 weeks and this resulted in a 6.4% brain creatine increase. Fourteen adult females, ages 37 years old, with amphetamine use and depression were administered 5g a day for 8 weeks and increased PCr by 4.4%.[6] Twenty-two females, 17 years old with selective serotonin reuptake inhibitor-resistant major depressive disorder, received 2g a day for 8 weeks (n=7) and had an increase in PCr by 4.6%. Those who received 4g a day for 8 weeks (n=8) saw an increase in PCr by 4.1% and 10g a day for 8 weeks (n=7) demonstrated an increased PCr by 9.1%.[6]

Creatine Supplementation on Cognitive Performance: Dolan et al[6] displayed the results of creatine supplementation on healthy humans and stated its supplementation can increase various areas of brain function and cognitive processing. Turner et al[10] conducted a trial to show the effects of creatine during periods of increased stress from injury or experimental hypoxia on central

executive functions, a significant sequela of traumatic brain injury.

Dolan et a[16] presents a double-blind, randomized, placebo-controlled, parallel-group trial (placebo 32, creatine 35), who were administered 0.3g/kg divided into 4 equal doses for 7 days in male and female children aged 10 to 12 years old. The children were given a Stroop test, Rey auditory learning test, trail making test, and progressive raven matrices. Brain creatine was measured randomly in 26 of the children in multiple brain regions, and the authors suggested the results displayed cognitive function and brain creatine were not affected by creatine supplementation.

In a double-blinded, randomized, placebo-controlled cross-over trial, 10 healthy males and 5 healthy females were exposed to severe experimental hypoxia to mimic the effects of a TBI and administered 20g of creatine a day, divided into 4 equal daily doses for 7 days with a 5-week washout between trials.[10] The cognitive tests were measured using magnetic resonance spectroscopy. They included a neuropsychological test battery comprising verbal and visual memory, finger tapping, symbol digit coding Stroop test, a test of shifting attention, continuous performance, alertness, and peripheral and corticomotor excitability.[10] Brain creatine content increased and counteracted hypoxia-induced effects during multiple tests, especially complex attention ($p=0.049$) in comparison to placebo. One week of oral creatine supplementation was able to increase brain creatine storage (1.62mmol/L) compared with placebo supplementation (0.90 mmol/L) with a trend of $p=0.07$.[10]

Acute Creatine Biomarkers of Brain Injury: In a meta-abalysis, Gan et al[11] discussed the highest yield blood biomarkers, including creatine kinase (CK) and its ability to provide insight into the underlying traumatic brain injury. Their study suggested CK is a good performance measurement which suggests stress axis activation and cellular damage of specific brain areas typically involved during concussive or TBI-related events. This category 1 study only reviewed documented concussive events with no follow-on treatment required, utilized 15 different biomarkers, and contained a total of 946 observations. CK was categorized as excellent based on the pharmacokinetic area under the curve of >9. CK measured area under the curve (AUC)=0.902 in the category 1 study.

A category 2 study analyzed patients who required a computed tomography scan post mTBI, included 23,316 observations and utilized 24 various biomarkers.[11] CK was also categorized as excellent based on an AUC=0.964. CK was not highly measurable in category 3 and category 4 studies, which studied delayed recovery after an mTBI and poor outcomes after severe traumatic brain injury.

Vagnozzi et al[12] investigated affected creatine levels involving 11 nonconsecutive amateur athletes and 11 healthy control subjects, ranging from 16 to 35 years old, who suffered a brain injury. Each subject of the study underwent magnetic resonance spectroscopy and proton spectroscopic examination 3 days post-injury followed by 3 additional magnetic resonance spectroscopy scans at intervals of 15, 30, and 45 days post-injury. The first 3-day scan revealed a significant increase in creatine ratio compared to controls ($p<0.01$). Additional increase was shown at 15 days in creatine ratio (+16%; $p<0.01$) in comparison to controls. Thirty days post-injury showed a decrease in creatine ratio concerning controls ($p<0.05$). There was also a negligible difference from the 30-day magnetic resonance spectroscopy to 45 days post-injury.[12] The authors concluded increases in total creatine in the brain help restore mTBI induced changes to cell membrane homeostasis and upregulate to proceed with cell repair.[12]

Glutamate Toxicity & Oxidative Stress: Cunha et al[13] demonstrated the protection creatine provides against glutamate toxicity and oxidative stress by implanting neuroblastoma cells treated with glutamate ranging from 5 to 80 mM into 14 female Swiss mice. The cells were also pre-incubated (24 hours) or co-incubated with creatine monohydrate in concentrations of 0.1 to 10 mM. Six mice were used per experimental group and measured by cellular viability of neuroblastoma cells post glutamate exposure, caspase 3 activity (an indication of apoptosis), dichlorofluorescein oxidation (indicating oxidative stress markers), nitric oxide production, and hippocampal slices of the brain.

During the study, differences were considered statistically significant when $p<0.05$.[13] A dose of 80 mM of glutamate caused a 43% decrease in cell viability, and creatine dosed at 10 mM significantly protected the neuroblastoma cells from cytotoxicity and apoptosis during caspase 3 activity. The same dosages were used for dichlorofluorescein oxidation, and creatine proved successfully to prevent an increase in oxidation 24 hours post insult, indicating antioxidant effects. Nitrite levels rose from 11.9 uM to 34.70 uM from glutamate doses of 60-80 mM; creatine completely prevented the additional formation of nitrite in all subjects. Mice were administered 100–300 mg/kg, PO, creatine acutely, or repeatedly for 21 days, and the hippocampus was examined for in vitro neuroprotection.

Discussion

A review of the currently available literature evaluating

the neuroprotection qualities and potential therapeutic implications of creatine supplementation in the treatment of brain injury complications supported unique and positive correlations. Prophylaxis and post-supplementation with relevance to time and dose-dependent metabolic alterations were examined. The most notable changes were witnessed in brain creatine levels post-injury, inhibition of cognitive functions during cellular hypoxia by simulated brain injury, the role of glutamate toxicity on brain creatine levels, and the importance of creatine biomarkers during brain injury.

Table 1. Creatine monohydrate (pre and post injury) treatment guidelines for traumatic brain injury from Joint Special Operations Medical Training Center.[16].

Uses and Safety	Minimal to no side effects observed in athletes and military personnel. Chronic intake of 5g/day is proven safe and poses no significant health risks.
Human Studies demonstrating evidence of increased resilience	No human trials have been conducted yet which examine a correlation between creatine and resilience to traumatic brain injury.
Animal Studies demonstrating evidence of increased resilience	Multiple animal studies have demonstrated a strong neuroprotective effect of creatine in animals subjected to mild cortical impact compared to controls. This effect was observed in animals given creatine as little as one day prior to injury and all the way out to four weeks prior to injury.
Human Studies demonstrating post injury treatment effect	There are no studies of the effects of creatine supplementation in adults, however two human trials in children ages 1-18 demonstrated significant improvement in several areas when compared to controls. Cognitive functioning, self-care, sociability, and communication skills had all shown improvement vs. controls. Trial details: Children between 1-18, with a GCS between 3-9, given 0.4g/kg/day for six months and initiated within 4 hours of the time of injury.
Animal studies demonstrating Post injury treatment effect	Animal studies revealed significantly better neurological function and significantly less brain damage than controls not receiving creatine. Creatine also significantly reduced the presence of several bio-markers indicative of cell damage. female rats experienced a decrease in depressive like behavior in a dose dependent manner. Male rats did not demonstrate a reduction in depressive like behavior.
Supplementation (exercise) Dose	5g/day

Prophylactic Versus Post Creatine Supplementation for Brain Injury Complications: Riesberg et al[9] explored creatine supplementation's benefits to modulate neuroprotection for athletes suffering from injury or TBI by addressing a previous randomized control trial. This randomized control trial demonstrated the efficacy of prophylactic creatine treatment in cerebral ischemia, a common sequela of traumatic brain injury on mice. An essential aspect of this study demonstrates the cerebral infarct of the creatine-fed mice was reduced by 56% compared to the controls. The creatine-fed mice benefited from the supplementation had a more remarkable ability to buffer the loss of ATP due to ischemic necrosis or apoptosis due to cellular demand, as witnessed in TBI.[9]

However, the actual benefits of creatine supplementation in mice were only clinically significant if lengthy pre-treatment or prophylactic administration was obtained pre-injury.[9] At least one month of creatine supplementation pre-injury was sufficient to support evidence of neuroprotection in the form of ATP buffering, an essential factor in mortality and post-injury cerebral complications.[9]

Post Creatine Supplementation in Children & Adolescents: Post-measurements of creatine supplementation in children and adolescents suffering from TBI exhibited enhanced improvement from sequela at 3 months post-injury, with statistically significant results at 6 months post-injury.[1] Additional improvements were seen in cognitive performance, such as awareness, personality, behavior, self-care, and communication skills.[1] The initial 3-month follow-up post-TBI demonstrated a more significant decrease in neurophysical and locomotion deficits, with 6-month results showing marked improvement in overall cognition. Creatine supplementation was associated with a decreased time of intubation and admission to the intensive care unit in these patients as well.[1] This reveals a potential correlation between the acute state's ineffectiveness with exceptional benefits during chronic TBI sequelae, especially those deemed more severe.

Creatine Brain Levels & Supplementation: Creatine's central role within the body is to facilitate rapid energy accumulation and growth during increased ATP degradation and cell death, an essential aspect of brain injury. PCr, the usable form of creatine that enters the cell and donates a phosphate group for ATP, is a significant component of maintaining cerebral function during TBI or hypoxic events.[10] A susceptible dosage strategy and length of supplementation appear as crucial factors in reaching adequate brain creatine levels to combat chronic complications. In the Dolan et al[6] 2019 meta-analysis, adult patients increased brain creatine levels over 7% with a 20g/day regime for 7 days. The most notable results were seen in the patients who increased brain creatine levels by over 14% with the same 20g/day dosing for just over a month.[6] An extensive ATP buffer generated by high brain creatine levels supports the notion of increased neuroprotection from chronic TBI sequelae. It seems evident through this research when patients experience an acute brain injury, it is unlikely the patient will immediately benefit from creatine supplementation since orally administered exogenic creatine is absorbed slowly into central nervous system tissue to eventually make an effect on brain creatine levels and provide potential ATP buffering.[14] Staff assigned to the Special Operations Combat Medical Course Skills and Sustainment Course, Fort Bragg, NC, present summarized data from Oliver et al[1] for appropriate dosing of

creatine monohydrate and evidence to soldiers attending the course for pre and post mTBI care (Table 1).

Creatine Supplementation on Cognitive Performance: Dolan et al[6] concluded the studies found correlation between creatine supplementation and cognitive performance is dose dependent. Creatine supplementation may significantly affect those suffering from energetic brain distress instead of the healthy adults studied.[6] However, a similar dosing strategy of 20g/day for 7 days prior to injury proved to be more beneficial to those suffering from a hypoxia-induced brain injury such as TBI.[10] This dosing strategy demonstrated a 9.2% increase in brain creatine levels, buffering ATP stores and allowed those stores to focus on ATP-consuming parts of the brain during an oxidative stress event.[10] These results supported the idea of creatine as a neuroprotective agent for neurophysiological function and increased cognitive performance during a hypoxemic state.[10]

Acute Creatine Biomarkers of Brain Injury: The results make an interesting correlation between acute creatine biomarkers and overall degradation of brain creatine levels post-TBI. Gan et al[11] suggested using creatine kinase (CK), an enzyme required to phosphorylate creatine to PCr, found abundant in oligodendrocytes, as a well-identified biomarker post brain injury. Vagnozzi et al[12] stated the study showed a brief period of brain vulnerability and hypometabolism, causing a significant depletion of creatine levels, mitochondrial dysfunction, and unregulated ATP supply within the brain post-TBI.[12] Levels of brain creatine were markedly decreased by 42% 24 hours post-TBI and steadily decreased over 30 days and 45 days.[12] These results are consistent with the importance of brain creatine levels during oxidative stress and could improve dosing strategies for prophylaxis and chronic conditions.

Glutamate Toxicity & Oxidative Stress: High levels of glutamate or glutamate excitotoxicity have been linked to low prognostic values and increased mortality rates in patients suffering from an acute brain injury, acting as a neurotoxin, causing apoptosis and mitochondrial dysfunction.[13] Acute treatment was unsuccessful in protection; however, repeated treatment up to 21 days using 10 mM of creatine blocked glutamate, reduced cell viability, and dramatically increased mitochondrial stability.[13] Glutamate excitotoxicity causes increased nitric oxide production and release within the brain leading to cell death. Creatine supplementation prevented any additional oxidation of nitric oxide, neurotoxic glutamate levels and has demonstrated positive results as a bioenergetic, antioxidant, and neuroprotective agent regarding glutamate toxicity sequalae in TBI.[13]

Gaps in Knowledge: Although there is concrete evidence to show the positive relevance of creatine supplementation for TBI, treatment guidelines utilizing creatine are not evident in the current literature. This may be due to confusion relating to creatine's effectiveness in the chronic setting versus the acute, where it seems to make its positive effects between 7 to 30 days. There is an absence of current literature demonstrating creatine's value as a treatment plan versus novel treatments such as hypertonic saline and mannitol or how creatine may supplement current treatment goals within the protocol. A review of the currently available literature lacked evidence of creatine supplementation use in prolonged field care or prophylaxis for members of the military who are at increased risk of TBI, may demonstrate the highest number of cases of TBI, and suffer the most long-term effects of TBI complications and sequelae. Past and present data still lacks the knowledge of creatine supplementation for the adult civilian population during TBI.

Limitations

This systemic review provided a concrete foundation for understanding the currently available literature regarding creatine usage for TBI, concussive events, potential neuroprotection, and associated post-injury complications. PubMed was the primary database used during this review, and bodies of research not searchable within PubMed were not utilized in this review. Selection bias of articles was avoided, as well as reporting bias during the results section. Yet, there is still a possibility for bias based on the need to support the specific intent of explaining the positive correlation between creatine supplementation during TBI complications.

Unfortunately, this topic has not been widely pursued within the preceding 8 years. Newer researchers have referenced previous articles and results dating back to the year 2000 to build a new case for research regarding the specific effects on TBI. More recent research which fell within the 8-year timeframe of this review focused on associated sequelae of TBI and not necessarily the direct impact of creatine on TBI in the emergency or long-term state, leaving a lot up to interpretation. The randomized controlled trials presented in past studies displayed positive data but only included children, adolescents, and mice, with no direct data correlating with adult supplementation during TBI. The articles' focus supported the paradigm of the review, with most of the data supporting the interaction between creatine as a neuroprotective agent as it applies to post-injury complications to include cognitive function, cerebral ischemia, and generalized recovery time. Positive themes presented throughout this review spark interest for newer research in the form of randomized controlled trials,

double-blinded studies using adults with stratified levels of TBI, ages 18-65, and gathering data on the early administration of creatine in the acute phase of injury through the chronic state.

Conclusion

This review of the currently available literature evaluated the neuroprotection qualities and potential therapeutic implications of creatine supplementation in the treatment of brain injury complications. During the review, it became increasingly apparent creatine does offer an obvious benefit to patients suffering from TBI and post-injury complications. Currently, available literature demonstrates creatine works well within a multidrug approach and shows substantial benefits to the patients suffering from severe TBI in the chronic state when cognitive function and neurophysiological sequelae are most prominent or likely. The treatment protocol of hypertonic saline or mannitol has proven efficacy within the acute phase, and creatine could be an excellent supplement for mitochondrial dysfunction and ATP buffering. Erdman et al[7] explores research for creatine supplementation for subacute health outcomes in military personnel and believes previous studies provide ample evidence for creatine in TBI. The results should be extrapolated to members of the military to discuss timing and optimal dose.

Two major themes arose from this review, dosing, and timing. Time and dose dependent metabolic alterations seem to be only exceptionally prevalent when given as a prophylaxis or if given acutely, results are only clinically significant after a month of supplementation. Although patients may need many therapeutic treatments to recover from TBI, especially in acute resuscitation, creatine shows superior efficacy as a neuroprotective agent in battling the chronic manifestations which lead to oxidative stress and cognitive function post-injury. The review is subtitled to demonstrate the tremendous overlap between TBI neuropathology and creatines role in restoring function; the most prominent was mentioned.[15] Currently, creatine is a highly underestimated and underutilized option due to a lack of continuity in research but suggests promising results. Members of the military are placed into varying medical situations with increasing application of austere medicine, or reliance on competence in prolonged field care. Creatine supplementation has the potential to provide service members or medics with an additional tool to bridge the gap between a poor or positive TBI prognosis.

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Successful Surgical Airway Performance in the Combat Prehospital Setting: A Qualitative Study of Experienced Military Prehospital Providers

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Abstract

Introduction: Military first responders are in a unique category of the healthcare delivery system. They range in skill sets from combat medic and corpsman to nurses, physician assistants, and occasionally, doctors. Airway obstruction is the second leading cause of preventable battlefield death, and the decision for intervention to obtain an airway depends on the casualty's presentation, the provider's comfort level, and the available equipment, among many other variables. In the civilian prehospital setting cricothyroidotomy (cric) success rates are over 90%, but in the US military combat environment success rates range from 0-82%. This discrepancy in success rates may be due to training, environment, equipment, patient factors and/or a combination of these. Many presumed causes have been assumed to be the root of the variability, but no research has been conducted evaluating the first-person point of view. This research study is focused on interviewing military first responders with real-life combat placement of a surgical airway to identify the underlying influences which contribute to their perception of success or failure.

Materials and Methods: We conducted a qualitative study with in-depth semi-structured interviews to understand participants' real-life cric experiences. The interview questions were developed based on the Critical Incident Questionnaire. In total, there were 11 participants—4 retired military and 7 active-duty service members.

Results: Nine themes were generated from the 11 interviews conducted. These themes can be categorized into 2 groups: factors internal to the provider, which we have called intrinsic influences, and factors external to the provider, which we call extrinsic influences. Intrinsic influences include personal well-being, confidence, experience, and decision-making. Extrinsic influences include training, equipment, assistance, environment, and patient factors.

Conclusions: This study revealed practitioners in combat settings felt the need to train more frequently in a stepwise fashion while following a well-understood airway management algorithm. More focus must be on utilizing live tissue with biological feedback, but only after anatomy and geospatial orientation are well understood on models, mannequins, and cadavers. The equipment utilized in training must be the equipment available in the field. Lastly, the focus of the training should be on scenarios which stress the physical and mental capabilities of the providers. A true test of both self-efficacy and deliberate practice is forced through the intrinsic and extrinsic findings from the qualitative data. All of these steps must be overseen by expert practitioners. Another key is providing more time to focus on medical skills development, which is critical to overall confidence and overcoming hesitation in the decision-making process. This is even more specific to those who are least medically trained and the most likely to encounter the casualty first, EMT-Basic level providers. If possible, increasing the number of medical providers at the point of injury would achieve multiple goals under the self-efficacy learning theory. Assistance would instill confidence in the practitioner, help with the ability to prioritize patients quickly, decrease anxiety, and decrease hesitation to perform in the combat environment.

Keywords: cricothyroidotomy; surgical airway; austere; military

Table 1. Participant inclusion/exclusion criteria.

• US Military or prior military • Have performed a cric in the combat environment- as defined by an area where combat operations are taking place; land, sea or air where kinetic operations are occurring • They were considered prehospital in their duties	• Those who were part of a surgical team • Role 2 or higher echelon of care • Performed cric outside of a combat environment

Introduction

In the past 20 years, the Global War on Terrorism has created many casualties, and airway compromise is one well-known preventable cause of mortality for those casualties.[1,2] Airway obstruction can result from facial trauma, airway swelling, loss of respiratory drive, and unconsciousness, among others. A compromised airway causes the body to circulate less oxygen, and an adjunct airway is needed to reestablish oxygen delivery. Standard airway adjuncts help open the airway but are not considered secure as they can easily become dislodged or obstructed. Additionally, many require operator assistance to continue moving air. According to the Joint Trauma System Department of Defense (DoD), surgical airways are the only ones considered secure. The surgical airway intervention, cricothyroidotomy (cric), is considered a secure airway and the only secure airway taught from the Emergency Medical Technician (EMT) level all the way through the surgeon level for both military and civilian populations.[3] The cric is also the final common pathway for almost all airway algorithms to obtain an airway should all other adjuncts fail.[4]

Trauma-related crics are generally performed in the prehospital setting (Role 1). The prehospital setting includes the geographical area both before and during patient evacuation from the point of injury up to the moment when the patient makes it to a dedicated surgical team, either an independent forward surgical team or at a Role 2/3. That is not a hospital per se, but the surgical teams offer a higher level of care, surgical intervention, blood products, and additional expertise. In the US military, those who perform pre-hospital medicine are usually EMTs (combat medics and Corpsmen), paramedics (paramedic trained, usually flight medics), physician assistants, and more rarely, emergency trained nurses and doctors. The success rates for the US military with crics range from 0-82%,3,[5-7] while the civilian prehospital rates range from 90-99%,[8-10] and the British military rates are >90%.[11]

Research about cric performance in the US military has highlighted various causes for difficulty in successful placement.[5,8] Some of these include training, equipment, patient factors, and the environment. There are also known procedure complications between techniques.[12] Training is unit-dependent; some units are on annual training events, and others are spaced out further. EMT level providers are considered the least trained in the medical provider continuum of education, but they are usually the only providers at the point of injury. The current requirement for the EMT level combat medic is annual simulation training on crics. No current requirement for cric training on live tissue exists. To add to the complexity, there are over 12 different techniques used to perform a cric.

Environmental influences such as low light or blackout conditions, temperature extremes, rugged or uneven terrain, and limited access to additional supplies further complicate the procedure.[8] In terms of equipment, there are more than 3 off-the-shelf prepackaged equipment sets and many more personally handmade kits.[5] For patient factors, the average Glasgow coma scale (GCS) score ranges from 15-3, and for those who require intubation, GCS is generally 8 (severe head injury) or less. The average GCS for casualties who received a cric was a 3 (completely unresponsive to any stimulus).[7] Other patient factors also play a role, such as anatomical differences, casualty-worn combat equipment, and differences in injury patterns.

In the research on battlefield crics, there is a lack of research addressing what prehospital providers who have performed crics think influences the success or failure of the procedure. Therefore, this study aims to identify the influences which contribute to the perceived success or failure of a prehospital surgical airway by the US military in the combat environment.

Methods

We conducted in-depth qualitative semi-structured interviews to understand participants' real-life cric experiences. The interview questions were developed based on the Critical Incident Technique and Questionnaire.[13-16] This study was approved by our Institutional Review Board.

Table 2. Participant demographics.

Participant	Branch	Year	Theater	Phase of care	MOS	Rank	Equipment	Additional Training
1	Army	2005	Iraq	Tactical Field Care	Medic	E4	Off the shelf	BCT3
2	Army	2005	Iraq	Established	PA	O3	Off the shelf	MC4
3	Army	2012	Afghanistan	Tactical Field Care	Medic	E5	Off the shelf	BCT3
4	Army	2016	Afghanistan	Tactical Field Care	Special Ops Medic	E5	Custom	SOM LTT
5	Army	2005	Iraq	Tactical Field Care	Medic	E5	Custom	LTT
6	Army	2017	Afghanistan	Enroute Evacuation	Flight Medic	E6	Custom	BCT3 and Cadaver
7	Army	2012	Afghanistan	Tactical Field Care	Special Ops Medic	E5	Custom	SOM LTT
8	Navy	2005	Iraq	Established	Special Ops Medic	E6	Off the shelf	NTTC
9	Army	2005	Afghanistan	Established	Medic	E4	Custom	BCT3
10	Army	2010	Afghanistan	Care under fire	PA	O3	Off the shelf	TCMC and LTT
11	Army	2018	Afghanistan	Enroute Evacuation	Trauma Nurse	O3	Custom	TCMC/TCCC/ECCN

PA: physician assistant; BCT3: brigade combat team trauma training; MC4: medical combat casualty care; SOM: special operations medic; LTT: live tissue training; NTTC: navy trauma training center; TCMC: tactical combat medical care; TCCC: tactical combat casualty care; ECCN: enroute critical care nursing

Participant Demographics: We initially put out an email request through the branch chiefs to elicit possible participants, which enabled the self-selection of participants. We obtained 5 participants through these emails. We followed this with snowball sampling, and an additional 6 participants were solicited. In total, there were 11 participants: 4 retired military and 7 active-duty service members (Table 1). We had 3 officers and 8 enlisted members. All enlisted members were junior enlisted at the time of their procedure. Five of the 8 enlisted members were entry-level EMT-Basic trained, while 3 were special operations (Table 2).

Data Collection: One 60-90-minute semi-structured interview was conducted per participant via Zoom or over the phone. Verbal consent was obtained from each participant before the interview was conducted. The interview posed a series of open-ended questions about the individual's lived experiences and the meaning the individuals attached to their cric experiences. Data were transcribed as participants completed the interview process. The data and interviews were de-identified to ensure the anonymity of participants. See Appendix 1 for interview questions.

Data Analysis: Braun and Clark's thematic analysis process guided the data analysis.[17] Two interview transcripts were randomly selected, and all 4 authors coded them independently. We then met to review our codes and identify themes. The initial themes were tested against 2 more transcripts and further refined by the team. The team then searched for connections across themes and generated overarching categories Table 3). When thematic saturation was reached, 2 more interviews were conducted to test the themes and ensure nothing was overlooked.

Table 3. Themes.

Broad Categories	Themes	Sample Quotations
Intrinsic Influences	Personal well being	The first one was memorable, because I was just like real nervous
	Decision and steps to perform	He eventually did get a cric. However, I was hesitant to do it at the time, because it was one of my guys
	Experience level	My best set up for success, helping someone else do a cric in combat
	Confidence	My confidence level far exceeded my competence level.
Extrinsic Influences	Assistance	The ER Doc was supervising because I told him "Hey, this is the first time I've actually done this on a real patient"
	Equipment	Our particular problem, for sure, was lack of familiarity with that piece of equipment
	Training	Ultimately live tissue training with as many repetitions as possible on the live tissue
	Patient specific factors	Really being able to identify landmarks on multiple personnel
	Environment	I didn't have time to debate you know? it's just that make decision and do it versus, you know, think about it

Results

Nine themes were generated from the 11 interviews conducted. These themes can be categorized into 2 groups: influences which are internal to the provider, called intrinsic influences, and those which are external to the provider, called extrinsic influences. Intrinsic influences

include personal well-being, confidence, experience, and decision-making. Extrinsic influences include training, equipment, assistance, environment, and patient factors.

Intrinsic Influences: The participants in this study indicated their perceptions of the success of the cric they performed depended on 4 intrinsic influences: personal well-being, confidence, experience, and decision-making.

Personal well-being includes the individual's physical and mental state. The individual's mental state was a huge influencer in the ability to perceive success and perform on the battlefield. Adrenaline and anxiety were critical influences in the participant's experience of the combat environment. Participant 6 noted, "My adrenaline flow is about a 1,000 times normal at that point because of the mission itself. And then, when I got my patient realized, my anxiety hit incredible."

Participant 5 said, "I just remember the smell of everything, and I just remember, like man, my heart was just like beating so fast." Physical fitness was as important as mental fitness.

Many participants were running or dragging patients to secure areas to treat them, which they suggested decreased their ability to perform due to fatigue. Those participants suggested rigorous physical training should be conducted to overcome physical withdrawal before the procedure.

Confidence and overconfidence were themes which influenced perceptions of success as well. Participant 5 stated, "Did one procedure. It went really well. I thought I was like, the man. Then, a month later, I had an American casualty who actually had ended up dying. I like totally (expletive) the cric up on that guy. Because I was like, overconfident."

Because of this overconfidence, he didn't follow his standard stepwise technique, which inevitably led to failure. Those with prior experience assisting or one-on-one supervision felt those aspects played a tremendous role in success and confidence not only for performing the procedure but also for setting up their specific equipment and developing their technique.

Participant 1 noted, "My confidence level far exceeded my competence level."

Participant 3 said, "It's not that simple when you cric someone's neck. I had done everything else properly. From my recollection as in, the incision was properly placed, landmark was found, everything was there. Just didn't give myself, the right opening, and I rushed it in like a drunk frat boy."

These are great examples of overconfidence and how it led to perceived or actual failure. The result of the procedure also plays into the mental health and prolonged traumatic stress the provider feels afterward.

Participant 6 described how it made him feel. "The outcome I didn't know. So, you know, that kind of sticks with you a little bit, and it's pretty... it's pretty vivid in my mind actually."

Very few providers received feedback from the next higher echelon of care; most did not know the overall outcome of the patient. These stressors can create barriers to confidence in the follow-on procedure, as suggested by the above participant.

Experience level with the equipment and procedure was instrumental in the ability to perform the procedure. Those with no experience with actual human casualties, either firsthand or with assisting another provider, hesitated to perform the procedure and felt less confident.

Participant 6 stated, "I might have been a little overconfident going into it and then, when it happened, I was oh, at a moment, the moment of realization, am I really this confident with it?"

Those with prior experience or assisting felt far more confident the second time. However, some success with a prior cric led one participant to be overconfident and fail a second attempt, as we saw above with participant 5. Furthermore, even when additional providers were available, without an expert nearby, failure was still possible. As participant 2 noted when he mentioned there were 3 or 4 providers. "So, it was not necessarily the blind leading the blind, but there wasn't really anyone who had a total level of expertise."

Those with hands-on experience with their equipment and with real patients felt experience helped them feel like they were successful in the field. Participant 1 was heavily influenced by the experience he got from his physician assistant prior to his cric. "I had the kit that I put together with the help of my battalion physician assistant, who was really, really experienced, and had already walked me through a live tissue cric."

This experience helped him perceive that his procedure was successful and attributed the success to experience with an expert. Participant 6 thought his prior experience on an actual patient was more important than any prior training. "My best set up for success, helping someone else do a cric in combat."

Making the call to perform the cric is one of the toughest decisions. Making sure to know the steps and follow them in order also plays a significant role in the perception of success. Participant 8 noted, "It's the decision to make the... to actually perform the procedure. Does this patient need it? We, or am I just being too aggressive here. That's the real dilemma I think when you're looking at your patient."

The decision to perform the cric should be clear-cut and based on the Joint Trauma System guidelines. However, many struggled with understanding the decision tree and when to perform the cric. Two participants suggested we must improve the decision-making process and take each step deliberately instead of jumping from a supraglottic airway adjunct directly to a surgical airway. Participant 1's recommendation was, "I think maybe the first step is to think through what interventions are available, and which one will be appropriate rather than rushing into procedure."

Extrinsic Influences: Five extrinsic influences affect the participant's perceptions of success with their cric: equipment, assistance, patient-related factors, environment, and training.

The equipment participants used to perform their crics was a key extrinsic influencer for the perception of success of the cric. Over half of the participants had a custom-made cric kit. They modified their kit either through practice with simulations or through the guidance of an experienced provider. The equipment they used played a critical role in their perception of success. Although everyone talked about their equipment, familiarity and repetition of cric procedures with their specific equipment led to the highest perceptions of success. One provider who was trying a new device for the first time and on a live patient was thoroughly confused about exactly how it worked, which inevitably led to failure. However, another individual, using the same piece of equipment for the first time, but had one on one oversight during the procedure, was successful.

Some of the equipment just didn't inspire confidence. Participant 7 elaborated, "If you've got a lot of subcutaneous tissue, have very much mobility in your neck, then putting in a 3-inch or 2.5-inch cric to the chance of it dislodging, I'm not comfortable with hanging a patient's life on that."

Participant 4 mentioned, "We generally ditch most of the stuff we didn't see is relevant, so you know, the alcohol swab in combat. We weren't too worried about the 4 by 4 gauze. The securing device originally used to come with them was pretty bad."

The lack of confidence in the off-the-shelf equipment resulted in many participants working with custom-made kits.

The next, most important extrinsic influencer was assistance. Almost all point of care and evacuation participants were alone as the single medical provider for their casualties. The 3 fixed-area participants had additional help from other medical providers. Those who were in areas with additional medical personnel felt more confident in their ability to perform. Those who were alone wanted help, and those who weren't alone still asked for supervision or a "sanity check" before performing the procedure, as participant 8 described.

Participant 6 also wanted assistance, "Nothing is better [than] to have two medics, you know. Is it overkill? It could be at times, but in some situation[s] like that, 2 people in the back, I think you get much better at success".

The environment of combat is significant and does play a role in the success of cric placement for multiple reasons. One participant performed care under fire, 2 performed during flight evacuation, 3 performed the task in a fixed aid station or area, and 6 participants performed the task during the tactical field care phase. Time constraints of the procedure and evacuation timelines also played a role. Time it takes to do the procedure and when the medical evacuation (MEDEVAC) will arrive influenced when or how soon the decision for a surgical airway was made. Of those who performed care under fire or tactical field care most stated the combat environment influenced their performance. From participant 4, "But you know, 2 out of my 3 crics were in a field... and at a target while the gunfight was still going on, while I had just been participating in the gunfight and then having to do it with a little bit of red light from my head lamp."

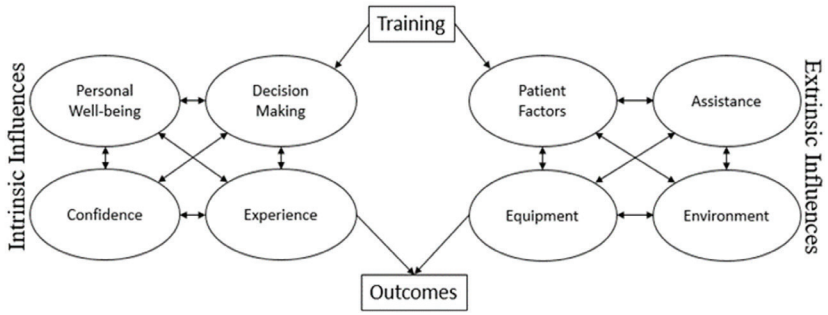
This quote brings out multiple layers of how the environment plays on anxiety, fear of imminent danger, and visualization of the anatomy. Participant 8 noted the effect of the timeline and additional patient load with this quote, "Had I had more time, I probably would have. I would have addressed his need for cric. I was the only medic on scene with dealing with the 3 patients."

This influence from the environment affected his decision tree, demonstrating many influences are interdependent on outcomes.

Patient factors also played a significant role in the ability to perform a cric. The responses from participants demonstrated the key importance of knowing the anatomy by touch. Being able to correctly identify the starting

location increases the likelihood of success as perceived by the provider. "Really being able to identify landmarks on multiple personnel" and "touch everybody's neck." (Participants 2 and 4)

Figure 1. Instrinsic and extrinsic influences.



There is a need for practicing identifying landmarks through soft tissue. It is of key importance to make sure practice is done on individuals with more soft tissue as anatomy is less pronounced. According to multiple participants, obscured vision due to the patient's blood was not a factor in success. Directly quoted from participant 4, "So on every cric I've done there [was] or has been blood, but it's never been a problem where I've had an issue visualizing".

This is contradictory to some of the previous assumptions about reasons for failure. However, no participant in this study identified blood as a significant influence in the success or failure of a cric.

Both intrinsic and extrinsic influences are affected by the training received before the procedure was performed. We derived multiple training-related responses from the interviews, including the type of training received, specifically, simulation-based training with mannequin, cadaver, or live tissue, training frequency, and the type of training plays a role in translating training to real-life performance. The training received varied between individuals but those with high volume, hands-on instruction conveyed the most confidence and firm belief their training directly contributed to their success. Participant 8, with his high volume, realistic training, suggested, "Train often and train hard for the guys about to deploy. Take advantage of every opportunity that presents itself, and I don't think there's ever a substitute for live tissue, patient models and cadavers."

Participant 3 stated, "Really do treat every situation as if it really is one of your guys there. Realistic training is everything".

Participants were keen on live tissue training and the ability for true biological feedback. Progressive training from anatomy classes to mannequins to cadavers to live tissue was the most common suggested progression. Most participants mentioned they wanted live tissue training as a culminating event. The suggested training timeline was focused around 3 months prior to deployment and at least a biannual refresher for those not deploying. However, those who were the most confident in their ability to perform had the most effective training—live tissue every 3-6 months, as noted in this response from participant 5, "I had a lot of live tissue training, and that really made me comfortable with the procedure. So, I knew all the steps really well. I could do them in the dark."

Another notable insight from participant 6, "Medical training wasn't as important as everything else, and I think we lose focus on that until we're needed, and that's the downfall."

The participants were commonly used for other tasks unrelated to improvement in medical skills. It was also mentioned instructors/trainers need to be fluent in the procedure and have the experience to back it up. There was concern about not receiving expert-level feedback. Rushing through the procedure and lack of previous training led to poor outcomes. However, those who had live tissue training every 6 months stated they felt confident but not overconfident, and they did have success with the procedure.

Discussion

This study identified intrinsic influences and extrinsic influences as having an impact on the performance of a cric. The intrinsic influences are personal well-being, confidence, experience, and decision-making. The extrinsic influences are equipment, environment, patient factors, and assistance. Both intrinsic and extrinsic influences are affected by training and affect the final outcome in the ability to perform a cric(Figure 1).

The intrinsic influences are interdependent and affect each other. Without one of the other influences of decision-making skills, confidence, and experience, it is very hard to develop a sense of personal well-being to overcome nervousness, anxiety, or fear. It is also hard to gain experience or confidence without positive physiological feedback from the training or through positive vicarious examples as mentioned by the participants and simulation research.[18-21] The learner must not be distracted and must be in the right state of mind to conduct valuable training. Feedback from the training is also important for developing self-efficacy, especially feedback from an expert.[22] Verbal cues and verbal persuasion in the correct performance are key elements to self-efficacy.[22] Performance outcomes from training give not only positive or negative results, but they also supply valuable confidence once the task is performed correctly. Performing high-quality repetitions increases experience, and performing the task correctly improves confidence.[23,24] These 2 aspects directly affect personal well-being by alleviating nervousness, anxiety, and fear through continued positive physiological feedback after each positive training outcome.

The extrinsic influences for success or failure in the performance of a cric are as vitally important as the intrinsic influences. These are also interdependent on each other. Assistance was available for only 3 of the participants, and having assistance can affect many aspects of extrinsic influences and self-efficacy. Allowing the practitioner, through deliberate practice, to have a "sanity-check" or to get positive reinforcement about this critical task is instrumental during training and during the critical incident. The assistant can also improve patient-specific factors by removing excess gear, positioning the airway, holding the surgical field steady, holding a light, or many other aspects of the incident. These circumstances still may not help if the equipment is faulty or it has never been used before, as we saw with one of the participants. The same can happen with the environment. When 1 participant performed a cric while still being subjected to enemy fire, they were forced to attempt the cric from an unfamiliar starting position. The extrinsic influences may be beyond personal control. However, training for those scenarios could potentially supply all the aspects needed for improving self-efficacy.

We all have heard from a young age we need to practice, as practice makes perfect. However, everything about how we practice makes a critical difference in performance outcomes.[25-30] In this study, both intrinsic and extrinsic factors were influenced by training. Through deliberate practice, participants could practice and improve their cric skills. The quality of practice with expert feedback and allowing the learner to process and integrate what was learned is vital.[4,31,32] Continued deliberate practice leads to improved self-efficacy. Continued self-efficacy leads to a positive feedback loop and improved confidence. Then the cycle continues again. The time for self-reflection and internalization of what was learned is equally important to the intrinsic influences and the ability to perform the task under pressure.

Intrinsic and extrinsic influences both affect outcomes. Training is the only major theme which affects all the elements of intrinsic and extrinsic influences, and it directly correlates to outcomes. Setting up deliberate practice scenarios while keeping the self-efficacy theory in mind would improve the areas participants said hindered their success. Bennett et al provided a bottom-up review which clearly showed the need for training.[8] Seven out of the 11 participants performed crics after the recommendations were made, but still the participants requested more training reinforcing studies which show mannequin-based simulation training provides valuable feedback and improves accuracy, timing, and success.[1,4,8,10,15,33-36] According to the participants of this study, initial training is important to understand the steps of performance and the decision-making process. However, after initial training, for critical tasks, participants wanted live tissue feedback after the mannequin-based simulation training is completed.[5,34] The repetitive finding for training is there is underlying self-realization right at the point of injury and is either overcome by previous training and self-efficacy, or there is a failure to perform. All the intrinsic influences force the individual to focus on self-efficacy and internal strife. The extrinsic influences are more dependent on deliberate practice with continuous challenging practice and expert feedback in order to overcome challenges.

Conclusion

This study highlights how practitioners in combat settings felt the need to train more frequently in a stepwise fashion while following a well-understood airway management algorithm. More focus needs to be on utilizing live tissue with biological feedback, but only after anatomy and geospatial orientation are well understood on models, mannequins, and cadavers. The equipment utilized in training must be the equipment available in the field. Lastly, the focus of the training should be on scenarios which stress the physical and mental capabilities of the providers. A true test of both self-efficacy and deliberate practice is forced through the intrinsic and extrinsic findings from the qualitative data. All of these steps must be overseen by expert practitioners. Another key is providing more time to focus on medical skills development, which is critical to overall confidence and

overcoming hesitation in the decision-making process. This is even more specific to those who are least medically trained and the most likely to encounter the casualty first, EMT-Basic level providers. If possible, increasing the number of medical providers at the point of injury would achieve multiple goals under the self-efficacy learning theory. Assistance would instill confidence in the practitioner, help with the ability to prioritize patients quickly, decrease anxiety, and decrease hesitation to perform in the combat environment.

Appendix

Appendix 1. Critical incident interview guide questions, page 1.

Critical Incident Interview Guide

Interview Background Information

Name of Interviewer: **Date:**

Person being interviewed

Job when you had to perform the cric:

Rank when you had to perform the cric:

Instructions:

Use this outline to help guide the Critical Incident interview. Try to focus on the events, behaviors, and actions. Avoid assigning blame or introducing biased opinions. Focus on the facts. Lead with the intro prompt and see further possible probing questions below.

Intro prompt:

Tell about a memorable time when you had to perform a Cricothyroidotomy, in a combat setting, trying to focus on what do think helped or hindered your success

Probing prompts
Who, What, When, Where: If not hit in the initial presentation; possible probing questions, use all, some or none

What happened?

When and where did it happen?

What was happening when you did this, care under fire, combat casualty care phase, evacuation or aid station, etc?

What happened that was beneficial or positive in outcome; was the cric successful?

Appendix Continued

Appendix 2. Critical incident interview guide questions, page 2.

What happened that was detrimental or had a bad outcome, did you try another airway first?

What led to the decision to perform a cric?

What happened before this, can you recall the GCS number?

What circumstances existed that caused the change between no airway, supraglottic, intubation and surgical airway?

What equipment did you use to perform?

What would you have done differently if you could do it over again; i.e initial training, annual training, equipment, supplies, level of provider, patient factors, etc?

What will you do differently in the future to be more successful?

Actions of Individuals

What did you do that helped or was effective?

What did you do that did not help or was ineffective?

What was the outcome of these actions?

Why did this help or not help the incident to occur?

What did you observe being done by others?

If you could change anything about the process of training or retraining, what would you change? (i.e., frequency of refresher training, depth or type initial training, access to training, etc)

Consequences of Actions

What was the outcome of these actions?

Why do you think the actions were effective or ineffective?

Why do you think the actions had a positive or negative outcome?

Closing Questions

What training did you have prior to the event?

What equipment did you use?

Did you have assistance from another professional?

Were there any patient factors that made it harder or easier to perform?

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Combating Fentanyl: National Guard Physician Assistants on the Front Lines of America's War Against Synthetic Opioids

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Abstract

There is a significant threat to global health security due to synthetic opioids, illicitly manufactured fentanyl (IMF), and nefarious uses of pharmaceutical based agents (PBA). Since 2014, increased distribution of synthetic opioids including IMF into the US through China, India, and Mexico has resulted in devastating consequences to the average street drug user. Additionally, clandestine lab operations for pill manufacturing and distribution have increased, along with unintentional drug overdoses due to drugs being laced with fentanyl or some other synthetic opioid derivative. Naloxone has been shown to be an effective and useful tool for reversing signs and symptoms of synthetic opioid overdose, though additional doses may be required depending on the analog. In addition to the risk of overdose in US civilians, other state actors have utilized fentanyl and its analogs as incapacitants resulting in significant numbers of casualties. The National Guard Weapons of Mass Destruction-Civil Support Teams (WMD-CST) have been on the front lines supporting federal law enforcement agencies with hazard identification and assessment. Physician Assistants (PA) are assigned to these units and provide the necessary skills and expertise to keep on scene personnel safe. This article aims to dispel some of the rumors and myths surrounding fentanyl in an effort to educate first receivers, first responders, and hospital providers. Lastly, this article provides a review of synthetic opioid production, overdose, hazards, treatment/countermeasures, decontamination for responders, and the potential use of synthetic opioids as WMDs.

Keywords: national guard; physician assistant; fentanyl; synthetic opioid; opioid; naloxone; narcan; pharmaceutical based agent; PBA; incapacitating agent; weapons of mass destruction; civil support team; CST

Introduction

During a personal interview, LTC Robert Dent, PA-C, a Weapons of Mass Destruction-Civil Support Team (WMD-CST) Physician Assistant (PA), provided the following perspective on synthetic opioids in America based on an event in 2016:

> *As an Army National Guard PA assigned to a WMD-CST, my role with fentanyl has grown over the last 5 years. It never occurred to me early in my career that fentanyl (which at the time meant nothing more than an analgesic for acute and chronic pain management) would become a significant public health hazard, requiring me to advise incident commanders (IC), first responders, law enforcement agencies, and hospital first receivers on dealing with it. In November of 2016, this became my reality. In an upper class suburb of a densely populated city, local and federal law enforcement agents raided the home of a 29 year old college dropout (Figure 1), who had*

Figure 1. 85th Civil Support Team, Drug Enforcement Agency, and other law enforcement agencies discuss a joint entry plan to obtain samples at local drug lab in order to perform hazard analysis.

been under surveillance for several weeks on suspicion of illicit drug distribution (Figure 2). Upon raiding this individual's home, authorities found a massive operational pill press capable of producing thousands of pills per day, and a second pill press being prepared for operation. In addition, over 1.5 million dollars in cash and nearly 1 million dollars in precious metals were recovered (Figure 3). More disturbing, was the large quantity of an unknown white powder. Upon identifying the large amount of powdered product and unknown agent, the house was declared a hazardous materials (HAZMAT) scene. This prompted a request for assistance (RFA) by the state's WMD-CST in order to assist with site characterization prior to federal law enforcement agents seizing evidence.[1]

At this juncture of the interview, LTC Dent began to describe his role as a PA for the WMD-CST, and a thorough description of the HAZMAT scene, both inside and outside the crime scene:

As the PA for the team, I provided immediate medical countermeasure plans to the unit commander and prepared the unit for exposures to potential unknown powders. We were also called to assist with the decontamination of responders and equipment, and asked to advise on how to mitigate the hazard. Over the next 18 hours, this upscale neighborhood became an active crime and HAZMAT scene. With the street cordoned with caution tape, our operators could be seen in Level A personal protective equipment (PPE) involving the use of a self-contained breathing apparatus (SCBA) taking samples and removing evidence from this house. The majority of the white powder was present in the building without packaging and in a loose state, but there was also one kilogram foil packages containing this powder. The loose powder was located adjacent to pill press machines, which were used to create a solid pill form, which would later be used to facilitate sale and distribution.[1]

LTC Dent goes on to describe how the WMD-CST is able to support local law enforcement by providing recommendations to guide follow on actions. It was at this stage, where he provides a thorough explanation of what products were identified in his case example of 2016 and how they were to be used:

The WMD-CST was able to use laboratory analysis to identify the hazard as fentanyl. Later, it was revealed the individual was using the pill press to create fentanyl tablets which appeared virtually identical to pharmacy supplied oxycodone. This was done in an effort to avoid detection. Additionally, these fentanyl tablets were used to adulterate alprazolam, in order to enhance its effect. Mass

Figure 2. 85th Civil Support Team LTC Dent prepares for mission involving fentanyl.

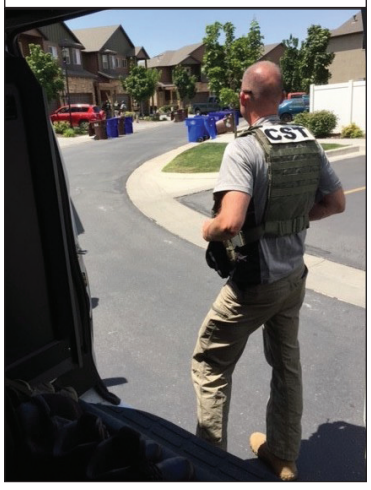


Figure 3. 85th Civil Support Team and Drug Enforcement Agency discover millions of dollars in cash within the building used for fentanyl pill manufacturing and distribution.

quantities of these fentanyl tablets were being produced and distributed to the local and regional community at large, contributing to countless numbers of drug overdoses in 2016, alone. The year 2016, as it turns out, was just the beginning of a 3-year span of back to back missions which involved pill press operations and synthetic opioid distribution. Many of these operations involved fentanyl or one of its derivatives, while others involved a host of other agents including oxycodone, alprazolam, and U-4770 (synthetic opioid which never obtained FDA approval, but is a popular illicit designer drug).[1]

Figure 4. Pill press found at drug lab was being used to manufacture fentanyl tablets for distribution.

At the end of our interview, when asked to summarize the impact of the WMD-CST PA on the outcome of this emergency, LTC Dent stated, "As a WMD-CST PA, I was uniquely suited to keep my unit and our fellow law enforcement agencies and first responders educated and safe during these missions. Thankfully, there were no life threatening casualties during these missions and everyone went home safe to their families."[1]

Background

Opioids are now the most common reason for accidental drug overdose fatalities in the US, with more than 1,000 emergency room (ER) visits and 91 fatalities per day.[2] Morphine is 25 times more potent than heroin, and fentanyl is 50-100 times more potent than morphine.[3] Illicitly manufactured fentanyl (IMF) has been around since the 1970s and was primarily used as an adulterant to heroin; however, the use of fentanyl became popular as a standalone drug and adulterant to other street drugs within the last 15 years.

From a medical treatment perspective, synthetic opioids are intended for the treatment of pain and trauma management in civilian and military settings. However ,opioids are easily accessed on the street and are often used as additives to other drugs, such as heroin.[4] For example, illicit drug submissions in Ohio testing positive for fentanyl increased 196% from 2012 to 2015.[5] Additionally, from 2012 to 2020, deaths from synthetic opioid overdose increased from 2,500 per year to more than 56,000 per year, a higher than 2,100% increase.[6] Multiple factors contribute to these statistics, including inappropriate prescribing practices of medical providers, but a significant cause is the increase of IMF, which has entered the street drug supply.[7]

Despite the risks of fentanyl, one study demonstrated only 1 out of every 3 drug users seen in the ER for opioid abuse realized they had used and been exposed to fentanyl, leaving 2 out of every 3 completely unaware.[8] The medical system has struggled to keep pace with the opioid epidemic and the introduction of vast quantities of synthetic opioids in our streets.[9] Though there have been regulatory and legislative changes made to combat the concern for poor prescribing practices, despite the intent, these changes likely contributed to an increase in illicit production of synthetic opioids as a primary source.[9]

Synthetic Opioid Production: The production of fentanyl analogs is a completely synthetic laboratory process. The 2 primary means of fentanyl analog synthesis are the Siegfried method and the more complicated Jansen method.[10] The DEA's Special Testing and Research Laboratory's (STRL) Fentanyl Signature Profiling Program (FSPP) identified 94% of the tested fentanyl in 2018 was produced by the Janesen method.[10] This more complicated chemical synthesis supports the utilization of formally trained chemists in more structured laboratory settings.

These formally trained illicit chemists have historically operated from the safe haven of the People's Republic of China. Drug dealers and users in the US are able to buy high purity fentanyl analog directly from these illicit Chinese laboratories, and, since 2014, China has been the primary source for fentanyl in the US.[11] Mexican cartels have also found a way to benefit from smuggling large amounts of fentanyl to the US primarily as a supply chain "middle man" along with limited domestic production as well.[11]

Over 2,500 lbs. of powdered fentanyl was seized by the US Customs and Border Patrol in 2019.[12] In the last few years, there has been an uptick in production and

distribution to the US from other Asian nations, primarily India.[11] In addition, dark web purchases account for a significant percentage of the fentanyl in the US, whereby the drug is packaged and shipped directly from suppliers in China, Mexico, and India. Generally, powdered product is shipped in foil packets which are then vacuum sealed in an attempt to avoid discovery by detection dogs. One kilogram of powdered fentanyl product can be used to make hundreds of thousands of pills and has a street value of approximately $900,000 US dollars.[12]

Figure 5. Various assortments of pills containing fentanyl mixed with either cellulose or adulterated oxycodone and midazolam found at clandestine pill manufacturing site.

Clandestine laboratory production of fentanyl analogues with pill press techniques in the US is historically rare, primarily because it can be obtained with relative ease and cost efficiency through the smuggling methods above. Figure 4 demonstrates an example of a pill press identified at an actual drug lab, where they were manufacturing fentanyl tablets for distribution.[1]

The extreme potency of these fentanyl analogs allows for only a small amount of product to be needed in order to produce significant end user effects. Pharmaceutical based agents (PBAs) were historically considered a low-risk threat to law enforcement and health care responders. Since 2012, due to the increased availability of fentanyl through the means described above, this has changed. The increase in illicit field pill press operations and drug mixing labs have raised the threat level, which has led to the increased utilization of CST's across the nation as an increasing number of clandestine fentanyl re-processing sites are identified and raided. CST's are requested by various civil authorities to respond to the threat, perform hazard assessments, and assist with mitigating the public health risks of these sites. Figure 5 depicts various assortments and mixtures of pills containing fentanyl identified at a clandestine pill manufacturing site.[1]

Synthetic Opioid Overdoses: There are 2 primary reasons that the US' current fentanyl epidemic is producing such an overwhelming number of overdoses. The first reason is the most obvious; there is simply more fentanyl being distributed to end users across the nation.[10] The second reason lies in the difficulty wholesale and street level drug dealers have in mixing these incredibly potent fentanyl analogs with the various binders, fillers, and other pharmaceutical materials, in amounts which will get someone high but not kill them. Similar to the difficulty in getting the same number of chocolate chips in every cookie, unfortunately, amateurs lack the means necessary to create a consistent dose of fentanyl in every pill.

Figure 6 demonstrates pictorial representations of high end counterfeit M-30's with gas chromatography-mass spectrometry (GC-MS) detected fentanyl analogs tested by the 10th CST with a glow germ powder mixed with common binders/fillers (mannitol/oxy blue) for 10th CST training exercise of first responders, and demonstrates the unevenly distributed amount of drug in each pill.[13]

Hazards to Healthcare Personnel: Common misconceptions regarding fentanyl include one touch can kill. law enforcement agent accidentally overdoses on fentanyl, new analogs of fentanyl are naloxone resistant, and dermal exposure is equal to respiratory exposure. Additionally, many are misinformed of actual personal protective equipment requirements and the factors which facilitate dermal absorption of these powder hazards.

Figure 6. Counterfeit M30's brought to the 10th Civil Support Team by local law enforcement; 10th Civil Support Team training prop showing ultraviolet (UV) active material unevenly distributed in pressed pills.

During the initial phase of exploiting pill pressing operations, there was significant concern in the first responder community about the

hazards posed by fentanyl powder (fentanyl hydrochloride) and the risks to first responders. This was primarily due to fentanyl's known toxicity in small doses, and the fact fentanyl can be effectively delivered transdermally through a patch. Headlines in the media included "Fentanyl: One Touch Can Kill," "New Strains of Fentanyl are Naloxone Resistant," and numerous anecdotal cases of law enforcement officers being exposed and intoxicated in the line of duty. The result of this notion was entire neighborhoods being cordoned, sometimes for days, and operators working in Level A PPE for hours on end to identify and mitigate a fentanyl pill pressing operation. In 2017, the American Academy of Clinical Toxicology published a just-in-time position statement which was critical in understanding fentanyl as a hazard and has guided PPE selection.[14] Figure 7 and Figure 8 depict 85th CST and DEA personnel entering crime scenes in different levels of PPE based on the phase of the mission and known downrange hazards.[1]

Figure 7. 85th Civil Support Team and Drug Enforcement Agency enter crime scene in level A personal protective equipment to perform site characterization and initial hazard assessment.

The following paragraph provides a summary of this position statement and the different routes of exposure. Powdered fentanyl is an inhalation hazard. Powdered products are highly unlikely to be airborne unless disturbed. Therefore, it is safe to operate in the vicinity of powdered fentanyl products with basic respiratory protection such as a properly fitted N95 mask.[14] Every effort should be made to avoid making powdered product airborne, to include avoiding brushing off clothing, use of firearms or explosives in the vicinity, and handling the product other than with caution and care. If operating in an environment where airborne product is likely, a higher level of respiratory protection, such as a filtering facepiece respirator (FFR) or air purifying respirator (APR), are recommended.

Figure 8. 85th Civil Support Team and Drug Enforcement Agency perform follow on entry into crime scene using level B personal protective equipment to obtain samples.

Fentanyl is also a possible ingestion hazard. The use of an N95 mask will filter out 95% of very small (0.3 microns) particles from getting onto the face and into the gastrointestinal tract. The particulate size of synthetic opioid powders ranges from 0.2 to 2.0 microns, depending on the means used to pulverize the powder.[14] Eating or drinking should not occur in the immediate vicinity of powdered product.

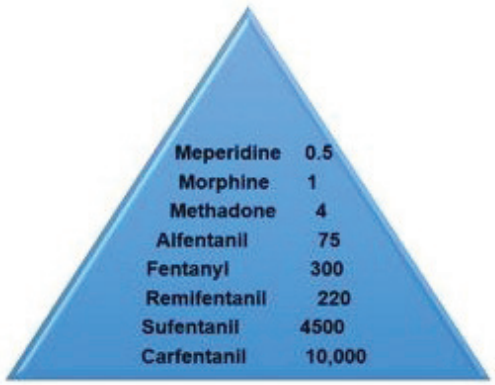
Fentanyl has a 30-fold increase in absorption across mucous membranes compared to the skin, and therefore ocular exposure presents a possible route for exposure.[15] One case report describes a male veterinarian who was splashed in the eye with 1.5 mg of carfentanil and 50 mg of xylazine. Though he performed thorough eye irrigation, he became lethargic and drowsy within the first 2 minute. Fortunately symptoms were reversed immediately with the administration of 100 mg IM naltrexone.[16] Although facial contact with liquid or powder opioids is unlikely, OSHA rated splash protection would be sufficient to prevent mucous membrane exposure to fentanyl.

Incidental dermal contact with powdered product is highly unlikely to be absorbed or cause intoxication. Coveralls and nitrile gloves are adequate for routine handling. Medicinal transdermal fentanyl utilizes a matrix designed to optimize delivery. Even with optimized delivery, it would take roughly 14 minutes of covering the bilateral palmar surfaces with transdermal patches to receive a 100 mcg dose.[17] In the event of contact with skin, physical removal followed by washing with soap and water is sufficient to prevent dermal absorption. Dermal absorption can be enhanced by breaks in the skin (abrasions, lacerations, or desquamating skin diseases like eczema). Dermal absorption can also be enhanced with the use of alcohol or lipid based hand sanitizers or lotions. It is standard policy to avoid using these products when the possibility of interacting with powdered fentanyl exists and instead stick with soap and water.

There has yet to be a single case of documented first responder intoxication with fentanyl verified with toxicology reports.[18] Despite multiple anecdotal reports of first responder exposure and intoxication,[19-22] to date all such reports have later been proven false.[18,23,24] When assessing a first responder for fentanyl intoxication, it is imperative to document the presence of respiratory depression which will guide administration of naloxone, and then

corroborate this with evidence of opioid intoxication using laboratory analysis. First responder incidents have been reviewed in detail retrospectively and determined not to be related to opioid toxidrome. Potential etiologies for these incidents include acute panic, anxiety, conversion disorders or an unrelated medical event. This issue highlights the need for continued education and training to reduce emergency responders' perceived overdose risk from exposure to fentanyl and other illicit synthetic opioids.[25]

Figure 9. Pyramid of potency: a comparison of opioids with morphine.[3,26,28-29]



Synthetic Opioid Treatment & Countermeasures: As a standard rule of thumb, opioid potency is measured in relation to morphine and this is termed the morphine equivalent dose (MED). The United States Drug Enforcement Agency reports that fentanyl is 50 to 100 times more potent than morphine,[26] and its rate of complications when not used under medical supervision is significantly higher, with increased rates of respiratory depression leading to anoxic brain injury and death. Figure 9 demonstrates a pyramid of potency, comparing other opioids with morphine.[3,26,28-29]

The 10 mg naloxone auto-injector is designed for fentanyl analogs such as carfentanil, remifentanil, lofentanil and ohmefentanyl, due to their higher affinity for mu opioid receptor (MOR) attachment and contains an increased dose, given to flood as many receptor sites as possible.[27] Carfentanil, a well known fentanyl analog used in veterinary medicine, is associated with a risk of intoxication and overdose due to its increased potency, which is reported to be 100 times stronger than fentanyl and 10,000 times stronger than morphine.[28-29]

Naloxone is a complete competitive opioid antagonist at the mu receptor site.[30-31] Naloxone also binds to kappa and delta receptors, and reverses the effects of opioids at the cellular level, is quick acting, and has minimal side effects.[32] Naloxone affects brain, brainstem, spinal cord, and gastrointestinal tract nerve cells. Fentanyl exposures typically require 1 to 2 times more naloxone than heroin, morphine, or oxycodone opiates. Additionally, the naloxone application is often dose-dependent for fentanyl.[33] There are no studies or case scenarios where a recommended dosage of naloxone has been quantifiably determined to reverse the effects of fentanyl analogs. Naloxone's half-life is 60-90 minutes.[34] The half-life of various opiates include morphine at 60-120 minutes, fentanyl citrate at 219 minutes, and carfentanil at 462 minutes.[35-37] Medical management following any synthetic opioid exposure should include the consideration of various PBA half-lives in order to provide more accurate long term care and management decisions.[35-37]

Medical management determinations are based on the specific agent, and the dose and route of exposure. Airway management is of the utmost importance in opioid overdose cases as depression of the respiratory center and drive to breathe can result in apnea and death. Routes of naloxone administration include intranasal, subcutaneous, intramuscular and intravenous. naloxone dosing is titrated to symptom management, so continuous supervision of the patient following an opioid overdose is imperative. When dealing with an unknown analog, and thus an unknown half-life, initial naloxone doses may cease effectively controlling opioid intoxication, resulting in a previously awake and alert patient developing loss of consciousness and apnea.[35-37]

Routes of naloxone administration include intranasal, subcutaneous/intramuscular, and intravenous.[28] The naloxone Auto-injector Rapid Opioid Countermeasure System (ROCS) dose is 10 mg, to more effectively reverse the effects of opiates, and can be administered through personal protective equipment.[12] Naloxone auto-injectors are utilized by military and first responders in environments where fentanyl analogues may be encountered or suspected.[11]

Naloxone resistance is a myth. The initial standard dose of naloxone should be sufficient to reverse most synthetic opioid overdoses. However, due to the potency of some agents, standard initial doses may be insufficient, and, therefore, multiple doses of naloxone over time will be required. In a review of fentanyl analog intoxications from multiple major US cities, even highly potent analogs such as furanylfentanyl and carfentanil were documented to have good responses with standard doses of naloxone. Some fentanyl analogs may require higher doses of naloxone, but this should not be confused with being resistant. Kang et al demonstrated in their rat brain model naloxone was able to displace carfentanil from receptor sites rapidly when assessed in vivo in

the thalamus.[38] To date, one patient has been identified who did not respond to naloxone reversal; however, later analysis revealed the patient had a blood pCO2 of 138, making reversal a futile venture.[39] As discussed in the Clark et al case review, it was determined the half-life of naloxone for natural opiates compared to the half-life for synthetic opiates (such as morphine, fentanyl, and carfentanil) was too short.[34]

Responder Decontamination: Decontamination of synthetic fentanyl analogs is dependent upon the surface being decontaminated. For patient decontamination, it is imperative to protect the airway from inhaled particles. Place an N95 or surgical face mask on the patient if airway management allows in order to prevent the inhalation of airborne powders. Physical removal of the agent is paramount and can be accomplished with a simple microfiber cloth. Clothing should be removed in its entirety and bagged as hazardous material (marked "fentanyl"). Following physical removal of gross contamination, a thorough soap and water decontamination is sufficient for skin. Eyes should be irrigated thoroughly in suspected eye contact. Patients who are exposed should be monitored for signs of opiate intoxication for 12 hours.

Equipment decontamination can be accomplished with physical removal of agent (microfiber wiping) followed by application of a decontamination solution of standard bleach or a pH adjusted bleach solution. Standard bleach solution is unreliable as it degrades over time. Over-the-counter bleach solutions may have a degradation time of up to 10% in the first week after production. This is due to bleach being made by percolating chlorine gas with water and hydrogen peroxide. When complete, there is an excess of 1-2% hydrogen peroxide. Residual peroxide makes the product unstable and releases chlorine gas but the bleach has less oxidizing capacity.[40] A widely available alternative is using a pH adjusted bleach solution with sodium dichlorisocyanurate (BruTab 6), which can be constituted fresh for every incident, has a effectiveness time of 6 hours, and can be applied with a simple spray device such as a garden sprayer. In an unpublished study, there was a very high success rate in decontaminating PPE and personal equipment grossly contaminated by a fentanyl hydrochloride dispersion using sodium dichlorisocyanurate. The few instances of contaminants detected in the cold zone (out of hundreds of samples), in retrospect, were determined to have inadequate contact time with decon solution. Two tablets in a 1-gallon garden sprayer are sufficient and have a shelf life of 6 to 8 hours. It is extremely important to ensure complete saturation and a 2 to 5 minute contact time before rinsing and drying the equipment, as fentanyl hydrochloride tends to be hydrophobic unless overwhelmed with decontaminating solution. Other solutions such as Dahlgren Decon are proven effective but not likely to be available to first responders.

Synthetic Opioids as Weapons of Mass Destruction (Incapacitating Agent): In 2002, an armed hostage situation took place in a theater in Moscow, Russia, which changed conceptions of the weaponization of opioids.[41-42] Russian Special Forces piped in a gas through the ventilation system rapidly subduing the armed Chechen assailants inside the theater as well as the hostages.[42] After piping the gas, the terrorists and hostages became unconscious and stopped breathing. Very few of the hostages received adequate airway management or naloxone countermeasures. A total of at least 23 terrorists and 129 hostage deaths occurred during this event.[41-42] Of those deaths, 125 hostages died from the aerosol and inadequate medical care after being rescued.[42] The Russian government did not disclose the components of the gas used, making medical care difficult.[42] The initial reports were the gas was a combination of fentanyl and halothane.[41] However, the time to incapacitation and sheer amount of gas needed to create incapacitation in such a large space would prove to be scientifically unlikely to have been achieved without alerting the gunmen.[41] After litigation from families of victims and survivors, Russian officials still would not disclose the true chemical makeup of the gas, so a study of clothing and urine from 3 survivors was used to discover the components.[42] Analysis of these items found the gas was a combination of 2 fentanyl analogs known as carfentanil and remifentanil.[42] Two of the 3 survivors reported incapacitation from the gas in less than 30 seconds from exposure.[42] Remifentanil is reported as 220 times more potent than morphine, and carfentanil as 10,000 times more potent than morphine.[26] The only known use of carfentanil on humans was during this incident. This case demonstrated the feasibility and potential of a PBA and fentanyl analogs to be used as a WMD, forcing the chemical, biological, radiological, nuclear, explosive response element (CRE) to take an active posture against this threat.

National Guard PA Role in Response: As a PA assigned to a WMD-CST, an all-hazards approach to training and equipment is utilized, ensuring the team is prepared for any medical situation they may encounter. The PA must be the subject matter expert in identifying the signs and symptoms of exposure, as well as be prepared to provide emergent treatment should an exposure occur.

Due to classification restrictions, specific training courses the PA completes cannot be shown here, but training includes the PA focus on a multitude of areas with specific focus on cardiac and respiratory management in

emergency situations, as well as emergency response and identification of symptomatology of synthetic substances. PAs attend courses with other CST members which help them learn and identify the pharmaceutical and chemical precursors, as well as lab processes which may indicate the presence of synthetic opioids and fentanyl production.

Equipment stockages are created in such a way to ensure the same all-hazards preparedness. The increase in prevalence and risk of synthetic opioids, and PBA presence in CST operations, has led to ensuring pharmaceutical and medical countermeasures are always immediately available to the PA, allowing for prompt treatment of any signs and symptoms of exposure, toxicity, or overdose. Common medical treatment for overdose includes naloxone, as discussed, and respiratory support by way of supplemental oxygen, airway management, and ventilatory support.

Evaluation and treatment must happen in rapid succession, and sometimes simultaneously to the decontamination process. While the patient response to medical countermeasures is often rapid, the PA must be cognizant of the delays in treatment and potential for rapid onset of respiratory depression or respiratory arrest after exposure to synthetic opioids and fentanyl.

Conclusion

PBAs such as synthetic opioids and IMF are a threat to our society and global health security.[43] As access and distribution of these drugs continues to become more prevalent across the nation, it is reasonable to expect an increase in drug user overdoses,[44] specifically because the manufacturers of these pills have little reason to have each tablet contain the same dose as the last. This is particularly concerning for opioid naive individuals who decide they want to experience a new drug and unknowingly use a drug laced with fentanyl or some other analog. Naloxone is an extremely effective and useful tool for reversing signs and symptoms, though some agents will require additional doses in order to maintain the desired effect of a conscious, breathing patient. Further education is needed to dispel many of the myths surrounding fentanyl and its derivatives; however, steps are being taken to educate the public, medical first responders, and hospital first receivers. In addition to the risk of overdose in US civilians, other state actors have utilized fentanyl and its analogs as what can only be considered a WMD. CST PAs will continue to be a stopgap and resource to the Department of Defense and the National Guard, especially in the event of an act of domestic terror involving these agents in the future.

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Accuracy of Needle Thoracostomy Site Selection among US Army Medics

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Abstract

Background: Tension pneumothorax is a prominent cause of potentially survivable death on the battlefield. Field management for suspected tension pneumothorax is immediate needle thoracostomy (NT). Recent data noted higher NT success rates and ease of insertion at the fifth intercostal space, anterior axillary line (5th ICS AAL), leading to an amendment of the Committee on Tactical Combat Casualty Care recommendations on managing suspected tension pneumothorax to include the 5th ICS AAL as a viable alternative site for NT placement. The objective of this study was to assess the overall accuracy, speed, and ease of NT site selection and compare these outcomes between the second intercostal space, midclavicular line (2nd ICS MCL) and 5th ICS AAL among a cohort of Army medics.

Methods: We designed a prospective, observational, comparative study and recruited a convenience sample of US Army medics from a single military installation to localize and mark the anatomic location where they would perform an NT at the 2nd ICS MCL and 5th ICS AAL on 6 live human models. The marked site was compared for accuracy to an optimal site predetermined by investigators. We assessed the primary outcome of accuracy via concordance with the predetermined NT site location at the 2nd ICS MCL and 5th ICS MCL. Secondarily, we compared time to final site marking and the influence of model body mass index (BMI) and gender on accuracy of selection between sites.

Results: A total of 15 participants performed 360 NT site selections. We found a significant difference between participants' ability to accurately target the 2nd ICS MCL compared to the 5th ICS AAL (42.2% versus 10% respectively, $p<0.001$). The overall accuracy rate among all NT site selections was 26.1%. We also found a significant difference in time-to-site identification between the 2nd ICS MCL and 5th ICS AAL in favor of the 2nd ICS MCL (median [IQR] 9 [7.8] seconds versus 12 [12] seconds, $p<0.001$).

Conclusions: US Army medics may be more accurate and faster at identifying the 2nd ICS MCL when compared to the 5th ICS AAL. However, overall site selection accuracy is unacceptably low, highlighting an opportunity to enhance training for this procedure.

Keywords: pneumothorax; training; performance; procedural skills

Introduction

Tension pneumothorax (tPTX) is a life-threatening condition occurring in thoracic trauma, representing one of the 3 most common potentially survivable deaths on the battlefield.[1,2] Prehospital management of this life-threatening condition is of significant interest in the military operational setting. Initial field management for patients demonstrating clinical evidence of tension physiology is needle thoracostomy (NT).[3] Proper NT placement is critical as failure to properly manage a tPTX may lead to worsening tension physiology and, ultimately, death.[4] A 2013 post-mortem analysis of combat casualties noted a successful NT placement rate of only 59% (although the role of the personnel performing these interventions is unknown).[5]

The Committee on Tactical Combat Casualty Care (CoTCCC) recently updated guidelines for the performance of this procedure at the second intercostal space, mid-clavicular line (2nd ICS MCL), or alternatively at the fifth intercostal space, anterior axillary line (5th ICS AAL).6 A prior cadaveric study demonstrated a high failure rate at the 2nd ICS MCL due to suggested factors of body mass index (BMI) and gender which may influence chest wall thickness at this anatomic site.[7] Both radiologic and cadaveric studies demonstrate the chest wall at the 5th ICS AAL to be significantly thinner than the 2nd ICS MCL.[8,9]

A 2015 study involving 25 Navy corpsmen compared successful NT placement rates between the 2 sites in a cadaveric model. Investigators noted higher success rates at the 5th ICS than the 2nd ICS (78% versus 18%, p=0.001), and increased mean distance from the correct position at the 2nd ICS. Additionally, participants rated the 5th ICS as easier for insertion.[7] These findings likely contributed to the impetus for a change in the CoTCCC recommendations on managing suspected tPTX to include the 5th ICS as an acceptable initial site for NT insertion.[6]

A later study in 2018 demonstrated a cohort of 33 emergency medicine residents could accurately identify the 5th ICS in only 48% of attempts.[10] These results are similar to another study noting in a group of 25 Advanced Trauma Life Support (ATLS) trained emergency physicians, while 88% correctly named the site of NT insertion as the 2nd ICS, only 60% were able to mark the site for insertion accurately.[11] These findings call into question the influence of the training intervention provided to the participants of the corpsmen study. In the study, participants underwent cadaver-based refresher training 2 weeks before data collection,[7] whereas Army medics are unlikely to receive cadaver-based refresher training before performing NT on the battlefield. That study also did not include cadaver characteristics of BMI and gender, despite noting these characteristics may influence the accuracy of NT site identification.

This study aimed to assess accuracy and speed of NT site selection among a cohort of Army medics. We compared these outcomes between the 2nd ICS MCL and the 5th ICS AAL. Secondarily this study examined the influence of model BMI and gender on the accuracy, speed, and ease of selection between sites. To date, we are unaware of any studies comparing accuracy and speed in NT site selection amongst US Army medics.

Methods

Outcome Measures: The primary outcome of this study was the accuracy of site selection between the 2nd ICS MCL and the 5th ICS AAL. Secondary outcomes included time to site selection. We compared results between the 2nd ICS MCL and the 5th ICS AAL among a cohort of US Army medics utilizing live models of varying body types. We defined accuracy as within 3 centimeters (cm) radially from the ultrasound-determined site. Time was measured in seconds from the time of drape removal to completion. We also conducted a subanalysis to determine model BMI and gender influence on accuracy of site selection. We assessed model BMI and gender influence by comparison of medic performance across 6 volunteers: 3 females and 3 males with varying body types.

Study Design: The Human Research Protection Office, US Army Regional Health Command-Central, qualified protocol 21-13612 as exempt from institutional review board oversight. This prospective observational study assessed Army medics' ability to locate potential NT sites using anatomical landmarks.

Population: The inclusion criterion for this study was US Army medics with military occupational specialty (MOS) 68W. US Army medics are nationally registered Emergency Medical Technicians-Basic and are often the first medical responders on the battlefield. Their duties include basic medical care, combat casualty care, triage, and training combat lifesavers.

We recruited volunteers from a convenience sample just before beginning their required annual refresher training at the Medical Simulation Training Center (MSTC). All participants completed initial training at least 1 year before data collection, which includes landmark identification and NT placement, typically conducted on manikins.

Data Collection: We gave volunteers a paper copy of informed consent for signature, and they retained a copy of an information sheet outlining the study procedures. We also recruited volunteer models from the same pool of participants and a few serving as refresher training faculty. Participants who served as models did not participate in NT site selection. Model participants underwent a separate written consent process with different information sheets delineating their participation, associated risks, benefits, alternatives to participation, and withdrawal. We then recorded the model participants' gender, height, and weight. The model participant pool consisted of 3 male and 3 female models.

After the models consented, study investigators preidentified the 2nd ICS MCL and 5th ICS AAL bilaterally utilizing anatomic landmarks, confirmed these sites

with ultrasound, and then marked each with a black light pen invisible without the use of a black ultraviolet light. For landmark identification, we followed CoTCCC guidelines.[6] Female models draped towels over their breasts for privacy, and investigators taped the towels in place to allow for adequate simultaneous exposure of the 2nd ICS MCL and 5th ICS AAL. We covered all models entirely with a sheet before each attempt. We then randomized participants to each model combination and the order of NT site selection. We conducted randomization using commercially available software.

Table 1. Model demographic data, accuracy and time to site selection by site.

Model	Gender	BMI	AAL accuracy, n/30 (%)	MCL accuracy, n/30 (%)	AAL median time to selection (IQR)	MCL median time to selection (IQR)
1	Female	23	9 (30%)	13 (43%)	13.5 (15.3)	9 (8.8)
2	Male	30	5 (17%)	10 (33%)	13.5 (11)	8 (8.3)
3	Female	31	2 (7%)	11 (37%)	13.5 (22.8)	9 (5)
4	Female	19	0	13 (43%)	11 (11)	8 (7)
5	Male	29	0	14 (47%)	12.5 (12)	10 (5)
6	Male	25	2 (7%)	15 (50%)	11.5 (10)	9.5 (8)
Total accurate, n (%)			18 (10%)	76 (42.2%)	$p < 0.001$	
Median time (IQR)			12 (12)	9 (7.8)	$p < 0.001$	

Body mass indez: BMI; anterior axillary line: AAL; midclavicular line: MCL; inter-quartile range: IQR

Time started when the sheet was removed from the model and stopped once the participant marked the landmark with a colored marker. Following the completion of all 4 NT site selections by the participant on each model, each site was inspected under black ultraviolet light and compared to the pre-identified site. We defined accuracy as the marked area being within 3 cm radially from the correct area marked by investigators. We chose 3 cm to avoid medial placement which might damage prominent vasculature in the chest cavity when selecting the 2nd ICS MCL. This distance was based on a prior cadaveric study which revealed multiple NCD placements at a mean distance of 3.1 cm from the target 2nd ICS MCL site did not lead to iatrogenic injuries.[7] We applied the same 3 cm standard to the 5th ICS AAL.

We then erased participant marks with alcohol swabs to avoid prejudice in site selection for the next participant. Once participants completed site selection with all 6 models, they were asked for feedback. Finally, they discussed how they chose their NT sites versus how the investigators identified them.

Data Analysis: We performed a pre-study power analysis for the primary outcome measure of accurate site selection rate. Based on prior studies by Taylor et al[10] and Ferrie et al,[11] we estimated a 90% accurate site selection rate for the 2nd ICS and 40% for the 5th ICS. Using a 2-sided α of 0.05 powered to 0.8, we required a sample size of 24 participants to detect a significant difference of 50% between anatomical sites. We requested 30 participants to account for a 25% dropout since we anticipated volunteers would leave early if the study ran beyond the scheduled duty day.

Data was analyzed using commercially available software. The primary outcome of accurate site selection rate was binary (yes/no) and reported here as percentages, which we analyzed using Chi-square testing. The secondary outcome of time was recorded in seconds and listed here as medians with interquartile ranges. We analyzed this data using Mann-Whitney test due to non-paramatric distribution. We also performed logistic regression to determine if model gender and BMI influenced the accuracy of site selection.

Results

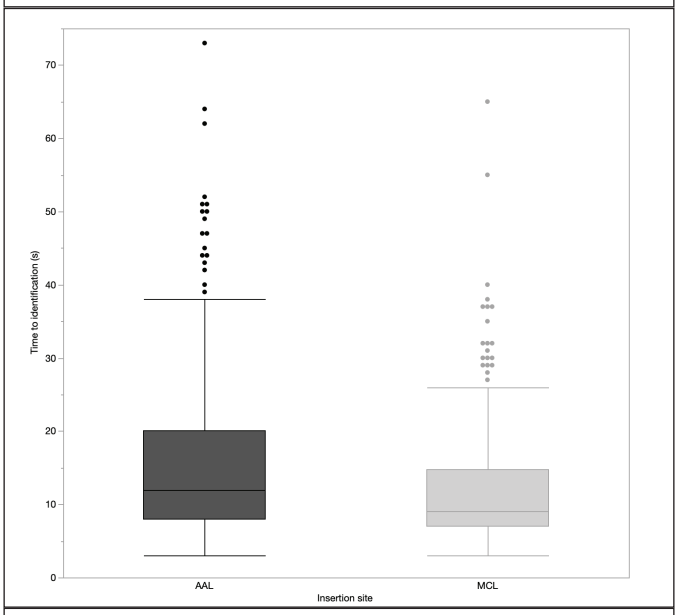
We recruited 20 participants and 6 models on the first day of annual medic refresher training at the Fort Hood MSTC. We collected all data on the fourth day of refresher training. All participants were US Army medics and had completed initial military occupational specialty (MOS) training. Five of the 20 volunteers removed themselves from the study without a stated reason. The 6 recruited models split evenly between male and female, with a BMI range of 19-31, and a mean of 26.17 (Table 1).

The 15 participants who completed the study performed 4 site selections on the 6 models, totaling 360 NT site selections: 1 at each of the 6 models' left and right 2nd ICS MCL and 5th ICS AAL. Participants demonstrated a significant difference in their ability to accurately identify the 2nd ICS MCL compared to the 5th ICS AAL (42.2% versus 10%, $p<0.001$), with an overall accuracy of 26.1% among all site selections. Similarly, participants demonstrated a significant difference in time-to-site identification favoring the 2nd ICS MCL over the 5th ICS (median [IQR] 9 [7.8] versus 12 [12] seconds, $p<0.001$) (Figure 1).

While noting a trend towards higher accuracy when selecting sites on female models (26.7%) versus male models (25.6%), this was without significance ($p=0.62$). Similarly, volunteers tended to demonstrate a lower accuracy when selecting sites on models with a higher BMI, with odds of accurate site selection decreasing by

1.2% (95% CI [-7.7, 5.8]) for each point increase in BMI; however, this relationship was also not statistically significant (p=0.74).

Figure 1. Time to site selection by site (in seconds).



AAL: anterior axillary line; MCL: midclavicular line

Discussion

Our data demonstrate US Army medics appear to be more accurate with NT site selection at the 2nd ICS MCL (42.2%) compared to the 5th ICS AAL (10%). In addition, participants targeted the 2nd ICS MCL with a median time of 3 seconds faster than the 5th ICS MCL overall. Model gender and BMI comparison did not demonstrate significant differences in NT performance.

Our study suggests US Army medics in this sample population to be more accurate and faster at selecting the 2nd ICS MCL than the 5th ICS AAL for NT. These results contradict previous literature, which reported a misplacement rate at the 2nd ICS MCL of 82% versus 22% at the 5th ICS AAL.[7] These disparate results favoring the 2nd ICS MCL may be due to training, given US Army medics are traditionally taught to perform NT at the 2nd ICS MCL. The performance of NT at the 5th ICS AAL was added to CoTCCC guidelines in 2018.[6] This change is somewhat recent, potentially limiting opportunities to widely learn and practice the performance of NT at this site and potentially influencing our results. However, we are unclear on the exact NT techniques practiced at advanced individual training, and training may vary between classes.

An interesting finding in this study was the overall accuracy of 26.1%, which is remarkably similar to a previous study which noted cadaveric learning (as opposed to slideshow-based education) led to placement accuracy of 25%.[11] Neither live nor cadaveric models are part of annual MSTC training, and the difference between human tissue and plastic training manikins is substantial.

While in this sample population US Army medics located the 2nd ICS MCL more accurately and faster this does not necessarily infer the incorrectly identified 5th ICS AAL site selections, if used for a real NT, would not adequately decompressed a tPTX. A cadaver-based study from 2011 found 100% (n=40) of NTs attempted in the 5th ICS AAL were successful compared to only 57.5% in the 2nd ICS MCL corroborates this.[8]

Further research on this topic should include efficacy comparisons of different training philosophies and interventions, specifically comparisons of live model training versus slide-based training on the performance of site selection and NT site selection. Interestingly, participants were observed utilizing 1 of 2 identification techniques for the 5th ICS AAL. They were observed to either count ribs or use the European trauma course hand technique, which involves placing the participant's hand in the axilla and utilizing the fifth digit as a marker of the fourth or fifth ICS. However, CoTCCC guidelines do not direct this technique. Future studies should include this information study development. Future studies should also assess site-specific accuracy among varied body types to optimize care for the range of patients encountered on today's battlefield.

The primary limitation of this study was the small convenience sample of participants from a single military installation, which significantly limits this study's generalizability. This small sample size led to underpowering, limiting the validity of comparative analyses. Participants performed site selection on healthy volunteer models in a controlled, simulated environment. These results may not be generalizable to severely injured casualties in an immensely stressful combat environment. Participants did not report their experience or training performing NT in general or specific to the 2 anatomical regions in question. Therefore, we cannot accurately determine the influence prior training may have had on study results.

Additionally, despite better site selection at the 2nd ICS MCL when using 3 cm radially as a standard, we cannot comment on whether accurate identification at the 2nd ICS MCL would be successful. We used 3 cm radially as this is the approximate distance lateral which would be sure to avoid underlying critical structures. However, 1 cm superior or inferior could be unsuccessful as ribs

may block the insertion of the needle.

Finally, it is important to note accurate anatomic site selection is only one of several confounding factors which may determine successful NT procedure performance. Training, environmental conditions, insertion technique, equipment, and anatomic variability can all influence successful NT performance. Failed NT attempts can still occur despite successful anatomic site selection as defined in this study. Likewise, successful attempts could be made outside of this study's defined area of accuracy. While we used 3cm radially as this is the approximate distance lateral which would be sure to avoid underlying critical structures, anatomy is highly individualized and may variably influence NT success and/or complications.

Conclusion

US Army medics demonstrate improved accuracy and faster NT site selection at the 2nd ICS MCL compared to the 5th ICS AAL. However, overall site selection accuracy is unacceptably low. This finding highlights an opportunity to enhance training with this potentially lifesaving procedure. US Army medics may benefit from training with human models of with a wide range of body types at both the 2nd ICS MCL and the 5th ICS AAL for increased familiarity prior to combat deployments.

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A Review of Intermittent Fasting as a Treatment for Type 2 Diabetes Mellitus

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Abstract

Introduction: The purpose of this review is to explore intermittent fasting (IF) versus continuous energy restriction as a treatment of Type 2 Diabetes Mellitus (T2DM). The precursor to diabetes is obesity, which currently threatens the Department of Defense's ability to retain and recruit adequate service members. Intermittent fasting may be an adjunct for prevention of obesity and diabetes in the armed forces.

Objectives: Weight loss and lifestyle modification are long-standing treatments for T2DM. The objective of this review is to compare IF to continuous energy restriction.

Methods: PubMed was searched from August 2013 to March 2022 for systematic reviews, randomized controlled trials, clinical trials, and case series. Inclusion criteria were studies which monitored HbA1C, fasting glucose levels, diagnosis of T2DM, ages 18-75, and a body mass index (BMI) greater than or equal to 25 kg/m2. Eight articles met these criteria and were selected. These 8 articles were separated into Categories A and B for this review. Category A includes randomized controlled trials (RCTs), and Category B consists of pilot studies and clinical trials.

Results: Intermittent fasting proved to have commensurate decreases in HbA1C and BMI compared to the control group, but not to a statistically significant degree. It cannot be said that IF is better than continuous energy restriction.

Conclusion: More research is needed on this topic as 1 in 11 people suffer from T2DM. The benefits of IF are apparent, but there is not enough breadth of research available to affect clinical guidelines.

Keywords: intermittent fasting; diabetes mellitus; glycemic control; lifestyle modifications

Introduction

Diabetes affects roughly 1 in 11 adults worldwide, and Type 2 Diabetes Mellitus (T2DM) encompasses 90% of the total figure.[1] The only country with more documented cases of T2DM than the US is China, so the condition is an ever-present malady medical providers deal with daily. Pharmacologic treatment focuses mainly on insulin secretion and sensitivity which cause a host of known and expected side effects. These medications work but are best when combined with lifestyle modification. There is ongoing research which argues lifestyle modification is more effective than standard medical care consisting of pharmacologic control of HbA1C.[2]

Intermittent fasting (IF) has the potential to positively impact the fight against obesity and improve the readiness of the US military and its recruitment. Obesity is the precursor to diabetes and poses a tremendous problem for Department of Defense recruiting. Currently, 19% of military men and women ages 18-24 would be unfit for service due to obesity. Most enlisted recruits come from the Midwest and Southern US, both of which

have the highest obesity prevalence in the country. Obesity costs the US military 1.2 billion dollars a year and results in decreased readiness, proficiency, and capability. IF may be beneficial for glycemic control and diabetes treatment primarily through the action of decreasing body fat percentage along with body mass index. Therefore, it may also be beneficial for treating obesity before the onset of diabetes occurs.[3]

Table 1. Category A articles: randomized controlled trials (RCT).

Article	Type of Fasting	Duration	HbA1C
Li et al[14]	300 daily calories	1 week	No significant change
Corley et al[10]	"2 and 5" style	3 months	Decrease
Carter et al[6]	"2 and 5" style	3 months	Decrease
Carter et al[13]	"2 and 5" style follow up	3 months-follow up	Increase
Kahleova et al[11]	2 large meals vs 6 small meals	3 months	Decrease
Sundfor et al[12]	"2 and 5" style	3 months	Decrease

Studies show IF has positively impacted biomarkers in aging, health, and disease. IF acts at the molecular level to stimulate stem cells, activate immune cells, and reduce autoimmunity overall.[4] It also has been shown to help relieve many common risk factors of T2DM and may be an adequate treatment. The difference with IF versus continuation energy restriction is the "refeeding" or "break-in fast" stage. This article review investigates whether IF can be used as an adequate treatment compared to continuous energy restriction in patients with T2DM.

Caloric restriction is an adequate treatment for patients with TD2M and has been shown to decrease all-cause mortality and improve physical and cognitive function.[5] The interest in IF as a therapeutic measure is high due to increasing patient compliance to treatment and the possibility of increased metabolic benefits. Carter et al[6] states the compliance issue is simple: It is easier to have patients fast for short durations versus an indefinite continuous energy restriction. The metabolic benefits are still not thoroughly verified. Still, the rapid movement from energy restriction to a normal state may improve glucose regulation, inflammation suppression, and increased stress resistance.[7] This benefit can occur weekly in most IF regimens instead of once in a continuous energy restriction regimen.

IF is a broad, multifaceted term. For this review, IF will be the umbrella into which a myriad of different diets fall. IF fasting in the literature is also known as fasting-mimicking diets (FMDs), time-restricted feeding (TRF) and intermediate energy restriction (IER). All of these terms encompass many different diets. The diets included in this review are 16-hour fasts with 8 hours of feeding, alternate-day fasts (24 hours of fasting, 24 hours of feeding), a 1-time fast of 1 week, and the most common, a "5 on, 2 off" approach, where patients fast for 5 days and eat a regular diet the next 2 days. The main takeaway is these different fasts result in vastly different physiologic outcomes. Therefore, when anyone reads a study on IF, FMDs, IERs, it is pivotal the reader notes the type of fast conducted. The fasting type, to include duration and caloric intake variability, is tremendously more important than the term the trial proctor uses to describe them. For this review, studies will be referenced by the author or the fast conducted as noted in Table 1 and Table 2.

There is no guideline on what lifestyle method is best. It has been shown intensive caloric restriction can lead to remission of T2DM in a relatively quick manner.[8] However, this can be too drastic for some patients. The median in between these lifestyle changes could be utilizing IF as a treatment. This review aims to analyze currently available data in regards to IF as a treatment of T2DM.

Methods

This study followed the Preferred Reporting Items and Systematic Reviews and Meta-Analyses (PRISMA) guidelines and the PRISMA-IPD statement.[9] This systematic review was conducted through a search of PubMed from August 2013 to March 2022. The MeSH terms used were "Type 2 Diabetes Mellitus" and "Fasting;" multiple keywords were used to collect as many relevant randomized controlled trials, clinical trials, pilot trials, and case series on IF and T2DM as possible.

The initial search string resulted in 712 articles. All books, documents, and articles before August 2013 were excluded. Further exclusion criteria included omitting articles without relevant titles or did not include T2DM in their study design, as many IF studies cover other disease processes. After filtering exclusion/inclusion criteria, there were 103 articles which needed screening.

Inclusion criteria were published case series, clinical trials, randomized controlled trials, and meta-analyses articles that monitored HbA1C and fasting glucose levels, diagnosis of T2DM from ages 18-75, and a BMI greater than or equal to 25 kg/m^2. Eight articles met these criteria and were selected. These 8 articles were separated into Categories A and B for this review. Category A includes RCTs, and Category B consists of a pilot study and clinical trial.

Results

IF has been shown to reduce risk for many health issues, but its efficacy as a treatment has limited research. There were several analytical metrics used in the selected studies on IF. Glycemic control and body composition (BMI or change of body fat percentage) were the foundation of these metrics; the others consisted of blood pressure, quality of life, and adverse reactions. The results are broken down first by analytical metric and further into Category A (RCTs) and Category B (pilot study/case series).

Table 2. Category B articles: pilot studies and clinical trials.

Category B Article	Type of Fasting	Duration	HBA1C
Furmli et al[15]	Patients 1/2: Alternating 24 hour fasts Patient 3: 3 24 hour fasts/week	11 months	Decrease
Arnason et al[16]	3 (2 week normal, 2 week 18-20 hour fast, 2 week back to normal)	6 months	Decreased

Glycemic Control: The majority of RCTs resulted in improved glycemic control. Corley et al,[10] Carter et al,[6] Kahleova et al,[11] and Sundfør et al[12] all had a statistically significant decrease in HbA1C levels. Carter et al,[13] the follow up in his 2018 RCT, marked an increase of HbA1C levels. Fasting glucose was measured throughout but was significant in Li et al,[14] where there was no observed improvement in HbA1C but a decrease in fasting glucose. Carter et al[6] concluded fasting is safe for patients with T2DM who do not use medication likely to cause hypoglycemia. Corley et al[10] measured glycemic events following their fasting regimen. They found a 2-time increase of hypoglycemic events overall on fasting days but a decrease in overall glycemic events on all days combined. Kahleova et al[11] concluded a decrease in fasting glucagon for the A2 group and an increased fasting glucagon in the B6 group. For category B, Furmli et al[15] showed a decreased HbA1C, and Arnason et al[16] showed a decreased fasting blood glucose level.

Body Composition: Every study in category A had a marked decrease in BMI or body fat percentages. Li et al[14] had the highest overall average reduction in BMI of 3.5-4.5%. Corley et al[10] showed a decreased BMI and body fat percentage but a larger decrease in body fat percentage. For Carter et al,[6] there was a significant decrease in BMI and body fat percentage in both the continuous energy restriction and intermittent energy restriction group; there was no significant difference between the 2 groups. Conversely, in Kahleova et al,[11] both groups showed a BMI reduction, but there was a larger reduction in the B2 group eating 2 meals a day compared to the A6 eating 6 meals a day. All category B studies included a decrease in BMI or body fat percentages.

Other Measures: Three of 6 Category A studies measured blood pressure, and 2 of those 3 showed a decrease. Li et al[14] showed a significant improvement in blood pressure, while Sundfør et al[12] showed a marked reduction in both systolic and diastolic blood pressure. Li et al[14] and Corley et al[10] included an increase in quality of life assessed by The Five-Item World Health Organization Well-Being Index (WHO-5). For Category B, Furmli et al[15] showed complete discontinuation of insulin as medication for all 3 patients involved in the case study.

Adverse Effects: Overall, the studies did not result in severe adverse effects or reactions. Adverse reactions noted in Li et al*14* were dizziness, fatigue, and headache. For Sundfør et al,[12] there was an increase of dizziness, mild headache, mild nausea, and temporary sleep disturbance for those in the intermittent energy group versus the continuous energy group. There were similar minor adverse effects noted in category B.

Discussion

Studies show IF has positively impacted biomarkers in aging, health, and disease. This article review investigates whether IF can be used as an adequate treatment compared to continuous energy restriction in patients with T2DM.

Type of Fasting: The type of fast conducted and the length of those fasts is arguably the most critical aspect of each study. A more in-depth look at each study's type of fasting is needed to interpret the data. If patient A fasted for 24 hours every other day and patient B fasted for 12 hours daily, there would be apparent physiological differences. Dietary modification of a fast for 1 week, regardless of the type, will most likely have a different result than a fast conducted for 3 months. This review incorporates studies that examine various types of fasting in terms of the number of hours fasted and the length of the dietary modification.

Li et al[14] conducted a 1-week, 1-time fast. When most people think of fasting, they think of a prolonged dietary modification for weeks to months. This 1-week, 1-time study aimed to elicit the action of fasting itself can be used as a supplement treatment for those with T2DM. The study utilized a 2-day low-calorie diet followed by a 7-day period. Participants received a liquid-only diet of water, tea, fruit juice, and vegetable soup, not to exceed 300 daily calories.[14] The patients then underwent a 3-day

low-calorie diet followed by an incremental increase in solid food. This study is monumental in that it analyzes the efficacy of a rapid fasting treatment. The other analyzed studies are prolonged and incorporated days where the patients could eat whatever they wanted. Li et al[14] was the single most restrictive study and the only study where solid food was completely removed.

On the opposing side, Corley et al,[10] Carter et al,[6] and Sundfør et al[12] all conducted the following fasting protocol: 2 days of fasting with 5 days of standard dietary actions. Corley et al[10] and Carter et al[6] allowed their patients to eat whatever they wanted, while the other restricted their patients to eat a Mediterranean style diet. This is the more traditional fasting protocol for scenarios where the purpose is measuring patient progress in a longitudinal manner versus acutely as in the 1-week fast in Li et al.[14]

The last RCT, Kahleova et al,[11] utilized an approach most view as the universal definition of IF as a whole: eating the same number of calories but in a smaller time window, all over a prolonged period. This is the average person's approach to take if they are doing an IF regimen, and what most people know fasting as. The study incorporated 2 large meals versus 6 smalls meals, each with the same caloric intake, over 12 weeks.

Category B studies mirrored the RCTs in terms of their fasting diversity. The critical difference was that Furmli et al[15] included a substantially longer fast of 7-11 months. This is the only available published study with a duration of such magnitude.

Glycemic Control: The cornerstone biomarker which helps determine diabetes mellitus is glucose. Glucose is tested through a multitude of different means, with HbA1C being the most reliable. HbA1C shows a patient's glucose levels for up to 3 months, and therefore, it is a quality prolonged treatment measure. Other glucose tests such as fasting blood glucose and portable blood glucose meters test the current level of the patient's glucose. Those levels are imperative in patient safety and awareness but not the most useful in monitoring long-term interventions.

Due to the importance of HbA1C, it is essential to note all but 1 RCT featured an improvement in their patient's levels. Fourteen showed neither an increase nor decrease in the patient's HbA1C levels but showed a sharp decline, thus improving fasting blood glucose. Due to the short duration of a 1-week fast, it is understandable the HbA1C measuring months of patient glucose was unaffected.

In addition, all but 1 study showed a marked improvement of HbA1C. The 24-month follow-up to Carter et al[6] showed an increase in HbA1C from the levels collected at the end of their trial. There was a significant decrease in Hb1AC levels resulting from their 12-month IF regimen in simple terms. Those same patients were measured 24 months post regimen, and all had a return of their previous HbA1C levels. This shows IF as a standalone, 1-time treatment is probably not reliable but may be advantageous when instituted as an aspect of a diet continuously.

A common worry of using fasting as a treatment for T2DM is hypoglycemic events. Carter et al[6] concluded fasting is safe for patients with T2DM who do not use hypoglycemia causing medications such as sulfonylureas or insulin.

Corley et al[10] concluded with opposite results displaying a twofold increase in hypoglycemic events on days where patients fasted but decreased events overall when combining fasting and non-fasting days. Objectively, this looks as though fasting is to blame but is not necessarily the case. There were no episodes of severe hypoglycemia, and most (59%) of the participants did not experience an event. Due to the inability to pinpoint the exact cause of most hypoglycemic events, there is a high likelihood the events had to do with individuals not correctly adhering to educational recommendations. Another possibility is they possessed individual medical characteristics which increased their chances of a hypoglycemic event. A key piece of information in both Carter et al[6] and Corley et al[10] is hypoglycemic events only occurred in patients who had events before starting the IF treatment. Overall, hypoglycemic events need to be recognized as a possible adverse effect when trying IF as a treatment for T2DM.

Kahleova et al[11] also noted a decrease in fasting glucagon for the B2 group and an increase in fasting glucagon in the A6 group, which was an encouraging finding. This was the only study to measure fasting glucagon and could be an important metric in the future. Glucose and glucagon directly correlate; therefore, low fasting glucagon (B2) resulted in a lower fasting blood glucose. Conversely, an elevated fasting glucagon level (A6) would spike blood glucose and cause abnormal glucose hemostasis. There are currently no treatments specifically to lower glucagon levels, highlighting the importance of this result. The data from this study should be noted for patients who do not have any issues with hypoglycemia

All Category B studies resulted in a decrease in patient HbA1C levels, with the most notable being in all 3 patients in the case series discontinued insulin use over

7-11 months, with 2 of 3 patients discontinuing all medication overall.[15] Although on a minute scale, this study is imperative because it shows the potential of what fasting can potentially offer when conducted for an extended period. Three patients in the same demographic as the other studies discontinuing the necessity of insulin is an outstanding result. What is even more astounding is there were zero adverse effects noted. This study is an excellent example of what a systematic and disciplined IF protocol can potentially accomplish.

Body Composition: Every study in Category A resulted in an improvement in BMI or body fat percentages. Li et al[14] had the highest overall average decrease in BMI of 3.5-4.5%, which is astounding due to only a week fast. This can be attributed to the extreme caloric deficit achieved (maximum 300 calories/day for 7 days). Corley et al[10] showed a decreased BMI and body fat percentage but a more significant decrease in body fat percentage. For Carter et al,6 the possibility IF may be better for weight loss than continuous energy restriction needs to be entertained due to the small size of the patient sample. Even though there was no statistically significant difference between the 2 groups, IF did have a higher percentage of weight loss but not enough to be statistically significant. Conversely, in Kahleova et al,[11] there was a more significant improvement for the B2 group eating 2 meals a day compared to the A6 eating 6 meals a day. This result correlated with Carter et al[6] and showed the IF and continuous groups might have had a significant difference if given larger sample size. All category B studies included an improvement in BMI or body fat percentages.

Supportive care proved crucial for compliance and weight loss in the analyzed studies. The 2 key takeaways for weight loss and compliance overall were the link between frequency of appointments with compliance and the ability to turn on the IF regimen when weight gain was expected. These studies and other literature show a clear link between appointment frequency with behavioral support and dieticians to overall compliance. The increased number of times a patient saw a professional, the better the result was.

In Sundfør et al,[12] patients had continuous weight loss during the first 6 months of the study, which ceased upon the termination of in-person counseling. They did, however, maintain their weight loss even though they had no more face-to-face sessions. This could be due to the pre-planned weigh-in from 12 months to the start date and the high frequency of cognitive-behavioral therapy held during the first 6 months. Carter et al[6] had a similar result as most of the weight loss occurred during the first 3 months of the trial; appointments were scheduled every 2 weeks during the first 3 months and every 2 to 3 months for the next 9 months of the study. There was a sharp decrease in patient compliance when the appointments decreased, which resulted in a pause of the weight loss. Even though compliance decreased, patients in the fasting group noted they could easily use it to prevent any foreseen weight gain due to its quick nature. It was easier for patients in the fasting group to resume their regimen (fast for 2 days and return to a normal diet) than for control group patients to reduce caloric intake consistently. Overall, the mental aspect of achieving success in any diet cannot be understated. A patient's mental capacity to deal with the difficulty of a diet change was directly impacted by the number of times they saw a provider.

Other Measures: Only 3 of 6 Category A studies measured blood pressure, and only 2 showed significant improvement. Li et al[14] showed a significant improvement in blood pressure in the 1-week fasting trial. Due to its swift nature, this metric could be crucial for patients with blood pressure issues who would benefit from losing weight. Sundfør et al[12] was the only "2 and 5" style fast which showed a statistically significant improvement of patient blood pressure.

Li et al[14] and Corley et al[10] included an increase in quality of life assessed by the WHO-5. The WHO-5 is a well-being index which measures how a patient feels after 2 weeks. A high score indicates a patient feels good and gives an idea of patient well-being outside of analytical metrics.[17]

For Category B, Furmli et al[15] showed the most impressive result of any analyzed study with complete discontinuation of insulin as medication for all 3 patients and an average of 12 days for outright insulin cessation. Therapeutic fasting and education were the treatment measures used. Patients received a 6-hour seminar on "the pathophysiology of diabetes, insulin resistance, education on macronutrients, and the principles of dietary management of diabetes including therapeutic fasting as well as safety."[15] The frequency of fast for this case series was undoubtedly difficult as 2 patients conducted alternate day 24-hour fasts and 1 patient tri-weekly 24-hour fasts; this meant patients only ate dinner on fasting days. The result was only possible with strong patient compliance and a close provider-patient relationship. The 3 patients had a provider visit every 2 weeks with constant feedback on progress. All 3 patients remained on the fasting regimen by choice. The main difference between this case series and other RCTs was the duration of the fast and amount of follow-up appointments. The seminar conducted in this case series mirrored other

education attempts made in the RCTs. This was the only study to utilize 24-hour fast and the only study to not stop follow-up appointments. This case series lays the groundwork for an RCT to be conducted similarly in the future.

Adverse Effects: The lack of adverse effects points to the safety of using the IF as a treatment modality. The only case where adverse effects were notable was in patients who had hypoglycemic events prior to entering the studies. When utilizing IF, providers need to make a concerted effort to closely monitor all patients, especially those with a history of hypoglycemic issues.

Limitations: For the collective review, it should be noted directly comparing the results of studies with different fasting techniques may not have comparable results. Another major thematic issue is the mixing of age groups, which may limit applicability to other groups. Some studies relied on patient reporting, which may miss data points. Patient enrollment was skewed toward those who were willing to make substantial lifestyle changes. IF is a newer concept as compared with continuous caloric restriction and may be why there are fewer available studies.[18]

Conclusion

Type 2 diabetes mellitus is a tremendous medical issue across the world and the US. The best treatments have shown to include a foundation of lifestyle modification supplemented with pharmacologic treatment as decided on by the patient and provider. It has long been known a decreased caloric intake will lead to weight loss, which will lead to improved HbA1C and outcome of TD2M. Analysis of comparing IF to regular caloric deficit diets shows several key data points, to include a larger amount of weight loss and a decrease in HbA1C. However, these values are across a spectrum of different types of diet and patient circumstances. Overall, the purpose of the review was met as studies show IF is a credible treatment option for T2DM, but it cannot be said IF is more effective than a diet of continuous energy restriction. Continued research, with larger patient populations, is needed to continue learning about IF as a treatment for T2DM.

Although not statistically significant, the studies of IF affecting T2DM are promising. If intermittent fasting can adequately treat T2DM, it can treat obesity. This would directly enhance military readiness and the ability to recruit adequate service members.

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Admissions Interviews: How History Can Pave the Way Toward a Holistic Future in Military PA Program Admissions and Hiring

Anne Wildermuth, PhD, PA-C, RD

Abstract

Admissions processes for graduate health professions, including physician assistant (PA) and medical school, were built over time through trial and error. Admissions process research was not common until the early 1990s, and it seemingly began because the system of admitting applicants solely on the basis of the highest academic metrics resulted in unacceptable attrition rates.[1,2] Recognizing interpersonal attributes were unique from academic metrics and critical to success in medical education, admissions interviews were added as a component of the admissions process and have since become nearly ubiquitous for medical and PA applicants.[1-4] Understanding the history of admissions interviews informs ways to optimize admissions processes for the future.

The PA profession was originally comprised entirely of military veterans with extensive medical training during their service; the number of service members and veterans matriculating has significantly decreased and is not reflective of the percentage of veterans in the US.[5-8] Most PA programs receive applications in excess of available seats; yet, based on the 2019 PAEA Curriculum Report, the all-cause attrition rate is 7.4%.[4] Given the large pool of applicants available to select from, it is valuable to identify students who will succeed and graduate. This is especially critical for the Interservice Physician Assistant Program, the US Military's PA program, to optimize force readiness by ensuring sufficient PAs are available.[9] Utilizing a holistic admissions process, considered best practice in admissions, is an evidence-based way to decrease attrition and support increased diversity, including increasing the number of veterans becoming PAs, by considering the breadth of an applicant's life experiences, personal attributes, and academic metrics.[10-13]

The outcomes of admissions interviews are high-stakes for the program and applicants, as they are often the final step prior to admissions decisions. Additionally, there is considerable overlap between the principles of admissions interviews and job interviews, the latter of which may occur as a military PA's career unfolds and they are considered for special assignments. Though numerous different interview modalities exist, multiple mini-interviews (MMI) are highly-structured, effective, and are supportive of a holistic admissions approach.[14-17] Through examining historical admissions trends, identifying a modern way to select applicants through holistic admissions can support decreased student deceleration and attrition and increased diversity, optimizing force readiness and supporting the success of the PA profession into the future.[17]

Background

Admissions interviews are a nearly ubiquitous component of the admissions process for graduate health professions training programs, including medical, physician assistant, and pharmacy school.[3] Historically, 99% of all US medical schools included an interview in their admissions process.[14] Interviews are perceived as important to both the program and the applicant and offer benefits to both. For programs, interviews garner insight into an applicant's personality and interpersonal skills, attributes which are challenging to assess using traditional academic metrics, like grade point average (GPA) and standardized test scores, and other application materials, like a personal statement.[18] Admissions interviews offer opportunities to gather information, make decisions, verify application information, and recruit applicants.[14] For applicants, interviews offer the opportunity to sell themselves, meet faculty and staff, and assess program fit. One small study of 53 interviewed

applicants to an internal medicine residency program revealed 86% of participants felt the faculty interview was a necessary part of the interview day, and 93% indicated it would be unacceptable to not complete a formal interview.[18] The Interservice Physician Assistant Program (IPAP), the US Military's PA Program, which trains currently serving Army, Air Force, Navy, Coast Guard, National Guard, and Reserve members, also utilizes admissions interviews.[9] Each service branch interviews and selects applicants for IPAP using different methods. Interviews are also a common component of the hiring process, and for PAs, interviewing for competitive military assignments may ensue as their military careers progress.

Table 1. Demographics of matriculating Physician Assistant students from Physician Assistant Education Association (PAEA) student reports in 2018 and 2019.

	PAEA Student Report 3 (2018)[6]	PAEA Student Report 4 (2019)[7]
N (Response rate)	4,845 (45.8%)	5,658 (54.2%)
Gender	Female 75.5%, Male 24.5%	Female 74.8%, Male 25%
Gender other than Male/Female	Data not collected	0.1%
Sexual orientation other than straight	5.7%	4.9%
Underrepresented in Medicine	9.7%	14%
Age Range (mean)	Age range 19-65 (25.6)	Age range 17-69; mean 25.6
Currently serving military or veterans	3.9%	5.2%

The PA profession was conceived based on a collaborative relationship with physicians for the purpose of expanding access to care by utilizing the experience of military-trained skilled healthcare providers in the civilian sector.[8] The first PA program at Duke University started in 1965, run by Dr. Eugene Stead within the Duke University School of Medicine, in an effort to address the nationwide physician shortage.[8] Dr. Stead developed the PA curriculum based on the rapid physician training model utilized during World War II, enrolling Navy Corpsmen who became the first PAs.[8] PA programs have been structured around the medical school model, and as such there are many similarities historically and currently between the medical school and PA school interview process.[4,14,19] Presently, 29.2% of PA programs are sponsored by an academic medical center which has a medical school.[20]

Though the PA profession originally was developed for veterans who received medical training during their military service, the PA profession has since seen low numbers of actively serving military and veterans matriculating into PA school. Per the Physician Assistant Education Association (PAEA) Student Report data from 2019, only 5.2% of matriculating student respondents had served.[7] It is likely many of these serving and veteran students are attending the IPAP, suggesting very low veteran enrollment at civilian PA programs nationwide. Low veteran enrollment in PA programs is surprising given that 45.5% of programs report special admissions processes for veterans and 49% report veteran preference in admissions.[4] A lack of diversity in numerous aspects has plagued the PA profession, and the PAEA, following suit from the Association of American Medical Colleges (AAMC), has advocated for holistic admissions and review, considered best practice in admissions in part to increase diversity (Table 1).[10] Optimally, the diversity of the PA profession should reflect the diversity of the American populous. Per the 2018 US Census Bureau survey, 7% of Americans are veterans of the US Armed Forces, and Post-9/11 and Gulf War veterans have very high levels of education, with more than three-quarters having at least some college experience.[5]

Holistic Admissions & Review: Holistic admissions refer to approaching the entire admissions process, from recruitment to matriculation, with consideration of the "whole" applicant, including the breadth of their experiences and the value they would contribute to the program and profession.[10] There are several reasons why holistic review of applicants is preferred, including the traditional considerable weight on standardized test scores and GPA may not accurately predict success and, furthermore, may disadvantage non-traditional or underrepresented students.[11] Holistic admissions have also been touted as a way to increase enrollment and retention for underrepresented students as an alternative to directly considering race as a preference factor, the legality of which has been debated in numerous US Supreme Court cases.[11]

Holistic review is the process of considering an applicant's experiences, attributes and academic metrics within the scope of an institution's mission; additionally, it considers the value the applicant could add not only as a student, but also as a member of the profession.[19] Holistic interviewing, a component of the entire process of holistic review, includes interview modalities which are mission-based and evaluate an applicant's life experiences and personal attributes. Though other interview modalities could evaluate an applicant's experiences and attributes, multiple mini-interviews (MMI), which are structured, fair, and can be easily designed based on a program's mission and values, are increasing in popularity and practice as higher learning institutions seek to evaluate applicants more holistically overall.[11]

Despite the increasing trend of reviewing applicants more holistically, the implementation of this practice provides some challenges, especially to graduate-level

education, where traditions, time constraints, and lack of evaluation tools may exist as barriers.[11] According to a study by the Council of Graduate Schools, 75% of masters level admissions are decentralized, meaning the individual academic unit is primarily responsible for the entire admissions process.[11] A potential pitfall of this setup is individual academic units may loosely follow the academic institution's goals or may choose to follow their own mission entirely when considering applications. For example, considerable research exists about how non-cognitive variables can be considered and assessed in admissions, but a decentralized approach to admissions might mean a program focuses on non-cognitive traits different than those the institution has identified as important.[12,13] As academic units are evaluating applicants at a time where they are vulnerable to the system and a competitive process, adhering to holistic review focused on the mission and the breadth of each applicant as a whole person is critically important.

Interview Structure: Interviews can be characterized as unstructured, semi-structured, or structured.[14,19] The American Association of Medical Colleges (AAMC) defines unstructured interviews as containing discretionary content without preselected questions and without a scoring rubric.[19] Conversely, structured interviews generally meet 4 specific criteria: interview content is developed based on a program or profession's mission, the questions are standardized, the interviewers are trained on the scoring rubric, and the interview is conducted by more than 1 interviewer.[14,19,21,22] Interviews may be deemed semi-structured if they fall in the spectrum between unstructured and structured.[14,22] Research indicates structured interviews, regardless of method, are more reliable, fair, and valid than unstructured interviews; the more structured the interview, the more accurate of an admissions tool it is.[14,19] Accuracy reflects what is objectively being measured by the admissions tool; in order for a tool to accurately reflect a program's mission and goals, it needs to be written to evaluate those mission and goals. A study by Blouin et al in 2010 comparing structured interviews and unstructured interviews in an emergency medicine residency program found the structured interview had improved inter-rater reliability compared to unstructured interviews, and unstructured interviews, while built to assess numerous domains, ultimately only measured a single dimension.[23] This same study found the structured interview was not more reliable overall than the unstructured interviews, largely because the structured interview was multidimensional in its assessment and the unstructured interview was unidimensional.[23] The authors concluded it is important for the assessment tool to reflect what is desired to be measured.[23] Interview structure increases accuracy, yet it remains critically important the interview tool is purposefully and intentionally built.

Interview Modalities: Numerous methods exist in which graduate health professions training programs interview applicants.[3,14] These methods include traditional interviews, panel interviews, group interviews, and multiple mini-interviews, and there are likely some situations where aspects of these types of interviews are combined.[3,14,24]

Traditional interviews are one-on-one interviews between an applicant and an interviewer.[3,14] Historically, traditional interviews have been unstructured and potentially conversation-like, the unstructured nature reducing reliability and validity as an admissions tool.[3,25] Traditional interviews also present increased opportunity for conscious and unconscious bias both for and against applicants because of their unstructured nature. Questions asked in traditional interviews may include things like, "Why do you want to be a [specific profession]?", which may result in receiving a coached, rehearsed response lacking in adequate substance to determine programmatic fit.[21] Traditional interviews can be improved by having applicants complete multiple such interviews and by utilizing scores from all interviewers and utilizing a diverse set of interviewers in the decision-making process.[19,25,26] Generally, however, it is not advisable to utilize traditional, one-on-one interviews to make high-stakes admissions decisions in graduate health professions training programs because of their low validity, low reliability, and increased opportunity for bias.[3,19,21,25,27]

Panel interviews significantly increase the level of structure compared to traditional interviews. Panel interviews are composed of 2 to 5 people who interview the applicant at the same time.[14] Typically panelists' scores are averaged or agreed upon by consensus, the former likely being the best strategy for mitigating bias.[14,19,21] Validity, reliability, and fairness are all increased in panel interviews when questions are standardized, when questions include behavioral or situational content, and when defined rating scales are used. Applicants may perceive panel interviews as particularly stressful or lacking an opportunity to "redeem" oneself, as there may be limited opportunities, perhaps just one, to present themselves to interviewers.[16] Interviewers may feel reduced anxiety when they are not the only interviewer of an applicant, as it takes pressure off individual decision-making in such a high-stakes process.[16] Panel interviews offer significantly more structure than traditional interviews, and despite some potential drawbacks based on applicant perceptions and opportunity for bias, are a reasonably efficacious interview tool.[14,16,19,21,22]

Very limited research on the use of group interviews in graduate health professions programs admissions exists, but it is important to discuss as some programs utilize this approach.[16,24] Group interviews are characterized by several applicants being evaluated by an interviewer or interviewers at the same time. Content may include a group activity where a consensus decision must be reached, debate of a relevant topic to the program, or individual applicants taking turns sharing in front of the group.[24] Because of the limited research in this method, the reliability, validity, and fairness of group interviews is unclear; these metrics, like with other methods, are likely affected heavily by the degree of structure utilized when creating the group interview process. One limited research study reported applicants viewed group interviews favorably overall; however, qualitative feedback indicated international applicants felt they would struggle in this setting when compared with domestic applicants.[16] It is possible group interviews may be more challenging to navigate for introverted applicants, even if they are ultimately a good fit based on the mission of the program. Group interviews, unless structured and clearly tied to a component of a training program's mission, may be best used with caution until increased evidence of their efficacy emerges.

Multiple mini-interviews (MMI) are station-based interviews, wherein applicants rotate among several stations on a timed schedule and answer a question or complete a scenario at each station.[15] Each station is scored by an independent evaluator, and scores from every station are utilized to calculate a total score.[15] Ideally, multiple mini-interview stations are created to support a program and profession's mission and goals.[15] MMI are thought to be the most structured of all interview methods as the station content is mission- and/or profession-based, the stations are standardized, and the interview is conducted by multiple interviewers.[14,15] Structure, and subsequently reliability, validity, and fairness further increase if rubrics are used for scoring and if interviewers are trained in the application of rubrics for this purpose.[14,19] Perceptions of MMI by both applicants and interviewers are generally positive regarding fairness, reduced opportunity for bias, and allowing for adequate differentiation among candidates.[16] One limitation of MMI is it can be an impersonal process, as each station is highly prescriptive; additionally, MMI may be time-consuming and logistically challenging to implement compared to other interview methods.[3]

History of Development & Use Trends of Admissions Interviews: Selection of applicants to matriculate in health professions programs is a high-stakes process; training programs desire students who are equipped to handle the rigor of coursework and navigate the curriculum and clinical integration successfully and professionally. It is critical to matriculate applicants who will not only experience success in the program, but also contribute to society as practitioners. Historically, panel interviews, where applicants would appear before several professionals for an interview, were heavily utilized in the selection process in addition to an applicant's history of academic achievement.[15] Individual, one-on-one interviews and small group interviews, where several applicants interact and are observed, are also frequently utilized in health professions admissions.[3] Though an improvement from historical admissions processes where only prior academic achievement was considered for selection, research suggests traditional panel interviews and less-structured one-on-one interviews may lack reliability and validity.[1-3,15] Several reasons for this may exist, including an applicant's ability to rehearse commonly asked interview questions, a lack of question and flow structure, and opportunity for substantial interviewer bias in traditional interviews.[3,15] These factors, more prevalent in panel interviews, can lead to selection of less-suitable applicants, which can lead to latent professionalism problems, inability to meet academic progression standards, or attrition of matriculants. MMIs provide a solution to many of the common pitfalls which render traditional interview styles less reliable predictors of student success.

MMIs were pioneered at McMaster Medical School in Canada in 2002. MMIs are modeled on the format of an objective structured clinical exam (OSCE), which many health professions students will complete during their training.[28] Because of the highly structured nature of MMI, its validity and reliability as an applicant assessment tool is higher than in less structured interviews.[15]

MMI stations are designed to assess attributes specific to a training program's mission, goals, and requirements; thus, the scenarios utilized can be individualized to meet a program's needs.[15] One of the critical components of a well-designed admissions process is to select for applicant attributes critical to success in the program and professionally but are difficult to teach or inculcate if not innately present (e.g., empathy, critical thinking). As an example, manual dexterity is important for dentists, so one of the MMI stations included in Foley et al's admissions and research at the University of Aberdeen conducted an MMI station on manual dexterity; this perhaps would not be a necessary inclusion for a different profession.[29] Stations are focused on applicant attributes, such as communication skills or integrity, and applicants' ability to logically work through a presented problem; they generally do not assess or require specific

medical, scientific, or other acquired knowledge.[15] Because MMIs are typically comprised of 4-12 stations, institutions are able to evaluate a wide-range of applicant competencies through the lens of unique evaluators at each station to gain increased perspectives about what the applicant may offer as a student and future health professional.[15]

MMIs are considered the preferred interview modality in holistic review of applicants because they assess specific non-cognitive traits associated with professional success and diminish opportunities for bias. Bias in applicant interviews can be conscious, where the interviewer is overtly aware of their skewed beliefs towards a particular group or attribute, or unconscious, where the interviewer is unaware of their skewed beliefs. Bias can regard a wide variety of traits or attributes, including traditionally thought of examples of race, gender, and socioeconomic status to less-considered examples like college athletics participation or attaining the undergraduate degree at a college versus a university. Spanning several health professions, medicine, dentistry, pharmacy, and physician assistant, the use of MMI has been associated positively with academic performance during training, OSCE performance, clerkship evaluation scores, and board examination performance.[29-32] Lower MMI scores in one study were also predictive of students who will experience academic difficulty after matriculation.[33] Two studies compared outcomes of panel interviews and MMI on ability to discern differences between applicants, 1 in medical school applicants and 1 in PA applicants, both finding MMI was a more effective differentiator.[34,35]

PA Education: Physician assistants practice medicine; they diagnose illness, develop and manage treatment plans, prescribe medication, and work in every setting from clinics to hospitals to the operating room.[8] The average length of PA training programs is 27 months, and its rigor reflects the considerable clinician responsibility.[8] Most programs require a didactic year, where students learn the foundations of medicine, pharmacology, clinical skills, and ethics, among other things, followed by at least 2,000 hours of clinical rotations.[8]

PAs are educated at a master's level, and the transition to intense, graduate learning can be a considerable challenge. The mean total credit hours completed in PA school is 112.6 (n=231, range 54-187, SD 21.2), which is incredibly high compared to the other master's programs.[4] The didactic phase alone, which has an average length of 13.3 months (n=236, SD 2.3), has a mean total credit hour volume of 65.3 (n=231, range 26.5-141, SD 15.7).[4,20] Full-time course load is traditionally between 9 and 12 hours for graduate education, and the volume of credit hours PA students are required to take each term considerably exceeds this norm.[4,20] In applied terms, the didactic phase of PA school often requires students be in class 35+ hours per week and study outside of class in evenings and on weekends to prepare for numerous written and in-person exams.

The IPAP was founded in 1996; before this there were separate Army and Air Force PA programs.[9] Currently, the IPAP accepts up to 240 students each year in 3 cohorts, depending on force needs, making it the largest PA program in the US.[9] The program is 28 total months, 16 months of phase 1 didactic training at Joint Base San Antonio and 12 months of phase 2 clinical clerkships at one of 30+ military installations which can support clinical training needs. Students PCS after phase 1 and complete all of their phase 2 clerkships in the same location.[9] The IPAP is housed in The Graduate School, Medical Center of Excellence. Matriculants come from all branches of the military, encompassing both officers and enlisted personnel. While in the program, students receive both a bachelor's degree at the end of phase 1 and a master's degree in PA Studies at the end of phase 2, at which time they are eligible to sit for the PA National Certifying Exam (PANCE).

PA Admissions: As of December 2022, there are 300 Accreditation Review Commission on Education for the Physician Assistant (ARC-PA) accredited PA programs in the US.[36] ARC-PA is the accrediting body for PA training programs, and the PAEA is the national organization representing PA education programs and educators. There is a paucity of data on trends in PA program admissions in the current literature; however, a PAEA program report based on a mandatory survey for member institutions, which included 236 programs, reveals some trends.[20]

The Centralized Application Service for Physician Assistants (CASPA) is a widely used admissions application tool and is a service of PAEA; it allows applicants to apply for multiple programs with 1 application.[37] Applicants complete a detailed application which includes demographic information, undergraduate coursework, transcripts, standardized testing results, patient care hours, employment, volunteer hours, a personal statement, and reference letters, among other components.[37] Grade entry and standardized test scores are verified as accurate by CASPA when official transcripts are sent; however, the remainder of data contained within the application is self-reported and remains unverified.[37] The 2019 PAEA Curriculum Report 4: Prerequisites indicates that 92.8% of PA programs (n=236) utilize CASPA

for their admissions.[4]

PA education programs are highly competitive, including the IPAP. In the 2017 academic year, the mean number of applications received per program was 1,078.6 with a mean of 65.5 students accepted.[4] This yields a mean of 16.5 applicants per available seat. Because of the large numbers of applications received, at an institutional or program level, pre-determined criteria is typically used to pre-screen applicants to decide who will receive an interview. Consistent with the wide variability in program makeup and setup, pre-screen criteria also varies widely; this remains true in the IPAP, where each service branch utilizes different pre-screen criteria and pre-requisites.[4,9] Pre-screen criteria consists of various GPA calculations (overall, science, non-science, and others), narrative or personal statement(s) (n=138, 59.7%), letters of reference (n=229, 97.4%), state residency, standardized testing (n=235, 53.2% of programs require the Graduate Record Examination), and likely others not clearly defined in published data.[4] There is not currently data available indicating how PA programs opt to use these various data points to set up their pre-screen scoring.

The 2019 PAEA Curriculum Report 4: Prerequisites delves into interview practices of programs. Overwhelmingly, and consistent with medical school interview practices, PA programs require an on-site interview for admission to the program (n=234, 96.6%).[4] Reasons for requiring an on-site interview included the opportunity to evaluate interpersonal and communication skills (n=224, 99.1%), evaluate professionalism and behavioral issues (n=213, 94.2%), assess applicant fit for the mission/goals (n=188, 83.2%), allow applicants to assess program fit (n=180, 79.6%), evaluate dedication to the PA career (n=174, 77%), and evaluate ability to work in teams (n=143, 63.3%).[4] There appears to be a wide variety of on-site interview formats utilized. Participating programs (n=225) could select more than one modality; the exact composition of interview modalities at each program is unknown. Interview modalities included individual, group/team, individual multiple mini-interviews (MMI), group MMI, and an other category (Table 2).

Table 2. On-site interview format utilization among Physician Assistant (PA) programs.

Interview Modality	n	Percentage
Individual	152	67.6%
Group/Team	138	61.3%
Individual MMI	64	28.4%
Group MMI	17	7.6%
Other	8	3.6%
Total	225	

It is important to consider current attrition data in PA education programs when considering variables whichmay predict programmatic performance. The 2019 PAEA Curriculum Report indicates 92.6% of students matriculated at the 208 programs completing this survey component graduated or were expected to graduate on time.[4] Of those who did not graduate or were not expected to graduate on time, there were a variety of reasons including dismissal, withdrawal, and deceleration (Table 3). Of the 208 programs who completed this survey component on student status at graduation, 87 programs indicated dismissing at least 1 student for academic reasons, 15 indicated dismissing at least 1 student for non-academic (including professionalism) reasons, 68 programs reported short-term deceleration of at least 1 student, and 87 programs reported long-term deceleration to the next cohort of at least 1 student.[4]

Table 3. Statuses for non-graduating or delayed-graduation students among 208 Physician Assistant (PA) programs.

Reason	Number of students (n)	Percentage of students
Academic dismissal	178	1.8%
Non-academic dismissal (e.g., professionalism)	18	0.2%
Withdrew: Medical Reasons	51	0.5%
Withdrew: Personal Reasons	138	1.4%
Decelerated: Short Term (<1 year late)	171	1.7%
Decelerated to next cohort	179	1.8%
Totals	735	7.4%

Discussion

Admitting people who can succeed in the military PA program and as military PAs is of the utmost importance for force readiness. Additionally, military PAs will likely enter the civilian medical workforce concurrently with or after their military career, strengthening the diversity and experience of the PA profession. Considerable implications exist for both students and institutions when students decelerate, withdraw, or are dismissed. Financial implications exist for the military and for the student, including but not limited to the cost of pre-requisite coursework and standardized exams, changing duty stations several times for training, and maintaining a sufficient PA workforce. Additionally, for both faculty and students, considerable psychological stress may come because of deceleration, withdrawal, or dismissal and navigating the associated processes. As such, it is critically important to identify the right-fit students for PA training programs, and holistic review and MMI are a practical path forward.17

There is very likely an overlap between admissions interviews and job interviews. Having a clear job description, aligning interview questions with the job requirements, and utilizing a high degree of structure in the interview format will likely reduce bias in the hiring process and make hiring decisions more

effective for the job at hand. As military PAs progress through their career, interviewing for selective and competitive assignments may very well be a reality. For those making hiring recommendations and decisions, utilizing holistic techniques is advisable to optimize outcomes.

The IPAP program has been extraordinarily successful, graduating competent, collaborative military PAs and leaders for decades who contribute to military medicine in all service branches. Utilizing holistic admissions practices across all PA programs will help identify the best-fit candidates likely to succeed based on a program's mission, values, and goals and will support increased diversity. Diversifying the PA profession and working towards the goal of mirroring the diversity of the US will strengthen the profession, allow patients to feel represented by those caring for them, and optimize opportunity for applicants working to gain access to PA training.

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Medic and Portable Pulse Oximeter Respiratory Rate Measurement Comparison to Waveform Capnography: A Prospective, Observational Study

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Abstract

Background: The second leading cause of preventable battlefield death involves airway management. Tactical combat casualty care (TCCC) guidelines emphasize combat casualty airway, breathing and respiratory evaluation, including respiratory rate (RR) measurement. The current standard of practice for the US Army medics is to measure the RR by manual counting. Manual counting methods are operator-dependent, and medics face situational stressors limiting accurate measurement of RR in combat settings. To date, no published studies evaluate alternate methods of RR measurement by medics. The purpose of this study is to compare RR assessment by medics against waveform capnography and commercial finger pulse oximeters with continuous plethysmography.

Materials and Methods: We conducted a prospective, observational study to compare Army medic RR assessments against plethysmography and waveform capnography RR. Assessments were performed prior to and following exertion at 30 and 60 seconds with both the pulse oximeter (NSN 6515-01-655-9412) and defibrillator monitor (NSN 6515-01-607-8629), followed by end-user surveys.

Results: Of the 40 medics enrolled over a 4-month period, most were male (85%), and reported between less than 5 years of military and medical experience. The mean manual RR reported by medics at rest did not significantly differ from waveform capnography (14.05 versus 13.98, $p=0.523$); however, mean manual RR reported by medics on post-exertional subjects was significantly lower than waveform capnography (25.62 versus 29.77, $p<0.001$). Time to medic-obtained RR was slower than the pulse oximeter (NSN 6515-01-655-9412) both at rest (-7.37 seconds, $p<0.001$) and at exertion (-6.50 seconds, $p<0.001$). While the mean difference in RR between the pulse oximeter (NSN 6515-01-655-9412) and waveform capnography in models at rest at 30 seconds was statistically significant (-1.38, $p<0.001$). There was no overall statistically significant differences in RR between the pulse oximeter (NSN 6515-01-655-9412) and waveform capnography in models at exertion at 30 seconds and at rest and exertion at 60 seconds.

Conclusion: Resting RR measurement did not differ significantly; however, medic-obtained RR considerably deviated from both pulse oximeters and waveform capnography at elevated rates. Existing commercial pulse oximeters with RR plethysmography do not differ significantly from waveform capnography and should be investigated further for consideration in fielding across the force for RR assessment.

Keywords: vital signs; military; medic; tactical combat casualty care

Introduction

Despite a decrease in direct battlefield conflict, improvement of prehospital casualty evaluation amongst American military personnel continues to be a focus.[1-4] Literature emphasizes the importance of proper airway assessment and management, revealing failure in this area is the second leading cause of preventable battlefield death.[5] Current tactical combat casualty care (TCCC) guidelines stress the importance of continued reassessment of respiration and breathing with proper documentation of care on a TCCC Card in combat

casualties as part of tactical field care.[6] This includes proper assessment for respiratory rate (RR), the number of breaths taken over a 1-minute period. The current standard of practice for the US Army medics, according to the military occupational specialty (MOS) 68W soldier's training manual, is to measure the RR by manually counting respiration for 30 seconds and multiply by 2 by counting the number of times the chest rises (inspiration) and returns to its normal position (expiration). Manual counting method while perceived as industry standard has its limitations and high likelihood of inaccurate results in clinical settings.[7] Additionally US Army medics prehospital role demonstrates added limitations to their ability to accurately measure RR, such as limited visibility, loud noise, and personal protective gear the patient is wearing in the combat setting. Inaccurate measurement may lead to inaccurate overall assessment, resulting in a negative effect on their health and wellbeing, especially those in the acute stage of illness. The importance of accurately measuring the RR when assessing a patient is paramount as an abnormal RR may be a precursor to an adverse clinical event or existent illness.[8-11] The importance of these skills is underscored by the publishing of Department of Defense Instruction (DoDI) 1322.24 in 2018, which requires all uniformed service members to be current in TCCC training.

Figure 1. Visual comparison of the pulse oximeter (NSN 6515-01-561-4889) (left) and the pulse oximeter (NSN 6515-01-655-9412) (right). Respiratory rate is shown on the pulse oximeter (NSN 6515-01-655-9412) in the top right corner of the display.

Yet, despite an emphasis on TCCC principles, 13.7% of prehospital documentation on TCCC cards across the US Army finds missing vital signs. Suboptimal documentation may stem from inadequate time for adequate annotation.[12] However, lack of vital signs suggests battlefield chaos may hinder patient assessments, including counting RR, possibly by a single medic performing multiple tasks. This conflict is highlighted by the lack of RR reported on TCCC documentation in nearly one-fourth of combat casualties and approximately 10% of cases involving airway management receiving after-action review commentary.[13,14] No published studies evaluate prehospital RR accuracy amongst military providers; however, emergency and critical care literature demonstrate significant deficiencies in RR assessment, including increased repeat assessments, low sensitivity for detecting abnormal rates, and impairment to recognize critical conditions.[15-17]

Amongst other innovations, the introduction of pulse oximeters in the battlefield setting 10 years ago enabled multitasking medics to continuously monitor heart rate (HR) and oxygen saturation (SpO2) without significant effort or distraction from other medical tasks.[18] Currently, the pulse oximeter (NSN 6515-01-561-4889) (Figure 1) is part of the standardized medical kit utilized by most field units. Like most devices, it is limited to HR and SpO2 functions. More recently, portable pulse oximeters added RR to their functions via plethysmography, which utilizes variable changes in arterial blood flow associated with inspiration and expiration to continuously calculate RR.[19-21] The addition of plethysmography to modern pulse oximeters enables continuous monitoring of 3 vital signs (RR, HR, and SpO2) from a device. However, despite advances in pulse oximeter technology, there is no significant military device fielding.

We sought to evaluate speed and accuracy of RR assessment performed manually by US Army medics against continuous plethysmography RR from enhanced pulse oximeters and waveform capnography RR.

Materials & Methods

The Department of Defense Regional Health Command-Central Institutional Review Board reviewed protocol #C2021.034d and determined it exempt. We obtained only deidentified data. All aspects of this study were conducted at Fort Bliss, Texas. Only active duty US Army medics with a military occupational specialty of 68W, between 18-44 years-old, with an enlisted grade of E-1 (private) to E-5 (sergeant), holding a current emergency medical technician (EMT) level certification, were included for participation. All models for RR assessment were healthy, active duty personnel and were excluded if they had artificial fingernails or nail polish, self-reported chronic cardiopulmonary conditions (such as asthma and reactive airway disease), or a physical limitation preventing safe use of a seated, stationary exercise bike.

In line with published standards, volunteer US Army medics were instructed to count the RR over the course of 30 seconds, from the time an investigator said "begin" to the time the investigator said "stop," and multiply that number by 2 for a total calculated RR over a 1-minute period. Simultaneously, investigators placed a pulse

Table 1. Medic volunteer demographics.

Characteristic	n (%)
Gender	
Male	34 (85.0)
Female	6 (15.0)
Age (years)	
18-25	24 (60.0)
26-35	15 (37.5)
≥ 36	1 (2.5)
Military Service (years)	
<1	5 (12.5)
1-5	25 (62.5)
6-10	9 (22.5)
≥ 11	1 (2.5)
Medical Experience (years)	
<1	10 (25.0)
1-5	20 (50.0)
6-10	9 (22.5)
≥ 11	1 (2.5)

Table 2. Comparison of medic volunteer respiratory rate measurement to waveform capnography.

Respiratory Rate (breaths per minute)	Mean Difference	Standard Deviation (SD)	95% CI for difference	*p*-value
Overall difference (manual vs. waveform)	-2.04	4.90	(-3.11, -0.97)	**<0.001**
At Rest: (average) **Medic:** 14.05 **Waveform:** 13.98	0.15	1.49	(-0.18, 0.47)	0.523
Post-exertion: (average) **Medic:** 25.62 **Waveform:** 29.77	-4.10	6.09	(-5.43, -2.77)	**<0.001**

Table 3. Frequency of respiratory rate differences between medic volunteers and waveform capnography.

Respiratory Rate (Absolute difference in breaths per minute)	Number (%)
At Rest:	
0	13 (32.5)
1	15 (37.5)
2	10 (25.0)
3	1 (2.5)
4	0 (0)
5	1 (2.5)
>5	0 (0)
Post-exertion:	
0	6 (15.0)
1	2 (5.0)
2	8 (20.0)
3	4 (10.0)
4	2 (5.0)
5	3 (7.5)
>5	15 (37.5)

oximeter (NSN 6515-01-655-9412) on the non-dominant ring finger, per manufacture recommendations. A box was placed over the model's pulse oximeter hand to conceal it from volunteers. Additionally, models wore an oral-nasal cannula connected to a defibrillator monitor (NSN 6515-01-607-8629) to measure waveform capnography for calculated RR as reference.

Medics first evaluated the RR while models were seated, at rest in a standardized chair. After medics reported the RR to the investigating team, they exited the room, and investigators recorded the reported RR, measured RR from the pulse oximeter (NSN 6515-01-655-9412), and waveform capnography RR. Models were then instructed to pedal a seated exercise bike device until their RR measured greater than 20 breaths per minute consistently over a 1-minute period on waveform capnography. Medics then re-entered the room, repeating the process of observing and calculating a RR. Investigators measured the RR at both 30 and 60 seconds for both the pulse oximeter (NSN 6515-01-655-9412) and waveform capnography for comparison.

We performed all statistical analysis using commercially available software. We analyzed continuous data as means with standard deviations (SD) and 95% confidence interval (CI) for differences, and paired t-tests. Agreement survey results comparing the one pulse oximeter (NSN 6515-01-655-9412) to the other pulse oximeter (NSN 6515-01-561-4889) were reported as ordinal data with medians and interquartile range (IQR). A Bland-Altman plot was used to compare 2 measurements of the same variable and their correlation to one another. We set the power at 0.8 and the alpha at 0.05. Assessing to detect 2 respirations per minute (rpm) differences with a standard deviation of 4 rpm between RR measurement methods in each group yielded a sample size of 34 matched pairs of data. We used matched pairs because measured RR are from the same patient, and additionally, both values are compared to the same waveform capnography value, which is also obtained at the same time as the other values. Two rpm was chosen for manufacturer-reported pulse oximeter (NSN 6515-01-655-9412) accuracy. We predicted drop-out due to unanticipated competing priorities to be 15-20% (5.1 to 6.8 medics); therefore, we requested a total of 40 US Army medics to participate in this study.

Results

Over a 4-month period, a total of 40 medics completed this study. Most were male (85%), averaging 24-years-old, reporting between 1 and 5 years of military and medical experience (62.5% and 50%, respectively) (Table 1). The mean model RR reported by medics at rest (14.05) did not significantly differ from reported waveform

Table 4. Medic volunteer time taken to obtain RR compared to the pulse oximeter (NSN 6515-01-655-9412).

Average time (seconds)	Mean Difference	Standard Deviation (SD)	95% CI for difference	*p*-value
At Rest: **Medic:** 32.88 **MightySat:** 25.50	-7.37	4.24	(-8.68, -6.06)	**< 0.001**
Post-exertion: **Medic:** 33.85 **MightySat:** 26.85	-6.50	4.95	(-8.03, -4.97)	**< 0.001**

Figure 2. Bland-Altman Plot of overall difference (manual – waveform capnography RR) compared to mean.

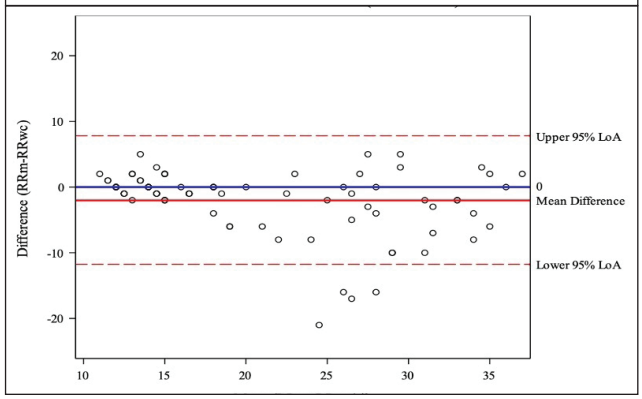


Table 5. Comparison of the pulse oximeter (NSN 6515-01-655-9412) to waveform capnography.

Respiratory Rate	Mean Difference	Standard Deviation (SD)	95% CI for difference	*p*-value
At 30 seconds:				
at rest:	-1.38	1.55	(-1.86, -0.90)	**< 0.001**
at exertion:	1.35	5.50	(-0.35, 3.05)	0.13
Overall difference	-0.01	4.24	(-0.94, 0.92)	0.98
At 60 seconds:				
at rest:	-0.30	1.09	(-0.64, 0.04)	0.09
at exertion:	1.50	3.92	(0.29, 2.71)	0.02
Overall difference	0.60	3.00	(-0.06, 1.26)	0.07

Table 6. Agreement survey comparing pulse oximeter (NSN 6515-01-655-9412) to pulse oximeter (NSN 6515-01-561-4889).

Question	*Median (interquartile range), Likert Scale 1 – 5**
pulse oximeter (NSN 6515-01-655-9412) easier to use	4 (IQR: 2)
pulse oximeter (NSN 6515-01-655-9412) more portable for field use	3 (IQR: 1)
pulse oximeter (NSN 6515-01-655-9412) more durable for field use	4 (IQR: 1)
pulse oximeter (NSN 6515-01-655-9412) preferred in prehospital setting	4 (IQR: 1)
**1 - Strongly disagree, 2 - disagree, 3 - neutral, 4 - agree, 5 - strongly agree*	

capnography (13.98, p=0.523) (Table 2). Following exertion, the medic-reported mean RR was significantly lower than reported waveform capnography (25.62 versus 29.77, p<0.001). While most medics estimated the RR within 2 seconds of the pulse oximeter (NSN 6515-01-655-9412) (n=38, 95%) (Table 3), most overestimated the RR by at least 2 seconds after model exertion (n=32, 80%), most by more than 5 breaths per minute (n=15, 37.5%). Time to obtain RR by medics was significantly slower compared to pulse oximeter (NSN 6515-01-655-9412) in models both at rest (-7.37 seconds, SD 4.24, p<0.001) and immediately after exertion (-6.50 seconds, SD 4.95, p<0.001) (Table 4). While the mean difference in RR between the pulse oximeter (NSN 6515-01-655-9412) and waveform capnography in models at rest at 30 seconds was statistically significant (-1.38, p<0.001), the difference did not exceed the 2 respirations *a priori* difference we assessed for (Figure 2). The RR measurements did not significantly differ in models at exertion at 30 seconds and at rest and exertion at 60 seconds (Table 5) (Figure 3 and Figure 4).

All medics completed the agreement survey comparing the pulse oximeter (NSN 6515-01-655-9412) and the pulse oximeter (NSN 6515-01-561-4889). Reponses support the pulse oximeter (NSN 6515-01-655-9412) is "easier to use," "more durable," "preferred to use in prehospital setting," and "more portable" than the pulse oximeter (NSN 6515-01-561-4889) (median 4, IQR 1) (Table 6).

Discussion

Our study comparing a RR obtained by US Army medics compared to waveform capnography demonstrates significant differences with increased RR; although, there was no significant difference with models at rest. There were no significant differences in RR obtained by the pulse oximeter (NSN 6515-01-655-9412) and waveform capnography.

Respiratory assessment is of interest in medical settings as part of initial and repeated patient assessments. There are many techniques for measuring RR, but their ease of use and performance compared to the gold standard of waveform capnography are not fully established.[22,23] This is the first study to investigate the level of agreement between RR measurements conducted using a manual approach by a military medic, plethysmography, and waveform capnography.

Investigators observed the US Army medics prefer to use the 15-seconds method due to efficiency and would likely use the 15-seconds method over the 30-seconds method when placed in a stressful scenario, such as providing care in a prehospital setting. It may be quicker to

Figure 3. Bland-Altman Plot of overall difference (plethysmography—waveform capnography RR) compared to mean at 30 seconds.

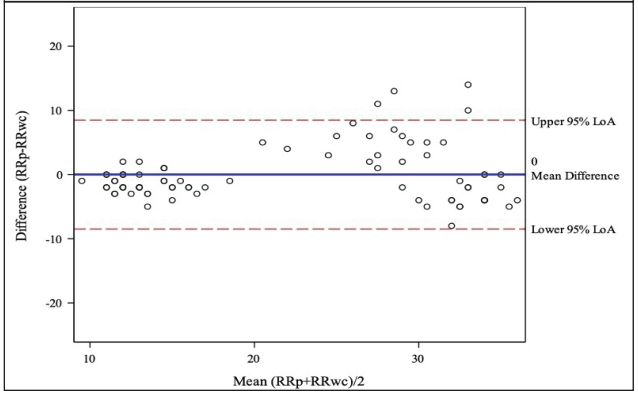
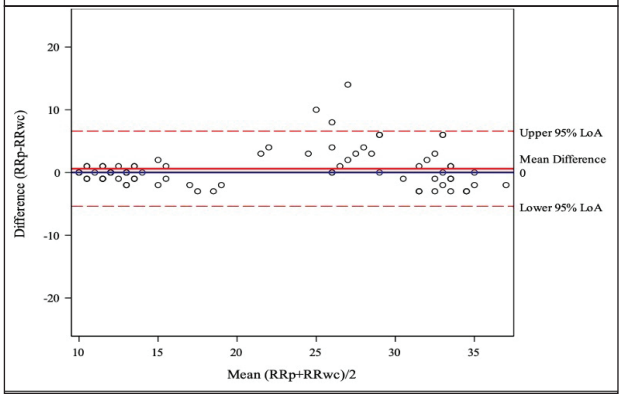


Figure 4. Bland-Altman Plot of overall difference (plethysmography—waveform capnography RR) compared to mean at 60 seconds.



obtain the RR using the 15-seconds method. However, given that the overall medic obtained RR was different by approximately 2 respirations when compared to the waveform RR at 30 seconds, counting RR using the 15-seconds method concerningly could lead to proportional increases in RR measurement inaccuracy.

We chose this area of study due to the lack of literature directly assessing RR measurement by US Army medics. Despite the benefits of portability, ease of use, and technological communications of the pulse oximeter (NSN 6515-01-655-9412), no existing studies evaluate this device against US Army medics in obtaining RR with reference to the gold standard of waveform RR in a human model. Similarly, there are no studies comparing time to attain RR by the pulse oximeter (NSN 6515-01-655-9412) in a human model, including no specific information from the company itself. Proper prehospital RR recognition is vital to appropriately assess casualties, recognize emergent conditions, and triage patients appropriately for intervention and evacuation. Despite its abilities to enhance evaluation, the real-world use of finger pulse oximeters remains limited, especially in initial Role I care, where appropriate triage is perhaps most vital and could influence previously-identified suboptimal assessment and documentation.[12] Further, survey feedback favoring pulse oximeter (NSN 6515-01-655-9412) over the pulse oximeter (NSN 6515-01-561-4889) indicate a willingness by US Army medics to field these new technologies.

Readers should understand. Although US Army medics in this study dealt with an isolated RR assessment in a controlled environment, in battlefield settings they are often charged with multiple tasks, limited time, and significant environmental stressors while attempting to perform lifesaving measures. Traditional manual techniques to pause and assess RR for an extended duration of time, then accurately calculate RR to incorporate in their initial assessment and triage is difficult at best. Our findings further necessitate the need to study vital signs assessment and RR accuracy in more realistic combat environments. Readily available technology like enhanced pulse oximeters show promise to provide improved accuracy of vital sign assessment while unburdening medics from these tasks, thus saving time, cognitive load, and risk of potential errors, and should be studied further for enhanced comparison. Future research should seek to expand on our findings to multicenter studies across other installations with larger sample sizes, to include different levels of expertise and simulated tactical environments to better simulate austere battlefield setting.

Limitations: The central limitation for this study is its single-center population, and given its relatively low sample population size compared to the remaining force of military medics, generalization may be difficult. Further evaluation for accuracy across wider and more diverse populations, to include other locations and an extended spectrum of military medical providers (such as physician assistants, physicians, advanced paramedics, and special forces medics) is important. All medics obtained RR without randomization of presentation, first obtaining RR at rest, and then elevated following model exertion. Our study unexpectedly discovered multiple medics reporting they "lost count" of the RR, and the model had to be reset, thus inadvertently risking a sequence effect with potential learning benefit for a subsequent attempt. Conversely, the use of a 30-second observational period needed to be doubled to determine a minute-long RR. Any error in counting on the medics' part would therefore also be doubled, thereby increasing any original discrepancy. Conversely, the pulse oximeter (NSN 6515-01-655-9412) performed admirably and well-within its advertised accuracy of 3 breaths per minute to the true RR defined by waveform capnography. Though our findings are reliable as they are conducted in more controlled conditions, and not the clinical implications of our findings should, however, be further tested in a randomized controlled setting.

Finally, we limited our model population to young, healthy, active duty soldiers to best replicate real-world battlefield patients, in a controlled environment to help prevent age-dependent and environmental confounders in evaluating RR assessment. However, these standardizations, in turn, limit generalizability to other populations and environments.

Conclusion

US Army medic RR measurement accuracy depends on the RR itself, with greater disparity at higher rates. In a controlled setting, medic-obtained RR significantly differed from the gold standard measured waveform capnography, while the pulse oximeter (NSN 6515-01-655-9412) did not. Additionally, the pulse oximeter (NSN 6515-01-655-9412) demonstrated a faster time to obtain RR when US Army medics used the traditional 30-second manual method. The pulse oximeter (NSN 6515-01-655-9412) should be further evaluated for consideration in fielding across the force in an effort to improve speed and accuracy of RR assessment.

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