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MILITARY MEDICINE

VOLUME 179 AUGUST 2014 SUPPLEMENT

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Proceedings of the 2012 Military Health System Research Symposium

Foreword

Since 2008, it has been my distinct honor to lead the preparations for the annual Advanced Technology Applications for Combat Casualty Care (ATACCC) conference. The year 2012 marked the first year that the Army, Navy, and Air Force cooperatively planned a meeting combining the separate ATACCC, Air Force, and Navy conferences into a single Military Health System Research Symposium (MHSRS) under the sponsorship of the Assistant Secretary of Defense for Health Affairs. In addition to Combat Casualty Care, the topic range was expanded to include Military Operational Medicine, Clinical and Rehabilitative Medicine, Military Infectious Diseases, and Medical Simulation and Training Technology. Of the 1,463 attendees, approximately 40% were from the Department of Defense (DoD) and the balance from academia and industry.

The strength of MHSRS is in the high degree of interaction between the attendees, not only scientist to scientist, but including deployed providers who delineate the real-time needs of battlefield medicine and industry partners who assist in developing solutions to meet those needs. These interactions have led to many new initiatives that are finding solutions to these difficult problems.

Many of the inaugural 2012 MHSRS trauma presentations were previously published in the Journal of Trauma and Acute Care Surgery (J Trauma Acute Care Sur 2013; 75(2 Suppl 2): S105–274). This special issue of *Military Medicine* publishes other key presentations from that symposium that have broad applicability to medical issues before, during, and after the deployment of troops to a theater of conflict. As outlined in the Preface by Col Todd Rasmussen, in addition to improving military medical practice, DoD-sponsored research greatly benefits civilian trauma and postinjury care, including the psychological aspects of stresses related to high-intensity situations. This issue provides additional justification for that assertion.

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Why Military Medical Research?

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The challenging circumstances that confronted military caregivers during the years of war in Afghanistan and Iraq established the imperative for military-oriented medical research. The burden of injury and illness resulting from this long period of combat operations, and the unique clinical and logistical considerations it engendered provide a compelling rationale for requirement-driven, well-coordinated medical research. Also referred to as "gap" driven and programmed, military trauma research is specifically aimed at providing readily deployable solutions to reduce morbidity and mortality from war-related injury.

From a strategic standpoint, the approach taken by military medical research is quite different from that sponsored by other federal research agencies, which typically fund investigator-initiated studies of interest to the scientific community, irrespective of the urgency of the question to society. Importantly, neither these agencies nor private foundations dedicate funding to injury research of the type or severity that can be anticipated in modern warfare including terrorism. Military research has been shown effective in reducing the case fatality rate during combat and has established itself as the centerpiece of the military's continuously learning health system.[1,2] It has also generated numerous advances that are being translated to improving civilian trauma care.[3] The following paragraphs of this preface and the articles in this supplement provide examples that serve to emphatically answer the question, "Why military medical research?"

Between 2005 and 2013, the fatality rate for service personnel injured in Afghanistan decreased by 50% while the severity of injury was increasing.[1,2] The reason for this unprecedented achievement is multifactorial, but two factors stand out. At the height of the wars in Afghanistan and Iraq, the military health system made (1) significant investments in requirement-driven, programmed trauma research, and (2) an extraordinary effort to codify a trauma system that identified emerging needs for research, and rapidly translated results from military research into best clinical practices. The first element was comprised of programmatic research performed by the individual services (Army, Navy, and Air Force) and through the Joint-service, Defense Health Program. The second was the Joint Trauma System or JTS, which has developed into the Department of Defense's (DoD) "go-to" entity for real-time process improvement to optimize survival and recovery of the warfighter. The swift translation of evidence from military research through the JTS to the battlefield represents a "first" in military medical history.

Recently formalized as a Defense Center of Excellence (DCoE), the JTS maintains the DoD Trauma Registry, which is the largest repository of combat injury and trauma management information in history.[2,4] In this capacity, the JTS and the process it supports serve as a fitting "bedside" to generate many of the clinical questions that need answers from military medical and trauma research. Many experts refer to the various DCoEs as the "bookends" to medical research (Fig. 1). In this context, the JTS's ability to identify relevant clinical gaps is the left-side bookend and the more than 30 evidence-based clinical practice guidelines maintained by the JTS are a fitting and right-side bookend.[5] Although this association continues to evolve, the relationship between the nation's Combat Casualty Care Research Program and the JTS is a compelling model with research bridging the chasm that would otherwise exist between clinical needs and relevant evidence to advance military trauma practice.

The other factor intertwined with military research is the sustaining educational and academic value of America's Medical School, the Uniformed Services University of the Health Sciences (USUHS), the nation's leadership academy for military health. Without the academic support provided by faculty and graduates from the USUHS, military research would be hollow. As depicted in Figure 1, the military-unique "Joint from the beginning" educational and academic excellence promulgated by USUHS provides the foundation for military research and its clinical bookends. Likewise, without sustained research investments, USUHS would be significantly constrained in advancing the field. Working together, the various DCoEs and USUHS comprise the elements of what the Institute of Medicine has referred to as a "continuously learning health system."[6] From the standpoint of combat-related injury, the benefits of this partnership are clear, but it is equally apt for other areas of health care, including infectious diseases, traumatic brain injury, rehabilitation, and psychological health. Underlying all of these activities is a robust military health system that has captured the wartime experience, integrated it with a medical research program and translated the experience and research into more effective care for warfighters and ultimately the American public.[3,7–9]

The final answer as to "Why military research?" becomes clearer as our nation approaches the terminal stages of war in Afghanistan. As reports of violent acts on U.S. soil become

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FIGURE 1. Military medical research with DCoE functioning as bookends. In this model, the DCoE (left) provides clinical input as to military-related gaps and requirements, but also receives the output of research and is responsible for integrating it into evidence-based clinical practice. The military-unique academic and educational properties of the USUHS provide the foundation for these activities (JC2RT = Joint Combat Casualty Research Team, NAMRU = Naval Medical Research Unit, RAD = Research Area Directorates, AF = Air Force, HPW = Human Performance Wing, MW = Medical Wing, NAMRC = Naval Medical Research Center, MTF = Medical Treatment Facility, CI = Clinical Investigation).

more frequent, so do reports on the translation of advances in military trauma care to the civilian community.[3,7–9] Many of the results stemming from military research have not only contributed to the survival and recovery of U.S. service personnel but also victims injured in civilian settings. Similar to the military experience, the need for improvements in hemorrhage control, resuscitation, en route care, and damage control surgery in the civilian setting are being propelled by reports of mass shootings, stabbings, and use of explosive devices. These events generate surges of casualties with injuries resembling those the military's health system has learned to manage in an optimized manner.[8] Although civilian health care is not the main objective of military research, American medicine and surgery rapidly advance when lessons learned on the battlefield are translated to civilian contexts. This was true after World War II and the wars in Korea and Vietnam. It will also be true after the wars in Afghanistan and Iraq. This is particularly real in the field of trauma care where little if any dedicated federal research funding exists outside that provided by the military.

In summary, military medical research is a vital national security strategy in responding to the unique needs of the injured U.S. service personnel in current and future combat scenarios. Military research bridges the gap between the "bookends" of the DCoEs and is a centerpiece of the military's continuously learning health system. Military research is based on the academic foundation at the USUHS and enhances the quality of study and education at that institution. Finally, as a matter of homeland security, many findings stemming from military research enhance the resiliency and response of the civilian population. For these reasons, the answer is "yes" to military research; not as a reactive strategy, but "yes" as a deliberate and sustained investment advancing care for service personnel and civilian communities alike.

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The Military Health System Research Symposium: A Short Retrospective

Col Patricia A. Reilly, USAF BSC

Now in its 21st year, the Military Health System Research Symposium or MHSRS (formerly known as The Advanced Technology Applications for Combat Casualty Care) is a unique international event. Growing from less than 200 to more than 1,500 annual attendees, it provides an academic-based venue to report the results of Department of Defense (DoD)-sponsored research while simultaneously serving as a collaborative forum for the planning and development of research studies aimed at optimizing care for service members in operational settings.

In 1993, a 2-day meeting was convened in Silver Spring, Maryland, to discuss advances in trauma medicine. Sponsored by the U.S. Army Combat Casualty Care Research Program, it consisted of plenary sessions and a small number of table exhibits and booths. In 1995, the conference moved to Fort Walton Beach, Florida, allowing the introduction of operationally themed exhibits at nearby Eglin Air Force Base. These included demonstrations of C-130 tactical night landings with mock patients, opportunities for researchers to attempt to record vital signs in helicopters with the engines running, and exhibits highlighting innovations in prehospital care and forward surgical care. As attendance rose, the meeting was moved to progressively larger facilities in Saint Pete's Beach and Fort Lauderdale, Florida. The 2012 meeting reflected the DoD's growing emphasis on joint collaborative research. For the first time, the services blended their specific research conferences into one joint meeting at MHSRS. In doing so, the scope of the meeting was expanded to include both trauma and nontrauma warfighter-related topics.

Throughout its history, the MHSRS has provided a centralized forum for reporting the results of pioneering trauma-related research. As of 2013, conference proceedings have been cited in military-specific trauma journal supplements more than 10,000 times (COL Dallas Hack, personal communication). In 2010, the Joint Trauma System reported combat casualty care data that demonstrated the tremendous progress made in lowering the case fatality rate for U.S. service personnel during the war in Afghanistan. Presentations from the United Kingdom on their prehospital management of severe trauma have changed approaches to patient en route care and medical evacuation/MEDEVAC. Additionally, there have been landmark reports related to the safe use of tranexamic acid and the resuscitative endovascular balloon occlusion of the aorta.

Establishing and nurturing research collaborations is a MHSRS hallmark. As a result of their annual meetings at the conference, The Technical Cooperation Panel/TTCP Technical Panel 12, Combat Casualty Care agreed to sponsor more than 30 million dollars in collaborative international developmental research. U.S. Special Operations Command's Biomedical Initiative Steering Committee, after discussions with researchers at MHSRS, aggressively pushed the development of products such as the fibrin bandage (fielded), the HEMCON bandage (fielded), and injectable sponge pellets for the reduction of internal bleeding (in development). A 2001 discussion between Walter Reed Army Institute Research and the University of Florida on the concept of biomarkers for traumatic brain injury (TBI) led to an exploratory project resulting in the first blood test for TBI to enter Phase III clinical trials. In 2013, conference experts from DoD and Veterans Affairs used MHSRS as their podium to discuss the future of mental health and TBI research in accordance with the President's National Research Action Plan. Finally, a sidebar discussion at the 2006 conference resulted in the formation of the Armed Forces Institute of Regenerative Medicine (AFIRM). Today, this is a multi-institutional, interdisciplinary network encompassing two large academic-clinical consortia spanning 28 institutions, the U.S. Army Institute of Surgical Research, and several dozen companies. The AFIRM is a recognized national research sponsor for developing advanced treatment options for our severely wounded service members (for more information, see http://www.afirm.mil).

Over the years, the MHSRS has been a focal point for reporting research trends related to combat casualty care, and for establishing fruitful inter-Service and international research collaborations focused on finding solutions for military unique capability gaps. It has evolved into the DoD's premier scientific meeting, and is the only national meeting that addresses critical advances in trauma and nontrauma medicine as it relates to the unique medical needs of service members.

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The Mixed Blessings of Smart Infusion Devices and Health Care IT

CAPT Christopher P. Nemeth, USNR (Ret.); Jeff Brown, MEd; Beth Crandall, BA; Corey Fallon, MS

ABSTRACT From July to October 2009, a team of human factors researchers evaluated the use of a commercially available infusion device among nurses at a tertiary care hospital in the Midwest. The study's purpose was to determine the factors that may influence the adoption and "best practice" use of smart infusion devices by identifying the human, technological, environmental, and/or organizational factors and to describe how they support or impede safe practices. The study's aim was to show how technology and individual and team behavior influence each other, as well as care performance and outcomes. Research team members shadowed nursing personnel as they performed routine care activities, and conducted cognitive task analysis interviews with nurses, an engineer, and a pharmacist. They identified key themes, and then made several systematic passes through the data to identify all instances of each theme and to collect examples and illustrative quotes. Although staff members were positive in their comments about the smart pump, observations and interviews revealed discrepancies between prescriptions and infusions, and "workarounds" to cope with the mismatch between interface design and actual care requirements. Despite "smart pump" capabilities, situations continue such as the need for clinicians to perform calculations in order to deliver medications. These workarounds, which make them and patients vulnerable to adverse outcomes, confirm prior published research by Cook, Nemeth, Nunnally, Hollnagel, and Woods. The team provided recommendations based on findings for training and interface design.

INTRODUCTION

This article reports on a study of "smart" infusion devices to determine the factors that may influence their adoption and "best practice" use. The study described the human, technological, environmental, and/or organizational factors that support or impede safe practices, including those that provoke improper operation. The study was conducted to show how technology and individual and team behavior influence each other, as well as care performance and outcomes.

BACKGROUND

The use of potent, short acting intravenous (IV) agents used in anesthesiology and critical care medicine requires precision and accuracy. This recent development in medical practice makes use of a larger number of pharmaceutical agents that are more potent and faster in onset/offset of action. Some agents such as those used in chemotherapy require complex, changing infusion schedules. Administration by means other than the blood (such as the spinal fluid) makes infusion practice even more complicated. These changes in patterns of practice as well as in pharmacology have created a need for multiple, carefully controlled infusion schemes. The perception was that the simple control loop of a gravity-fed drip could not provide it. The evolution of small, cheap microprocessors led to the creation of infusion pump systems that could perform consistently and accurately.

By 2000, most infusions in U.S. hospitals were provided by electronic infusion devices, making them one of the most widely used information technologies in the clinical setting.[1] By 2006, the estimated installed base of external infusion pumps in U.S. hospitals and other health care settings totaled over two million devices.[2] By 2010, the "...use of infusion pumps for IV medication administration is now commonplace and essentially mandatory."[3]

Infusion devices provide the benefit of controlled administration of fluids and medications to patients, and the pump itself is a fairly simple mechanism. The ability to serve additional clinical needs by expanding pump features has led to the evolution of "smart pumps" (Fig. 1). Characteristics that set them apart from traditional infusion methods include: "(1) the ability to incorporate a large medication library into the device, (2) the ability to alert users of potential use errors, and (3) the ability to collect usage data, which can be used to improve work practices."[4]

Use of these devices has presented clinicians with unforeseen complications that pose significant safety implications for clinicians and the potential for harm to patients. The report of the Association for the Advancement of Medical Instrumentation/United States Food and Drug Administration (AAMI/USFDA) 2010 pump summit noted "Between Jan. 1, 2005, and Dec. 31, 2009, more than 56,000 adverse events and 710 deaths associated with infusion devices were reported to the USFDA—more than for any other medical technology. During this period, there were 87 pump recalls."[5] That same year, the USFDA launched an ambitious campaign[6] to improve pumps in the face of "rampant problems" causing "many pump mishaps" that "stem from faulty design and engineering, particularly in terms of software and user interface."[7] In the following year, Cummings and McGowan[8] published a roster of issues that nurses have to be aware of to avoid problems such as "programming and administration errors, even when clinicians use drug libraries."

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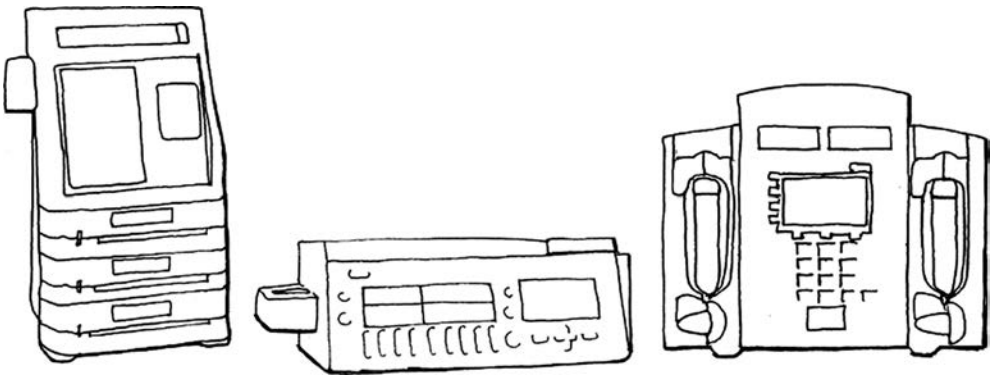

FIGURE 1. Illustrated examples of commercially available "smart" pumps.

This article describes some of the mixed blessings of increased features and safety concerns that infusion devices pose for patients. Study results have implications for military patient care in particular, as "force protection in Joint doctrine covers everything from personnel services," to "medical support, and combating terrorism."[9]

OBJECTIVE

From July to October 2009, Crandall et al[10] evaluated the use of a commercially available infusion device among nurses at a tertiary care hospital in the Midwest. The purpose of the study was to determine how infusion device "smart" features affect clinical practice. As a pragmatic inquiry, the research effort sought to understand the effect of smart pump introduction through a naturalistic look into the experience of those who use it. The research is an ethnographic field study[11] that is designed to reveal actual clinical practice by understanding individual and team behavior and work processes related to infusions.

METHODS

Methods are essential to expand understanding beyond individual ability and experience, and also help to prevent the effects of presumption and bias. No single method is adequate to accurately describe human behavior. Because of this, more than one method needs to be used to triangulate the subjects of study to avoid bias that use of a single method can induce. The research design for this project included a 3-day mixed method qualitative field study combining 9 hours of observation and formal interviews at a Midwestern hospital. Use of a qualitative approach makes it possible to inquire about selected issues such as the use of a smart pump "in great depth with great attention to detail, context and nuance" without being restrained by predetermined analytical categories.[11]

The sample for the study included nine nursing personnel who operated a commercially available "smart pump" infusion device on two representative units of the medical–surgical population served by the hospital, a biomedical engineer, and a pharmacist. All data were collected in accordance with the sponsor's human subject requirements, including obtaining consent before conducting research.

The research team used proven observation and interview data-gathering methods that revealed the context in which judgments and decisions are made to find out how clinicians in this study actually think and function under time-pressured, uncertain and high-risk conditions.

Observations

Observational methods are used to discover the characteristics of actual work settings and the ways that people perform work there. Observation exposes the researcher to the lived experience of clinicians, free from presumptions about what their work is or how they do it. The research team members shadowed nursing personnel as they retrieved and prepared medications outside of patients' rooms, checked medication orders, set up the infusion device, and infused medication using the device.

Firsthand observations of the work setting were a necessary source of cognitive performance data, but did not provide data on context and motivation. For that reason, the research team needed to use interviews to find out what their participants noticed, to learn what information they sought and what they ignored, and to find out what leads them to act in a certain way.

Interviews

The research team conducted Cognitive Task Analyses (CTA)[12] with the nurses, a biomedical engineer, and pharmacist. CTA is a family of tools and techniques that can be used to elicit, analyze, and represent cognitive aspects of performance, as well as the operational context in which work is performed. Structured CTA interviews typically reveal how subjects manage attention, manage risk and uncertainty, detect problems, conduct mental simulations, recognize patterns, make perceptual discriminations between subtle cues, make sense of disparate data, construct mental models, apply strategies and heuristics, derive inferences, and recognize typical

events and anomalies. Findings from CTA studies have been used extensively in system development, training design, safety research, organizational and workplace design and many other areas of applied cognitive research in a wide diversity of settings and task domains. CTA methods can typically be used to ensure that a system will be useful, usable, and understandable. CTA methods have been used extensively to study real world cognition, and to develop cognitive systems engineering applications such as information systems and displays. Incident-based methods such as the Critical Decision Method and Knowledge Audit have proven particularly useful to illuminate aspects of expertise, and reveal the subtle perceptual cues, sense of typicality, extensive mental models, and situational understanding that underlies proficient performance in time-pressured, dynamic settings.

In this project, CTA methods enabled the team to not only understand both individual and team cognitive performance but also to learn the subtly nuanced, less evident practices that nurses developed in order to use infusion pumps.

Data Analysis

To analyze the data they collected, the research team documented every interview with notes and audio recording, and created an electronic data record for every interview. They took all data into consideration by "triangulating": using multiple methods including incident accounts, case histories, examples, and in situ observations. They used this multiway deliberation to develop reports about clinician cognitive work that are grounded in the lived experience and actual behavior in their operational context. The team then identified an initial set of key themes, and then made several systematic passes through the data to identify all instances of each theme and to collect examples and illustrative quotes. The approach provided a way to identify and document the cognitive processes behind their behaviors and judgments.

RESULTS

The study found that, in the opinion of nurse study participants, the implementation of the smart pump has so far been a substantial success. At the same time, though, the research team found that there is a need for further investigation into system, performance, and organizational factors that affect nurses' understanding of how the pumps operate. Further research is also needed to understand how nurses choose to manage and workaround system challenges. There were numerous examples of nurses using pump safety features in the manner other than how they were intended to be used. The study data suggest that even with features that are intended to promote safe use, nurses still experience conditions that may induce error, or waste time and resources. The study produced a number of findings that addressed how individual and team behavior and smart pump technology affect each other. A portion of them are included here.

Patient Safety

When nurses were asked what they liked most about the pumps, increased safety ranked highest. The research team saw this as evidence that safety is a central feature of nursing practice at this hospital. Nurses expressed the opinion that the smart pump was an improvement over the pump that was previously used at the research site, particularly in terms of safety. Even so, they described work practices that risked compromising safety.

Nurses' perceptions of safer operations were based on the fact that pump programming features included hard and soft limits, automatic calculations based on patient weight, medication warnings, and exact programming of drugs and concentrations. Even so, nurses found that pump programming limits can make it difficult to follow physician orders or to take patient differences into account. For example, they were unable to program the pump to infuse medications at a rate lower than 0.5cc/hour.

Work Process Issues and Workarounds

Nurses described a number of instances in which they needed to deliberately enter information into the pump that differed from the information that was displayed on the IV bag they were hanging. Nurses reported a few instances when the prescribed drug was not programmed into the drug library that made it necessary to develop local "workarounds." Most often, these deviations related to volume, with nurses sometimes entering more or less than the amount indicated on the bag. By entering more or less volume than is actually in the IV bag, nurses could work around the limitations caused by their inability to adjust alarm settings. Another workaround related to switching the pump display back and forth between the primary and secondary IV bag.

Nurses reported occasions where type, dosage, and/or rate of medication delivery programmed into the device did not match the bag label, or where the medication order did not match the medication delivered. That made it necessary to compare the medication order with the bag label and enter that information into the pump. Nurses found that this active engagement discouraged routine behavior.

Situations continue to occur in which nurses must conduct calculations for medication delivery, which are often done quickly and "in the head." Many of the nurses recognized the loss of some skills, particularly skills required for conversions and figuring out doses.

There was also considerable variability in nurses' descriptions of how the pump works, which suggests variability in mental models (the internal concepts that people develop about how and why something works the way it does).

Medication Dose and Rate Discrepancies

By requiring the user to select a dose, the interface provides a safety check that can prompt communication and clarification among the nursing staff, pharmacy, and the physicians.

Although nurse–pharmacy relations were exceptionally good, nurse reports contained examples in which pharmacy order filling did not necessarily agree with the physician written order. Nurses reported instances of mismatches where the type, dosage, and/or rate of medication delivery that was programmed into the pump did not match the bag label, or where the medication order did not match the medication that was delivered. In some instances, nurses programmed these discrepancies on purpose. For example, there are medications that physicians order in micrograms/hour, whereas pharmacy fills in milligrams. Because of such conflicts, nurses must be alert for the change and figure out how to convert back to micrograms in order to dispense the correct amount of medication in the right amount of time.

Pump Drug Library

Although nurses considered the drug library feature a plus, the feature also posed a number of difficulties. The library currently uses generic drug names and nurses do not always know generic medication names. The user must enter the first two letters of the desired drug, and then the pump's search engine populates the display with every drug in the library that begins with the two letters. Exceptions are needed to uniquely identify medications and fluids. That may slow the search process for nurses who are new to working with the pump.

Pump Alarms

Nurses found that pump alarms caused undesirable distractions that interrupted their work. For example, the 30-minute "bag near-empty" alarm often does not fit nurses' work preferences or the patient's care plan. Having to respond to the "upstream occlusion" alarm can distract nurses from more critical tasks.

Having the same alarm for all problems makes it difficult to know whether a quick response is necessary. The audible alarm only informs the nurse that there is a problem with the pump, but it does not help the nurse to figure out the nature of the particular problem. It can be difficult to tell which one among the many pumps that are connected to a patient is generating the alarm, and a nurse must look at each display to identify which pump is sounding. Acknowledging an alarm by pushing a button on the pump temporarily silences it. If the underlying problem is not resolved, though, the alarm will sound again and require further attention.

Implications for Training and Knowledge Transfer

Pump interface design is beyond the control of clinicians, which puts them in the position of having to adapt their behavior to compensate for difficulties these devices present. This is typically attempted through training. In training, nurses should hear information about the most relevant functions and potential challenges that they may encounter, and have opportunities to apply learning through case examples. The manner in which training is developed and presented needs to take individual learning differences into account. The time between training and pump deployment should be as short as possible.

Variable knowledge about the pump translates to variability in how nurses work with, and work around, the pump. Some of the misinformation in this instance is likely being communicated through one-on-one mentoring and informal communication among nurses. Inconsistent training may lead nurses to direct their attention to different information, miss critical information, or respond prematurely or inappropriately to events.

DISCUSSION

The results of the study demonstrate that the infusion device is not simply a piece of equipment, but is instead part of a sociotechnical system[13] that includes multiple elements: people (nurse, physicians, pharmacists, suppliers, managers), work processes (pump programming, infusion, patient care, team coordination, training), supplies (tubing, medications), equipment (the pump), software (the interface, information systems), and organizations (the hospital, manufacturers and subcontractors, professional and governmental organizations) as Figure 2 illustrates.

Nurse–pump interaction and pump interface variability created both desirable as well as unforeseen outcomes. Additional Smart IV pump studies mirror the study's findings that are related to the user interface, mental models, and workarounds.

Rajkomar and Blanford[14] echoed recommendations in the AAMI/USFDA summit report[5] and our study, emphasizing that the entire clinical work context needs to be taken into account by pump developers. Their ethnographic study findings noted how work context complexity affects pump use in the intensive care unit, from volume counter resetting to sticking labels on syringes, checking on pump performance, and more.

McAlearney et al[15] found nurses programmed the infusion pump manually instead of using the pump's programming features, which defeated the pump's safety features. Carayon et al[3] cautioned that ". . .the use of the special pump safety features, e.g., the built-in dose error reduction system, is not mandatory. In fact, users can continue to use the dose-rate calculator in the pumps or hand calculate the infusion settings and proceed with administration, thereby bypassing the protection inherent to the drug library and dose double check." After using a Smart IV pump for about 1 year, the Carayon study found nurses' perceived ease of use in emergency situations was much lower compared with other traits that are related to efficiency.

Nunnally et al[16] study of a 40-member sample including attending physicians, residents, and intensive care unit nurses concluded that infusion device complexity lies hidden beneath layered, nested menus with irregular branching. The complexity of the menu structure, which was referred to as the "menuspace" of the device, appears to defy any attempts at mastery. Even skilled users in the sample appeared to have

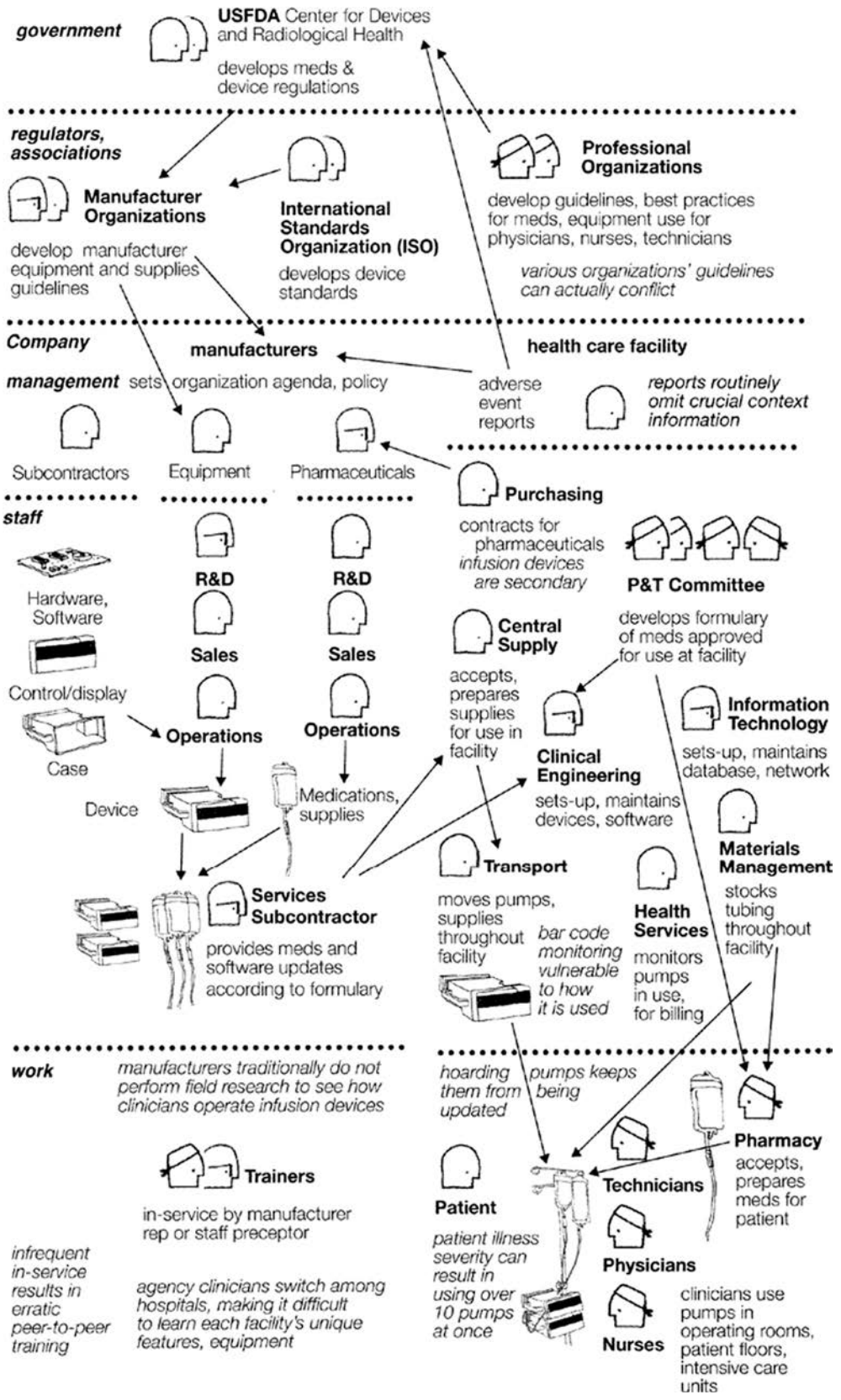

FIGURE 2. Infusion device as a sociotechnical system. Copyright © 2008 Cognitive Technologies Laboratory. Reprinted with permission.

a working knowledge of only a small portion of the possible pathways that could be used to program the device. That made becoming "lost" very likely and suggests that there are deep difficulties with interface design.

A prospective, randomized time-series trial of pump data for 744 cardiac surgery admissions found that IV medication errors and adverse drug events were frequent. For example, infusion practice violations included 571 (25%) instances of bypassing the drug library. The study concluded that "technological and nursing behavioral factors must be addressed if these pumps are to achieve their potential for improving medication safety."[17]

To provide clinicians with the equipment they need, device manufacturers must reflect actual clinical practice in their interface designs so that clinicians do not need to develop workarounds that put both them and patients at risk. The real obstacle in the development of sophisticated medical devices such as infusion pumps has been to understand the complex operations of health care systems in which these devices exist. How can health care IT systems such as an infusion device be configured to best support clinical practice? Klein et al[18] proposed traits that IT systems need to participate in a highly adaptive human work domain such as patient care:

(1) Fulfill the requirements of a Basic Compact to engage in "common grounding" activities—an agreement to facilitate coordination, to work toward shared goals, and to prevent team coordination breakdowns;
(2) Able to adequately model other participants' actions vis-à-vis the joint activity's state and evolution—able to coherently manage mutual responsibilities and commitments to facilitate recovery from unanticipated problems;
(3) Be mutually predictable—the mental act of seeing ahead, with the frequent practical implication of preparing for what will happen;
(4) Be directable—able to deliberately assess and modify others' actions as conditions and priorities change;
(5) Able to make pertinent aspects of their status and intentions obvious to their teammates—make targets, states, capacities, intentions, changes, and upcoming actions obvious;
(6) Able to observe and interpret signals of status and intentions—able to signal and form models of teammates;
(7) Able to engage in negotiation;
(8) Enable a collaborative approach;
(9) Able to participate in managing attention;
(10) Help to control the costs of coordinated activity

The study of real world work requires methods that are able to understand it and the social sciences and engineering—specifically cognitive psychology, sociology, and human factors—have the means to do this. For example, Nemeth and Cook[19] proposed features of infusion devices to make them more observable and controllable. Understanding the user work setting and behaviors through intensive study using cognitive systems engineering methods (including CTA) makes it possible to design from the user to the system. Such study examines how experts develop and use artifacts as a way to deal with real world problems. Rigorous scientific study yields insight into what truly aids expertise of those who care for patients in the Department of Defense health care system.[20]

CONCLUSIONS

Understanding how clinicians do their work will show how to best design devices for clinicians, and how clinicians will be able to make better decisions. Despite "smart pump" capabilities, the results of Crandall et al[10] show that circumstances continue to exist in which clinicians must perform multiple activities to manage pump operation, including programming, in a complex work setting. These workarounds, which make them and patients vulnerable to adverse outcomes, reflect published work by multiple researchers including Carayon, Cook, Klein, Nemeth, Nunnally, Hollnagel, and Woods.

Clinicians must perform calculations to deliver medications, manually adjust volume, calculate drip titration, make unit conversions, adjust rates, and sometimes override the pump's hard limits in order to enter the full set of delivery parameters. These and other issues related to infusion pumps will continue to put clinicians and patients in jeopardy until these devices accurately reflect work settings and actual clinical cognitive work.

ACKNOWLEDGMENT

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En Route Care Patient Safety: Thoughts From the Field

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ABSTRACT The purpose of this study was to describe the patient safety culture of en route care in the United States Air Force aeromedical evacuation system. Almost 100,000 patients have been transported since 2001. Safety concerns in this unique environment are complex because of the extraordinary demands of multitasking, time urgency, long duty hours, complex handoffs, and multiple stressors of flight. An internet-based survey explored the perceptions and experiences of safety issues among nursing personnel involved throughout the continuum of aeromedical evacuation care. A convenience sample of 236 nurses and medical technicians from settings representing the continuum was studied. Descriptive and nonparametric statistics were used to analyze the quantitative data, and thematic analysis was applied to the qualitative data. Results indicate that over 90% of respondents agree or strongly agree safety is a priority in their unit and that their unit is responsive to patient safety initiatives. Many respondents described safety incidents or near misses, and these have been categorized as personnel physical capability limitations, environmental threats, medication and equipment issues, and care process problems. Results suggest the care of patients during transport is influenced by the safety culture, human factors, training, experience, and communication. Suggestions to address safety issues emerged from the survey data.

INTRODUCTION

United States Air Force Medical Service (AFMS) personnel deliver health care in austere and unique environments such as aeromedical evacuation (AE) and expeditionary medical units. Almost 100,000 patients have been transported in the AE system since Operations Iraqi and Enduring Freedom began.[1] A unique component of military health care is the aeromedical transport of the sick and injured from the battlefield to definitive care. Along the transport continuum, there are numerous handoffs from expeditionary facilities to tertiary medical care facilities requiring ground, rotary, and fixed wing movement under austere and sometimes threatening environments. Delivering emergent care to seriously ill and injured military personnel in an aircraft places unusually high demands on nursing and medical personnel to provide safe quality care under the most difficult circumstances.

Patient safety is an area with a high potential impact if neglected, and it is dominated by human factors considerations. In 2002, the Institute of Medicine reported that medical mishaps account for many avoidable unfavorable medical outcomes, making hospitalization as dangerous as driving on the nation's roads and highways in terms of risk.[2] Safety in aeromedical transport is more complex compared to the inpatient setting due to concurrent aviation safety and patient safety issues.[3] Safety concerns in the AE system are uniquely complex because of the extraordinary demands of multiple patients of varying acuities and care needs delivered in a confined space, multitasking, time urgency, long duty hours, complex handoffs, limited resources, and multiple stressors of flight. The USAF AE system is the only entity in the world capable of moving large numbers of complex patients over long distances.[4]

Studies on patient safety and the safety culture regarding AE patient care are limited. The main focus of safety in the literature is the safety of the flight operations, not the care delivered in the aircraft.[5] A study from Israel during their war with Lebanon in 2006 focused on this aspect of AE, along with a descriptive analysis of patient conditions and care. There was a brief mention of difficulties with information transfer during handoffs due to dangerous battlefield conditions. The authors also discussed a compromise in the level of monitoring and care available in flight because of the unexpected number of injured soldiers evacuated. However, this did not appear to affect outcomes because transport times were short and there were few critical patients per flight.[6]

In a study of communication errors in an air medical transport service as documented in quality and safety assurance reports, the researchers found the errors were largely unrecognized by the reporting staff. Errors identified related to patient safety centered on miscommunication about the patient's condition. The most common errors reported were

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about flight operations and logistics. The authors called for an improved system to identify common errors and therefore improve safety.[7]

The increasing complexity and volume of patient care in hospitals worldwide has driven focus on interventions to ensure patient safety and improve quality. Interestingly, safety checklists first used in military aviation have emerged as effective tools to accomplish this goal. In the book "The Checklist Manifesto," surgical safety expert and author Atul Gawande champions the use of checklists to reduce harm and ensure adherence to standards proven to improve outcomes.[8] Robbins points out that the checklist is a tool fostering quality through teamwork and communication. Furthermore, the culture must support the use of the checklist and the collaboration it supports.[9] Haugen et al[10] found that institution of a surgical safety checklist had a limited impact on safety culture within the hospital they studied. Members of this research team have studied the use of a checklist to improve communication during patient handoffs in simulated en route care.[11] Positive results led to planning of more study of this intervention in AE. Currently, there is an ongoing qualitative study with focus groups also by this research team that is focused on the safety culture in AE.

The goal of the AFMS AE system is delivering patients safely and efficiently to the appropriate destination.[12] The system has an extensive record of transporting thousands of patients safely from Iraq and Afghanistan.[13] However, provider education and training as well as processes vary across the en route care system and may contribute to errors and adverse events. The AFMS has put in place a patient safety program for AE, but this program is modeled after those developed and intended for the civilian health care setting and may not be the best fit for en route care patient safety. Additionally, even though the AE process is regulated by Air Force Instructions, the Contingency Aeromedical Staging Facilities (CASFs) and Aeromedical Staging Facilities (ASFs) do not fall under the same system. The CASFs and ASFs are the ground-based units, usually colocated with a military treatment facility, where patients receive care if they do not require inpatient admission, while waiting for the next flight in their AE journey. These patients are still considered to be in the AE continuum of care while on the ground in these facilities.

The purpose of this study was to investigate self-reported perceptions of the safety culture among personnel in the USAF AE system. Workplace attitudes, beliefs, and culture may impact the safety of patient care.[14] The patient safety concerns of current en route care providers and possible solutions to patient safety issues were explored. This study is part of a larger ongoing project in which both quantitative and qualitative methods are being used to analyze patient safety in AE. The overall study will examine whether patient safety programs in AE are adequate, where they can be improved, and where more intervention is needed to ensure the safety of our injured airmen, sailors, soldiers, and marines. Because the AE environment is substantially different from the civilian health care environment for which patient safety programs are well studied, this research is overdue. Additional areas of study may be identified.

METHODS

An internet-based survey explored the perceptions and experiences of safety issues among Air Force, Air Force Reserve, and Air National Guard personnel involved throughout the continuum of care. The survey was made available to nursing personnel in the AE system over a 14 week period through a broad enrollment message that was distributed several times to all currently operating AE squadrons, CASFs, and ASFs. Voluntary respondents entered the online survey via Survey Monkey (SurveyMonkey.com, Portland, Oregon). The total number of personnel that received the invitation is unknown. The survey had advanced security protection to maintain participant confidentiality, was in compliance with the Air Force Personnel Survey Program,[15] and was approved by the Survey Office. Ethical review and a determination of exemption from oversight were obtained from the Air Force Research Laboratory and the U.S. Army Medical Research and Materiel Command Office Institutional Review Boards.

The survey was adapted from the survey of safety beliefs and practices conducted by the Air and Surface Transport Nurses Association. Psychometric properties of the tool were not provided.[16] The survey included demographic information; questions about close call, near miss, or safety incidents with discrete choices; and 13 Likert-type items addressing staff, crew, and patient safety. Likert responses were rated on a 5-point scale from 1 = strongly agree to 5 = strongly disagree. Modified to include free-text fields, the survey provided an opportunity for respondents to write narrative comments about their experiences regarding safety issues. This mixed method exploratory design utilized quantitative and qualitative methods as an empirical approach. Collection of qualitative data was imperative because of the purpose of the study, which focused on exploring the intricate details of the human experience.[17] These methods allow researchers to deduce scientific evidence from participants' thoughts and words that cannot be fully understood through questionnaires and descriptive statistical analysis.

Descriptive statistics and nonparametric techniques were used to analyze the survey data. All statistical analysis was done using PASW Statistics 18.0 (SPSS, Chicago, Illinois). All of the qualitative data entered into the free text fields was analyzed using thematic analysis to identify themes emerging from the accounts of the respondents' experiences of patient safety issues. Intercoder reliability was assessed by two researchers coding the data and comparing the results to establish dependability.

RESULTS

Quantitative Data

Two hundred and fifty surveys were collected and 236 surveys with complete demographics and Likert items were included in the analysis. Characteristics of the sample are presented in Table I.

Staff/Crew Safety

Scores on the Likert-type items indicate that over 90% of respondents agreed or strongly agreed with all of the six staff and crew safety items in the survey (Fig. 1).

Patient Safety

Scores on the Likert-type items indicate that over 90% of respondents agreed or strongly agreed with six of seven questions regarding patient safety. The final item on the survey regarding whether the mission or patient safety was more important had a mixed response, with 6% of the respondents neutral and 54% disagreeing with the statement that the mission takes precedence over patient safety. These results are shown in Figure 2.

TABLE I. Respondent Characteristics

Variable	Value	Significance
Officer (Nurse)	132 (56%)	
Enlisted	104 (44%)	
Unit of Assignment		
AE Squadron	153 (65%)	
CASF/ASF	73 (31%)	
Other Medical Facility/Unit	10 (4%)	
Status		
Active Duty	184 (78%)	
Air Force Reserve	42 (18%)	
Air National Guard	10 (4%)	
On Flying Status	142 (60%)	
Age (Year)	36 ± 10.3	Not Significant
AE	37 ± 9.5	
CASF	34 ± 12	
Gender		Not Significant
AE		
Male	71 (43%)	
Female	93 (56%)	
CASF		
Male	34 (40%)	
Female	52 (60%)	
Rank		$p = 0.008$
AE		
Officer	102 (62%)	
Enlisted	62 (38%)	
CASF		
Officer	39 (45%)	
Enlisted	47 (55%)	
Years of Military Experience	11.5 ± 8.0	$p = 0.004$
AE	12 ± 8	
CASF	11 ± 9	
Years of AE Experience	4.6 ± 6.2	$p = 0.002$
AE	5.6 ± 7	
CASF	2.5 ± 5	

Flying Status

Further analysis was performed using the χ^2 test to compare responses of AE squadron personnel with those from the CASF and other units, and those on flying status with nonflyers, to determine if the perceptions of safety vary by training and job classification. Some participants were in the ground units while on flying status. Analysis of current unit of assignment (AE squadron versus CASF/ASF) showed no differences, whereas significant differences were found on three items for those on flying status versus nonflyers. These differences were for the items, "I can speak up about staff/crew safety issues," χ^2 (1, N = 236) = 10.05, p = 0.002; "I have adequate staff/crew safety training," χ^2 (1, N = 236) = 8.32, p = 0.004; and the statement "Staff/crew safety is a priority in my organization," χ^2 (1, N = 236) = 5.24, p = 0.022. Those not on flying status endorsed more neutral or negative responses than those on flying status for each of these items in the staff and crew safety section of the survey.

Close Calls, Near Misses, or Safety Incidents

Forty percent of all survey respondents reported experience with an event that they would characterize as an en route patient close call, near miss, or safety incident. AE System safety mishap reports were completed for 87% of these incidents. One respondent indicated that her unit submitted over 120 AE System safety mishap reports in a year.

Among the individuals who indicated that they had experienced an event, 48% indicated a change was made to address the incident, whereas 35% indicated that no change was made. Data were missing from the remaining respondents. Six percent of these respondents indicated that processes were already in place to prevent untoward safety occurrences. Six percent of respondents reported that even when processes did not work and potential problems were identified, they were not aware that any changes were made.

Qualitative Data

Forty-one percent of all the respondents provided a narrative to describe safety incidents or near misses. The narrative data were analyzed qualitatively by thematic analysis to identify patterns or themes: eight main themes were identified. All of the themes have also been identified in the qualitative focus group study data currently being analyzed by this research team. Several issues with medications were identified by 26% of these respondents. Two medication-related issues were administration of medications that did not match the physician orders and inadequate pain medication administration. The latter problem was discussed in light of the often jarring movement the injured patient experiences while moving to the plane and the time it took to get the patient to the flight line and aboard the plane, both of which contributed to the patient experiencing more than expected pain. Nine percent of respondents said that ordered

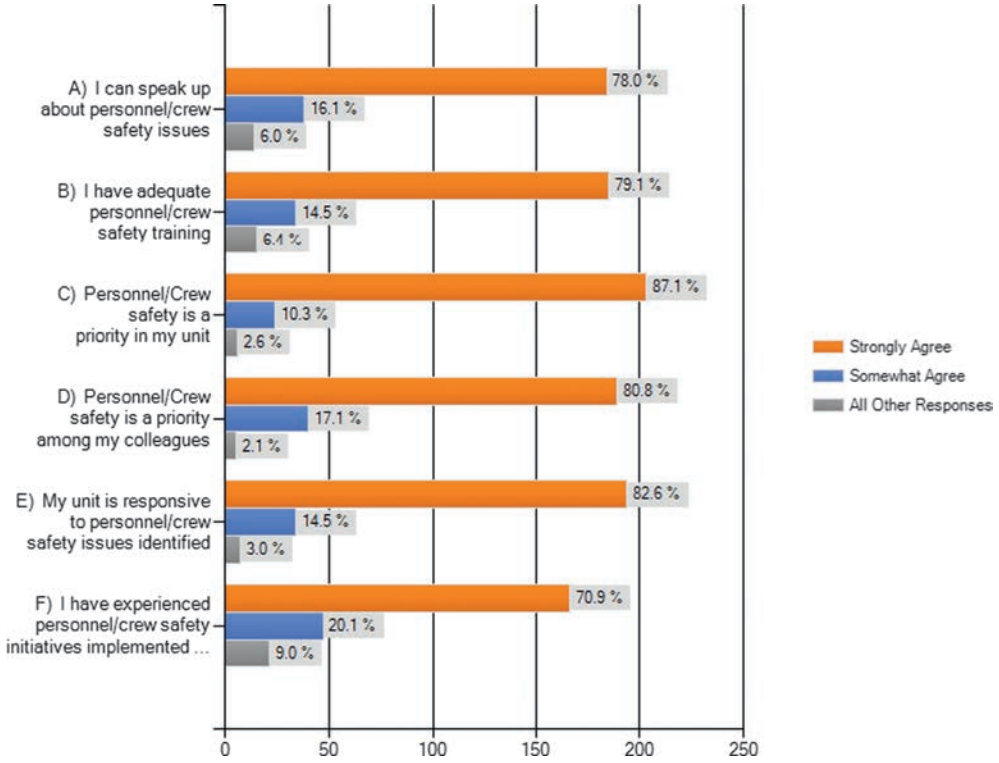

FIGURE 1. Likert item responses for staff/crew safety.

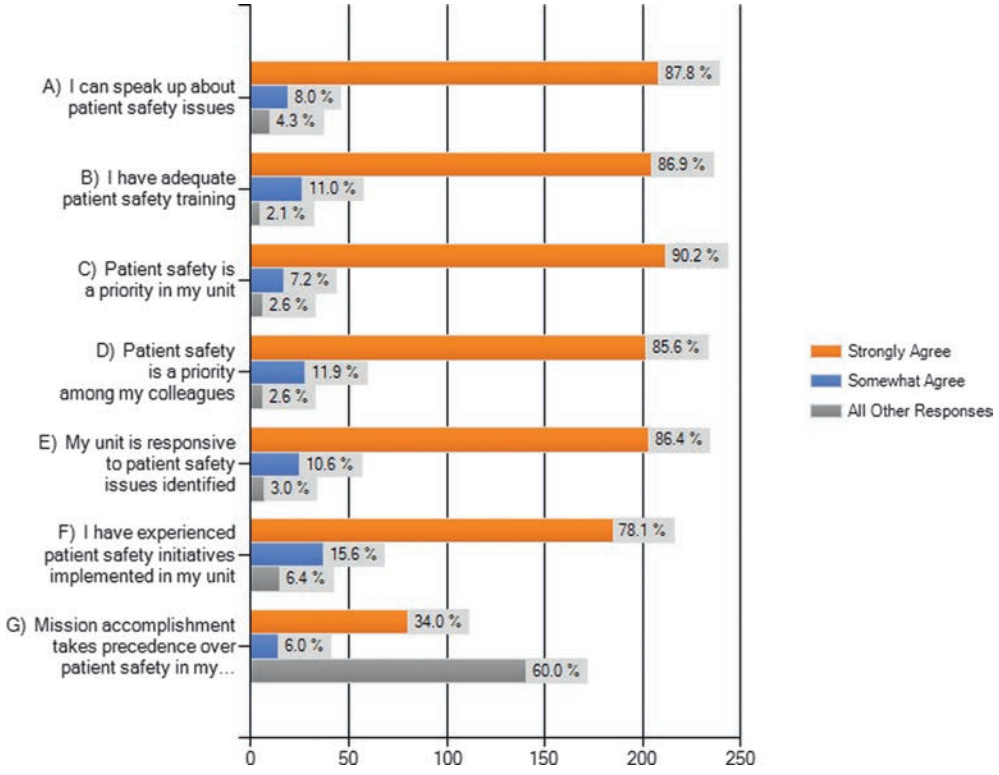

FIGURE 2. Likert item responses for patient safety.

medications were missing from the supply provided by the ground facility.

The issue of planning for providing care in the isolated environment of an aircraft in flight also emerged as a theme 5% of the time. Equipment that did not have power cords or needed equipment that was not provided for the flight was identified as a theme in 10% of the responses. An inadequate supply of oxygen for the entire flight and missing medications, paperwork, or physician orders were other examples of safety issues discussed by 20% of the survey respondents. Respondents described the response of the flight crew or Critical Care Air Transport Teams to mishaps with oxygen. They discussed that training, experience, and planning ensured a response that overcame the problem, avoided patient injury, and allowed for continuation of needed care. Four percent described how the patients were not adequately prepared for the flight and corrections had to be made quickly on the flight line.

An issue with moving patients on litters was mentioned by 15% of respondents. Unsafe litter strap and backrest application, miscommunication of litter carry commands, inadequate strength of litter bearers, rushed loading, and tripping or slipping on the aircraft ramp were all examples of near misses or safety mishaps involving patients being moved on litters.

Four percent of respondents discussed inadequate strength or height of personnel involved in care in the AE continuum as affecting care delivery. One individual discussed mission demands creating fatigue and affecting her ability to take a break and eat, which, in turn, affected performance. This issue of physical readiness has been discussed by participants in the ongoing focus group study.

Handoffs and communication were discussed by 11% of respondents. Handoffs between the CASFs and the crew at the plane were described as a time when following procedures was very important to avoid unsafe conditions for patients and personnel. This is also a time when there is tension between the desire to meet scheduled departure times and provide adequate handoffs. Disagreement between the nursing staff and the flight surgeons on patient condition and readiness to be transported was also identified. Incidents of two patients deteriorating in flight were described, noted to be unanticipated, and resulted in positive outcomes due to timely and appropriate interventions by the AE nursing crew.

Finally, 5% of respondents described how the aircraft environment itself has dangers. They experienced incidents such as a loss of pressure, a drop in altitude, a near-crash, and a door malfunction. All of these incidents had positive outcomes and were reported. Table II contains exemplars of close calls, near misses, and safety incidents experienced by the survey participants.

TABLE II. Exemplars for Close Calls, Near Misses, and Safety Incidents

Medication Issues
"Medication was discontinued but given to nurse during hand-off"
Oxygen Supply
"The PT Lox malfunctioned. Fortunately we had another one."
Equipment
"Patient didn't come out to flight line with all appropriate equipment"
Human Factors
"The team was not strong enough"
Training
"Patient improperly secured to litter with backrest"
Communication
"The requirements were not communicated properly so we would have enough"
Patient Preparation
"Patients were not loaded on litters and we had to transfer them on the flight line"

Safety Culture

The responses given by participants in the free text fields of the survey reveal several insights into the safety culture. Overall, the responses indicate that the AE environment has a positive culture of safety, identified in the literature as a work environment where concerns are shared without trepidation, the leadership listens to suggestions to improve safety, free communication regarding safety is encouraged and well received, and events are reported.[18] Respondents indicated that submission of a report of a safety issue is well received, and actions taken to address the issue are communicated throughout the AE system. Equipment problems and other events that occur during a flight are handled by the crew anticipating the problems or quick thinking that is fueled by flexibility, training, and experience.

In contrast, responses regarding the CASF safety culture were not as positive. Respondents whose current unit was a CASF (40%) felt that there were many safety issues in the CASF, and the safety culture in these units is not as mature as in the AE squadrons and not in line with AE system requirements. Where the CASF and AE personnel interact the most, and arguably the most vulnerable time for patients and their safety, was identified as enplaning. This is when the handoff from the CASF to the AE crew occurs, and the patients are loaded onto the plane in preparation for transport.

Need for experience and training were themes identified by 5% of respondents. Training of ground personnel in the CASF and those who support AE operations, such as litter teams, was identified as an ongoing issue. Participants indicated that litter bearers, who were often volunteers from nonmedical units, constantly had to be trained. The CASF personnel in deployed locations experience as little as 1 day of overlap to learn the mission upon arrival in theater. This is especially concerning because CASF operations cannot be learned in an equivalent civilian or home-station environment. Also discussed was the focus of training in the AE system on the planes and flight, when clinical skills also need to be emphasized, especially in less experienced personnel. Respondents also discussed that other military services and non-AE AF personnel lack understanding and training on

requirements to enter patients into the AE system for transport. One respondent indicated that he thought the standards for safety may be different for active and Reserve and Guard AE squadrons.

Mixed messages delivered by leadership regarding the priorities in the deployed environment also were discussed. In their narratives, 5% of respondents indicated that safety was always a priority, whereas 4% said that mission accomplishment was communicated as a more important objective. For example, pressures to take off on time sometimes created potentially unsafe conditions on the flight line during handoffs and patient loading. One respondent noted that in the area of responsibility, command structure and service specific procedures, documentation, and regulations do not support cohesive management of patient safety during transport from point of injury to the continental United States (CONUS).

Communication was cited as a key to a positive safety culture. Lack of communication, from the individual to the strategic level, negatively impacted safety according to respondents. Three percent of respondents indicated that Critical Care Air Transport Team, AE, and CASF personnel clashed due to lack of understanding of each other's missions and poor communication and interpersonal skills. Also discussed was the communication of patient condition and readiness to fly that occurred between the flight surgeons and the flight crew. Conflicting assessments were thought to contribute to possible safety problems, and communication in these situations was strained. Finally, the new computer documentation system that serves to communicate patient condition and care delivery during flight was cited by one respondent as not user-friendly for the flight crew. The respondent felt the system time consuming, taking time away from patient care. This idea has also surfaced in the focus group study. Exemplars of the respondents in the category of safety culture can be found in Table III.

Proposed Solutions or Focus Areas

A final field in the survey allowed the respondents to provide additional comments. Thirteen percent of all the survey respondents entered comments. Unsolicited possible solutions and areas to focus efforts on safety issues were provided in the narratives. One proposed method to address some of the medication issues was to have medication procedures in AE mirror new initiatives that have been introduced in hospitals over the last few years. These included medication zones and no interruptions during medication preparation and administration. Another respondent suggested that the services standardize AE preparation procedures and forms across active, Guard, and Reserve units and across services. Another suggestion was to improve communication of patient and supply needs from ground personnel to AE flight crews. Another idea was to model the AE electronic medical record after civilian flight documentation systems. This would include more checkboxes and less free texting fields.

Ensuring clinical competency of nursing personnel was also cited as an important measure to safeguard patients while in the AE continuum. Training of all personnel who carry litters was suggested. Measures to ensure this is accomplished at both CONUS and deployed locations are important. Addressing strength and height requirements for personnel was also suggested, with a focus on waivers. Safety programs in the CASF need to be standardized and aligned with those of AE units. One respondent suggested that the AF evaluate crew staffing to ensure right numbers and mix of personnel on flights. Also cited was the need to address handoff issues and improve this process. Finally, it was suggested that the AF develop a training program for units and forward operating bases that prepare patients for transport.

TABLE III. Exemplars for Culture of Safety

AE environment has robust culture of safety
"Safety recommendations/issues are communicated well across continuum"
"I have not been in a squadron, home station or deployed, where pt safety was not a priority"
Time pressures can create unsafe situations
"Trying to have on-time take-offs . . . the crew feels the need to rush"
CASF versus AE training
"There was only one day overlap between redeploying CASF and newly deployed CASF"
"AE culture is defined by highly trained individuals that are flexible and 'able to think on their feet'"

DISCUSSION

Very positive responses regarding perceptions of crew and patient safety were received in this survey. All questions regarding issues of crew and patient safety had at least a 90% agreement rate. Thirty-seven percent of all respondents reported that mission accomplishment took precedence over patient safety. Fifty-two percent disagreed or strongly disagreed. Even with these results, 80 individuals cited experiences involving a mishap, close call, or near miss. Problems related to moving patients long distances to different facilities, such as not enough medications, supplies, or battery life; failure of equipment; and incomplete paperwork, are unique to the AE system. They are linked to care being delivered in the austere environment of a plane. This environment is isolated and without support from respiratory, pharmacy, logistics, and other departments available in hospital settings. Some equipment issues have been addressed through the development of the Patient Movement Item Program, in which equipment is tested in flight and designated for AE, and there are policies and procedures governing the equipment approved for flight. Knowledge of the Patient Movement Item Program, as well as restrictions on

equipment allowed on flights, is important information to widely disseminate.

All potential needs of the patient must be considered and planned for before the flight. Anticipating the patient's needs is sometimes difficult, especially for an inexperienced clinician. Ground personnel also often do not have flight experience, which complicates the task of planning for care in the air. Ensuring clinical competency is also a very complex issue as it involves nurses and technicians across active, Reserve, and Guard units and flyers and nonflyers. The age and experience of CASF personnel were measured to be less than AE personnel. This may impact safety and safety perceptions. CASF personnel can come from a variety of backgrounds and specialties, do not have a specific Air Force Specialty Code, and do not require the training similar in intensity and scope of that required of the AE crew. These differences as well as the required training for AE personnel may have contributed to the different attitudes regarding crew safety that were seen when comparing those on flying status with those who were not. This interesting finding needs further exploration in future research.

Communication was identified as being at the heart of many safety issues and was offered as the solution to some of the problems. For example, communication of supply and oxygen needs must occur across the AE continuum. Efforts to improve communication during handoffs, such as the Situation, Background, Assessment, and Recommendation (SBAR) report sheet instituted in Bagram Air Base's CASF in 2011, should be evaluated for system-wide implementation. The DuFour simulation study of using a SBAR checklist is another step in this process improvement.

A limitation of this research is that more active duty than Reserve and Guard members participated. The personnel composition of CASFs and ASFs fluctuates, whereas Reserve members may be responsible for up to 80% of the AE missions from theater to Germany and CONUS. The response rate is also unknown. Another limitation is that the study asked for perceptions of participants, which could be influenced by many factors occurring at the time of the study, and may not be reflective of the system's safety culture. The free text fields allowed narrative responses, but unlike in a focus group or interview, further explanation or clarification could not be obtained from the respondent.

CONCLUSION

These data suggest the care of ill and injured patients during transport is influenced by the safety culture, human factors, training, experience, and communication. Current success in the transport of patients in the AE system is phenomenal. Very few deaths have occurred, which is laudable given the acuity of some of the critically ill patients who have been transported very long distances. However, safety issues occur often. Not all respondents agreed that there is a strong safety culture, and the reasons for this need to be identified. We must address the safety concerns and correct system issues so that our success continues.

Results highlight the need for further investigation of the safety culture and initiatives in this unique environment. The differences found in responses from those in the AE system versus the CASF and ASF need to be studied in light of group differences. Exploration of personal narratives opened new areas of future investigation regarding patient safety and quality of care throughout the AE continuum. Results from the Focus Group study will provide further insight to guide improvements in safety culture and patient safety practices.

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Effective Teamwork and Communication Mitigate Task Saturation in Simulated Critical Care Air Transport Team Missions

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ABSTRACT Background: Critical Care Air Transport Teams (CCATTs) are a critical component of the United States Air Force evacuation paradigm. This study was conducted to assess the incidence of task saturation in simulated CCATT missions and to determine if there are predictable performance domains. Methods: Sixteen CCATTs were studied over a 6-month period. Performance was scored using a tool assessing eight domains of performance. Teams were also assessed during critical events to determine the presence or absence of task saturation and its impact on patient care. Results: Sixteen simulated missions were reviewed and 45 crisis events identified. Task saturation was present in 22/45 (49%) of crisis events. Scoring demonstrated that task saturation was associated with poor performance in teamwork (odds ratio [OR] = 1.96), communication (OR = 2.08), and mutual performance monitoring (OR = 1.9), but not maintenance of guidelines, task management, procedural skill, and equipment management. We analyzed the effect of task saturation on adverse patient outcomes during crisis events. Adverse outcomes occurred more often when teams were task saturated as compared to non-task-saturated teams (91% vs. 23%; RR 4.1, $p < 0.0001$). Conclusions: Task saturation is observed in simulated CCATT missions. Nontechnical skills correlate with task saturation. Task saturation is associated with worsening physiologic derangements in simulated patients.

BACKGROUND

Current combat casualty care involves the management of patients with complex wounding patterns in critically ill patients across a broad continuum of care. An important part of the current paradigm is tactical and strategic aeromedical evacuation of critically ill patients. Critical Care Air Transport Teams (CCATTs) play an essential role in the delivery of en route care and are specially trained by the United States Air Force (USAF) to care for patients in a variety of platforms.[1] Teams are composed of three medical personnel (a physician, a nurse, and a respiratory therapist) who are trained in critical care treatment and delivery in an austere environment. Each team is responsible for caring for as many as six critically ill patients as well as operating and transporting their equipment, including portable ventilators, invasive monitoring, and infusion pumps.

The combination of high patient acuity, stress of flight, and need for expertise with a wide assortment of medical equipment raised the concerns that these teams may be at risk for task saturation during the delivery of en route care. This, in turn, may lead to degradation in team performance and patient care. Task saturation occurs when required duties exceed the capability to execute them within a given period of time. Task saturation has been previously studied in the field of aviation and is viewed as a contributing factor to pilot error and loss of aircraft.[2] Despite the similarities between elements of aviation and critical care medicine, the prevalence and impact of task saturation in the care of patients with complex conditions have been poorly studied. We feel that the potential occurrence of task saturation during CCATT missions is of critical importance as it may lead to degradation in the quality of patient care.

In this study, we determined the incidence of task saturation among USAF medical personnel during simulated CCATT missions and identified associated performance characteristics as well as the impact of task saturation on patient care.

METHODS

Current CCATT training includes a 2-week CCATT basic course at the USAF School of Aerospace Medicine followed by an advanced course at the Center for Sustainment of Trauma and Readiness Skills at the University of Cincinnati Medical Center in Cincinnati, Ohio. The advanced course consists of a series of didactic lectures focused on the care of the injured and critically ill patient; live patient care on the trauma surgery service, in the surgical and neurosurgical intensive care units, and in the emergency department at the University of Cincinnati Medical Center in Cincinnati; tabletop discussions; and several simulated CCATT missions. The simulated missions take place in a dedicated facility that replicates many aspects of flight conditions inside a USAF KC-135 airframe during low light conditions, including decking, stanchions, lighting, aircraft noise, and the CCATT equipment allowance standard. Scenarios for simulated missions are developed using patient movement data recorded during previous CCATT patient movement missions.

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Institutional Review Board approval for the study was granted by the University of Cincinnati as well as the USAF and consent was obtained from 48 CCATT trainees. Sixteen CCATTs were videotaped during performance of identical simulated missions over the course of 6 months. The designated mission involves the care of two critically wounded warfighters: one patient with severe burns and an inhalation injury and one patient with bilateral lower extremity traumatic amputations. This scenario was delivered on the Medical Education Technologies, Human Patient Simulator (CAE Healthcare, Sarasota, Florida) in the KC-135 simulator at the University of Cincinnati Medical Center in Cincinnati, Ohio. Video, audio, and simulated patient data, including vital signs, were recorded from multiple camera and audio sources. A member of the CSTARS cadre was positioned inside the simulator and functioned as Aeromedical Evacuation Medical Crew Director.

The simulation scenario contained predefined "crisis events," defined as an adverse change in a patient's condition, such as worsening hypotension, hypoxia, self-extubation, or cardiac arrest. These events were time stamped during the recording for later evaluation.

Experts in critical care and medical education reviewed the videotaped missions and evaluated team performance during each crisis event utilizing a rating tool adapted from studies attempting to identify barriers to effective teamwork during cardiac arrests[3,4] as well as a previous study evaluating team performance during an anesthesia crisis.[5] The principal categories of evaluation include teamwork, communication, mutual performance monitoring, maintenance of standards and guidelines, task management, procedural skill, and equipment management. Four performance characteristics were evaluated in each domain to achieve the final score. In addition, each evaluator noted the presence or absence of task saturation during each crisis event as well as the outcome of the intervention (adverse outcome vs. no adverse outcome). A numeric scale was used to assign teams a score from 1 to 10 in each of the performance domains.

Logistic regression analysis was used to determine the association between performance domains and task saturation for these two groups, and a Fisher exact test was used to determine the association between task saturation and adverse clinical outcomes.

RESULTS

We analyzed 16 simulated missions with a total of 45 crisis events. The training scenario was designed to have 2 predetermined crisis events in each mission for a total of 32 crisis events during the study. In 4 of the 16 missions, the team's care during a planned crisis event led to occurrence of additional crisis events.

Evidence of task saturation was present in 22/45 (49%) of crisis events (Fig. 1). There was asymmetry in team susceptibility to task saturation (Fig. 2). Twelve teams demonstrated evidence of at least one episode of task saturation. Four teams showed no evidence of task saturation. Of teams with task saturation during crisis events, three had a single task saturation crisis event, whereas the remaining had more than one (Fig. 2).

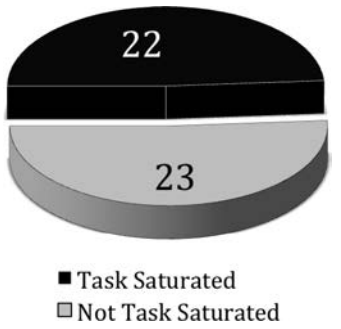

FIGURE 1. Incidence of task saturation among 16 CCATTs during a simulated mission. Approximately half of the 45 crisis events showed evidence of task saturation.

FIGURE 2. Distribution of task-saturated events across 16 CCATTs. Four teams showed no evidence of task saturation at any time during the simulation.

We examined team performance in detail in the areas of teamwork, communication, mutual performance monitoring, maintenance of standards and guidelines, task management, procedural skill, and equipment management. Given the complex patient care environment, we hypothesized that the occurrence of task saturation would be associated with task and equipment management. When we performed data analysis of the scores in each domain, we found that the occurrence of task saturation was associated with poor performance in the domains of teamwork, communication, and mutual performance monitoring, but not maintenance of standards and guidelines, task management, procedural skill, and equipment expertise (Fig. 3).

Additional analysis indicated that performance in each domain was differentially associated with task saturation. Odds ratios (ORs) favoring task saturation were greatest for communication (OR = 2.08), followed by teamwork (OR = 1.96) and mutual performance monitoring (OR = 1.9; Fig. 4).

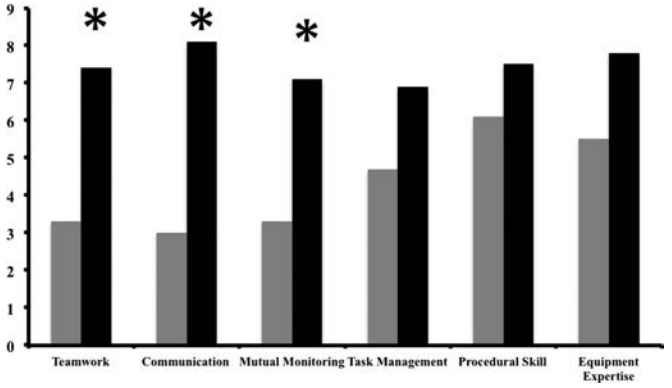

FIGURE 3. Results of team performance in six domains of performance. Vertical bars represent global rating (grey = task saturated, black = not task saturated). *Teamwork, communication, and mutual performance monitoring were statistically different between groups that were task saturated vs. those that were not task saturated. No significant differences were found in the domains of task management, procedural skill, and equipment expertise. *$p < 0.05$.

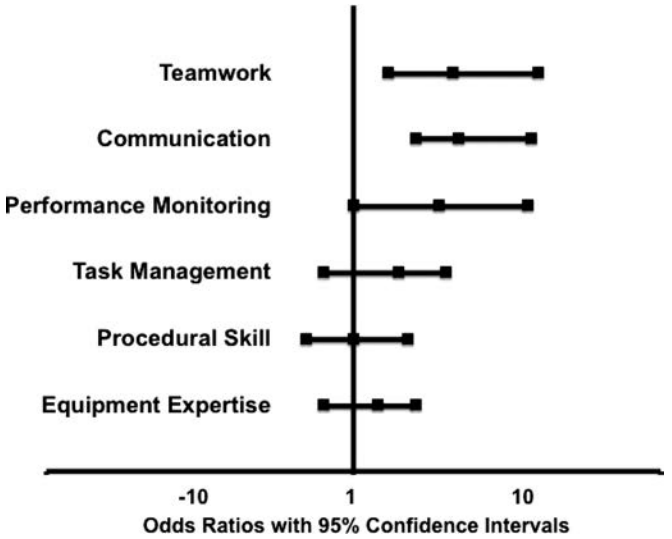

FIGURE 4. ORs displayed as a Forest Plot. Vertical line represents an OR of 1.0 demonstrating no association between the domain of performance and the presence of task saturation. Teamwork and communication strongly correlate with task saturation and performance monitoring remained significant. Task management, procedural skill, and equipment expertise all failed to show significance.

We analyzed the potential effect of task saturation on patient outcomes during each crisis event. Adverse outcomes, as defined by worsening physiology, were more common when teams were task saturated as compared to non-task-saturated teams (91% vs. 23%; relative risk 4.1; 95% confidence interval 1.84–8.77, $p < 0.0001$, Fig. 5). A logistic regression analysis was used to determine the impact of a 1-point increase in each of the scores across the domains of performance. When these subcategories were analyzed, those that had the greatest impact on the likelihood of improving

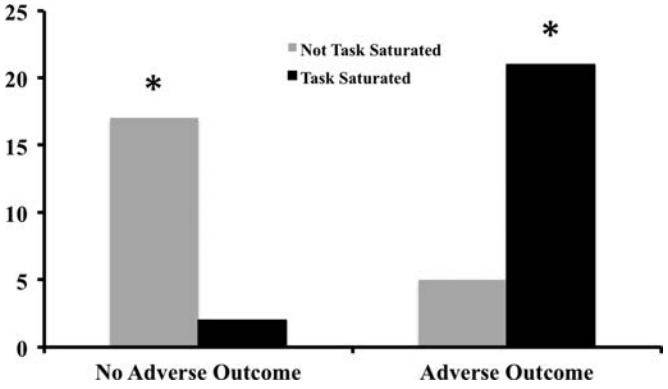

FIGURE 5. Adverse outcomes were significantly associated with task saturation when compared to non-task-saturated events. $p < 0.0001$.

team performance were knowledge sharing (OR = 2.66, $p = 0.06$) and reevaluation (OR = 2.39, $p = 0.05$).

DISCUSSION

In this study, we examined the occurrence of task saturation during simulated CCATT patient care missions. Our data indicate that task saturation is a common occurrence in this setting; is related to poor teamwork, communication, and mutual performance monitoring; and leads to adverse simulated patient care outcomes.

Care of critically ill and wounded casualties in combat zones has evolved dramatically in the past 30 years. Along with increasing use of damage control procedures in far forward settings, increased emphasis has been placed on stabilization and rapid evacuation of casualties.[6] Military medical experience, especially surrounding the Battle of Mogadishu, where nearly 50% of casualties required evacuation,[7] led to the development and establishment of CCATTs.

In current practice, CCATTs are a rapidly deployable resource and a primary component of the USAF's aeromedical evacuation system. The goal of a CCATT is to turn almost any airframe into a flying intensive care unit within minutes. The team consists of three highly specialized members (physician, critical care nurse, and respiratory therapist) trained to handle the complex, critical nature of patients in hemodynamic flux who require continual stabilization, advanced care, and may even require life-saving invasive interventions during transport. The availability of CCATT patient transport has changed the approach to combat casualty care, allowing ongoing delivery of care en route to the next facility and enabling the rapid transport of patients out of theater to increasing levels of specialized care. During the 6-year period between 2001 and 2006, a reported 3,400 CCATT missions were performed in support of Operations Iraqi Freedom and Enduring Freedom.[8] In the 12-month period between 2005 and 2006, 134 patients were transported between Balad Air Base, Iraq, and Landstuhl Regional Medical Center, Germany.[9] The mean injury severity score of the trauma patients transported during this study period was 20, and

57% were mechanically ventilated.[9] This indicates a high degree of complex critical care and the potential need for life-saving interventions en route and has been reported by others.[10,11]

Task saturation, also known as task overload, occurs when the number or complexity of task requirements exceeds the ability to execute them at a high level. Although task saturation may occur during any complex work set, it is especially important in the medical setting, as it may lead to degradation of the effectiveness of patient care delivery. Task saturation occurrence has been suggested in such disparate work sets as triage of trauma patients,[3] cardiac arrest resuscitation,[3] evaluation of surgical floor patients,[12] and operating room crises.[5]

Task saturation may increase with increasing complexity of the care environment. The CCATT patient care environment is challenging at baseline and becomes dramatically more complex during crisis events in flight. Although the incidence of critical events during CCATT missions is unknown, some inferences may be made from existing data. Lehman et al examined the occurrence of adverse events during rotary wing transport in a combat environment over a 7-month period. They found that more than 50% of patients required mechanical ventilation and 20% required vasoactive medications during flight. The rate of crisis events was high, with in-flight clinical deterioration occurring in 30% of patients and equipment failure in 17% of flights.[13] Another recent study examined critical events during civilian air transport, revealing that critical events occur at least once for every 12.6 hours of transport time.[14] Taken together, these data suggest that critical events likely occur with regular frequency during CCATT missions, increasing the challenges of caring for patients in this environment and potentially leading to task saturation. Our data confirm that the resuscitation and clinical management of critically ill patients require not only sound medical judgment but also competency in nontechnical skills such as leadership, problem solving, communication skills, and resource management.[15] As emergencies with acutely ill patients can arise in any CCATT mission, effective crisis management is crucial. These nontechnical skills have been described as "crisis resource management."[16] The concept is similar to crew resource management and has been studied using validated tools in the medical community. Our work reinforces that the domains of performance associated with crisis resource management are essential to mitigate task saturation in simulated CCATT missions and may have important implications for current CCATT advanced training.

The CCATT advanced course is currently focused on the care of critically ill and injured patients as well as expertise in the CCATT allowance standard. Studies of team performance in operating rooms as well as our current study demonstrate that professional experience alone does not automatically lead to the acquisition of nontechnical skills.[17] According to our study, suboptimal teamwork, communication, and mutual performance monitoring placed a team at risk for task saturation. This is consistent with past research showing that poor communication, failure to establish leadership, strained interpersonal relations, and lack of preparation increase the risk to patients undergoing an operation.[2,17] Communication failure has been demonstrated in 30% of team exchanges in the operating room. It was shown to be the primary root cause of patient harm in 70% of sentinel events.[18] Teamwork and performance monitoring have been demonstrated to influence outcomes in other medical settings,[19,20] and their influence in our current study confirms the importance of CCATT training before deployment.

There are three recognized coping mechanisms that people employ when faced with task saturation.[21] The first is "shutting down," where someone either quits the task or takes frequent breaks. This is the most harmless of the coping mechanisms, mainly because it is evident that the person is no longer executing his/her mission; the mental collapse is not being masked. Another coping mechanism is "compartmentalization," where the person acts busy but accomplishes little. People employing this mechanism may make lists, shuffle things around, and create the illusion of doing work, thus masking that they are task saturated. This coping mechanism is also characterized by linear thinking, where tasks are completed one at a time without regard to priority. Task saturation is hard to identify in these people because they look busy. The final coping mechanism is "channelizing," also known as "target fixation." It is estimated that 80% of task-saturated people cope by channelizing. This is when a person becomes intensely focused on one thing at the expense of everything else. Other tasks are neglected and ignored and new tasks accumulate. We saw evidence of these coping mechanisms during the simulated missions. Compartmentalization manifested itself as teams moving equipment around or walking around the simulator without making any forward progress. We also witnessed linear thinking, with low-priority tasks being completed before high-priority ones. Channelizing occurred as well, with teams at times congregating around one patient to intubate him while the other patient suffered from worsening hypotension.

The harmful effects of task saturation have wide implications within the field of medicine. Our data suggest that degradation in teamwork and communication during crisis events may lead to task saturation, with associated negative impact on patient care. We suspect that these findings extend beyond the CCATT environment and that our findings are applicable to many high-complexity care environments. Future efforts to mitigate task saturation should focus on improving teamwork and communication during crisis events.

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A Review of the Evolution of Intraosseous Access in Tactical Settings and a Feasibility Study of a Human Cadaver Model for a Humeral Head Approach

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ABSTRACT In the tactical setting, intraosseous (IO) access has become popular to treat hemorrhagic shock when peripheral intravenous access is difficult or impractical. The traditional sites most commonly used by combat medics, corpsmen, and Pararescuemen (PJs) include the sternum and tibial tuberosity. Recent studies have shown that the humeral head (HH) is an appropriate and effective access site for IO infusion and fluid resuscitation in the clinical setting. In this procedural feasibility study, we assessed the ability of 26 U.S. Air Force PJs to perform HH IO placement on fresh, unfixed human cadavers over two consecutive cadaver lab training sessions. Following a formal didactic session, which highlighted proper patient positioning and technique, the PJs were instructed to attempt to place an IO needle using both a drill and manual driver. Once performed, correct placement was reviewed by a physician and confirmed by aspiration of bone marrow. Rates of success were calculated on first and second pass. First pass success rates were 96% and 90.5% for the drill and driver, respectively. Both devices achieved 100% success by the second pass. Military field personnel would benefit from a HH approach, especially in the care and management of patients of explosive injuries.

INTRODUCTION

Tactical Combat Casualty Care in Operation Iraqi Freedom/Operation Enduring Freedom has led to the popularization of intraosseous (IO) access to treat hemorrhagic shock when peripheral intravenous (IV) access is impractical or impossible. This has been an important advancement since medics, corpsmen, and U.S. Air Force (USAF) Pararescuemen (PJs) are not trained to insert a central venous catheter, the placement of which is indicated in the civilian environment when there is a need for IV therapy and the peripheral system is inaccessible. Without the practice of IO placement, there would be many instances in the field where patients may be in shock and fluid resuscitation could not be implemented because vascular access could not be obtained.

Consensus exists among experienced military and civilian trauma surgeons and medics that there is a need to devise an algorithm for fluid resuscitation in combat casualty scenarios. As part of this algorithm, IO infusion is considered an acceptable substitute to peripheral IV infusion and venous cutdowns when IV access is unattainable.[1] Similar consensus regarding fluid resuscitation and the use of adult IO access was reached following a Delphi study by members of the UK Defence Medical Services.[2]

Injury patterns to the extremities, combined with environmental and tactical conditions, as well as technical difficulties, constitute the major barriers to peripheral IV access in the tactical setting.[3] Logistical constraints, hypotension, and mass casualty incidents may also lead to delays in obtaining vascular access in the field.[4] Cases have been described in the tactical setting where multiple IO sites were utilized for fluid resuscitation and stabilization when heavy initial blood loss, the anatomic location of the injuries, and gross wound contamination prevented peripheral IV access from being established.[5]

The use of IO devices provides a fast, easy, and reliable mode of venous access in a variety of settings. Cooper et al reports a 97% success rate of IO access within the emergency department and tactical environments. Their study also demonstrates the versatility of IO access, citing that crystalloids, packed red blood cells, fresh frozen plasma, analgesics, ACLS drugs, antibiotics, and drugs for both rapid sequence intubation and maintenance of anesthesia were all delivered successfully through IO lines. Because they can be securely placed and held, the use of IO needles may prove more reliable and result in fewer complications than peripheral venous cannulae in the tactical setting.[3]

IO infusion via the sternum or tibia is a feasible means of achieving rapid vascular access and drug delivery with similar outcomes and hemodynamic effects as IV access.[6] A review of 98 cases at autopsy revealed that the sternum and proximal tibia are the preferred sites for IO access, and that sternal IO placement can be performed at an 80% success rate.[7] Sternal IO devices using spring-loaded needles were the initial device of choice for many years, and combat medics became very comfortable using them. The ceramic plate in body armor may prevent injury to the underlying soft tissues and bone, making the sternum an optimal IO insertion site in tactical settings.[3]

Tibial IO placement became popularized in American prehospital civilian care, especially within the pediatric population. Eventually, tibial IO devices and insertion techniques

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were adapted and adopted into military practice. Studies have shown that military medical personnel can be taught and are highly successful (95%) in the placement of tibial IO infusion needles.[8] The first choice site of IO access by the Spanish military medical staff in Afghanistan was the anterior tibial tuberosity, and attempts were highly successful; in the prehospital setting, 76% of IO lines were successfully inserted, whereas 100% of IO placement attempts at the military hospital were successful.[9]

As the Pararescue Tactical Evacuation experience in Operation Enduring Freedom grew over the decade, the preferential use of the humeral head (HH) as an IO insertion site became apparent. This can be described in part by the complications and contraindications associated with sternal and tibial IO insertion in the tactical setting. For sternal IO placement, contraindications include suspected sternal fracture, previous sternotomy, and cardiac arrest with the need for chest compressions. Contraindications of tibial IO placement include suspected fracture at or above the insertion site, trauma to the extremities, and lower limb loss or amputation.[10] The most significant barriers to sternal IO access in the tactical setting involve the inability to perform adequate and high quality chest compressions during cardiopulmonary resuscitation (CPR) and the lack of access to the sternum by the presence of body armor. Potential risks associated with tibial IO access include minor fluid extravasation and severe compartment syndrome of the lower extremities.[11] Complications may also arise if IO needles are not properly removed or if they break during removal.[12]

The nature of the injuries experienced in modern warfare may influence the availability and feasibility of IO access sites. In a prospective observational study assessing prehospital lifesaving interventions in a combat zone in Afghanistan, it was discovered that explosion was the mechanism of injury in 60% (n = 601) of patients.[13] Other sources indicate that explosions caused by improvised explosive devices (IEDs) account for approximately 70% of all battlefield injuries.[14] Blast injuries from IEDs are most commonly associated with trauma to the chest and/or lower extremities or result in lower limb loss, making sternal and tibial IO access impossible.[15] In these situations, the HH may be the preferred, and perhaps only, site for IO access.

One of the most compelling reasons why the HH approach to IO access became so popular may simply be due to a technical issue resulting from environmental conditions. When a patient is in the back of a Pavehawk helicopter, his or her head is against the door, obviating proper provider positioning to place a sternal IO. Also, USAF PJs have recently become more aggressive about placing bilateral IO lines simultaneously, a practice that is also routine in the British Medical Emergency Response Team helicopters when IV access is unattainable.[16]

PJs do not get opportunities to train and develop this technique at home in a clinical setting. Therefore, PJs, as well as most other medics, have to rely on bone models and didactic presentations to learn how to perform proper HH IO placement. For many, the first attempt at performing the procedure is on a live patient in hemorrhagic shock from gunshot wounds or amputations from a blast injury, most likely in the field or helicopter under adverse conditions (dark, noisy, vibrating, banking, under enemy fire, etc.). Needless to say, there are no opportunities for failure, and often not many opportunities for do-overs.

As a result, we have been looking to improve training opportunities. Advanced, high fidelity simulators have been developed and used to teach IO infusion techniques in the early treatment stages of a mass casualty chemical warfare scenario. Vardi et al[17] reported a 73.4% simulated survival rate in the IO group compared to a 3.3% survival rate for the controls. Additional review of the study results shows that of the 72 IO attempts, 64 (88.9%) were successful and all health care providers were able to achieve successful IO placement within three attempts.[18]

A secondary study focused on the training of anesthesiologists to treat chemical warfare casualties utilized intubation simulators of patients of various ages from newborn to adult, advanced full-scale simulators, and standardized patients. Results showed that 22 of the 25 participants (88%) agreed that the simulation scenarios were realistic and all 25 participants found the simulation-based education model better than traditional training methods.[19]

In a study to determine which IO devices were relatively easy to learn and use in the Special Operations environment, medical care providers attended a lecture explaining appropriate IO use, viewed videotapes on the injection models, and practiced with demonstration units in a classroom environment. Afterward, the study participants were randomly assigned one of the IO devices and asked to perform a sternal or tibial IO placement on a cadaver. Results showed at least a 94% success rate across all devices and favorable insertion times in comparison to peripheral IV catheter placement.[20]

Cadaver laboratories have afforded the opportunity to practice advanced procedures such as crico-thyrotomies and chest tubes. We have expanded this to other procedures, and in doing so, have learned that attempting IO insertion on thawed fresh frozen cadavers allows one to aspirate marrow to confirm correct placement. Although cadaver testing has been used to validate the design criteria of adult IO devices for both prehospital and battlefield environments,[21] no reports have been made of the use of cadavers in the education and training of IO infusion techniques for military personnel. Cadaver laboratories afford PJs a controlled environment with direct medical oversight and allow them to practice the procedure many times, developing muscle memory and confidence. The ability to develop automaticity by repetition of life-saving procedures is critical for combat medical providers who may be performing these interventions for the first time, in hostile environments, and under enemy fire. The use of cadavers is all the more profound because of the inability to obtain clinical training, due to both an absence of opportunity,

as well as onerous regulations that do not allow PJs to work on patients in the United States.

In this cadaver feasibility study, we describe our training experiences with and assess the ability of Air Force PJs to learn and perform HH IO access on fresh human cadavers and validate our methods as a training tool for this technique.

MATERIALS AND METHODS

Study Design

This was a procedural feasibility study of HH IO access using a human cadaver model.

Setting

Data was collected over two consecutive cadaver lab training sessions for USAF PJs from the North Shore-LIJ Bioskills Center (Lake Success, New York).

Tissue

The cadavers were fresh, unfixed human adults with normal upper extremity anatomy. There were four cadavers available per session.

Experimental Protocol and Procedure

There were 26 PJs over the course of the two sessions. Only four individuals had previous experience placing HH IO devices. The procedure for the HH approach was as follows: The PJs were first instructed by one of the authors (SR) on proper patient positioning. PJs were instructed to adduct and internally rotate the cadaver's arm by putting the hand on the umbilicus. Then, using the pads of the second through fourth fingers, PJs identified the spherical HH which is located inferior to the acromion and lateral to the coracoid process. The needle loaded in the drill is then passed through the skin from a direct anterior trajectory until it is in contact with the bone (Fig. 1). The drill is then activated, and as soon as it penetrates the cortex, (an obvious palpable loss of resistance) the trigger is released. The stylet is withdrawn and a syringe is attached. Aspiration of bone marrow confirms successful placement along with proper seating of the needle (Fig. 2).

FIGURE 1. USAF Pararescueman demonstrating the primarily anterior trajectory of IO needle insertion while localizing the spherical humeral head with the left hand.

FIGURE 2. USAF Pararescueman demonstrating the attachment of syringe and performing bone marrow aspiration following successful IO needle placement into the humeral head of a fresh, unfixed human cadaver.

A second iteration was performed with a manual driver and a 40-mm needle. The technique involves placing the needle against the bone and using a twisting motion with pressure in order to pass it through the cortical bone. After a rapid loss of resistance, the stylet is withdrawn and the syringe is attached as it was using the drill device. After instruction, all PJs were able to demonstrate correct patient positioning and knowledge of the anatomy by identifying the HH and showing where they would drill.

The PJs did not practice inserting the IO needle until their first attempt. Once accomplished, the placement was checked by a physician and confirmed by aspiration of bone marrow. Rates of success or failure were calculated based on first or second pass success.

RESULTS

Twenty-six operators performed the HH approach using the IO drill device. Twenty-five achieved success on the first attempt, and the twenty sixth achieved success on the second attempt. The miss was related to an improper initial tangential trajectory of the IO drill, which prevented access to the humeral head.

Twenty-one operators performed the HH approach using the manual driver. Nineteen were successful on the first attempt and two were successful on the second attempt.

The first pass success rates were 96.0% and 90.5% for the drill and the driver, respectively. Both devices achieved 100% success within two attempts.

Limitations

There are several limitations of this study worth noting. Although relatively large to comparable studies that use a human cadaver model, a sample size of 26 operators may limit our ability to generalize results across the entire population of USAF PJs and combat medics. Varying levels of participant experience may affect the reliability of our results as some of the operators had experience inserting IO needles using the HH approach before conducting the study. It is possible that operator skill may have been artificially inflated because of performance immediately following instruction and demonstration of the procedure by an experienced instructor.

Because of limited access to fresh, unfrozen cadavers for military training, the authors would like to acknowledge that a total of 47 procedures (26 drill and 21 manual driver) were performed on four cadavers. With each cadaver having two humeral heads, a total of eight sites were available for IO needle insertion. Bias may have been introduced immediately following the first successful placement, as subsequent operators could potentially use the site of skin puncture as a landmark for their own attempts. We do not believe this was a remarkable source of bias, as the puncture marks were not large enough to be easily visualized, and, more importantly, each PJ was required to demonstrate successful localization and identification of the HH by palpation of tactile landmarks before attempting IO insertion. Additionally, aspiration of bone marrow was necessary to confirm successful placement of each IO needle, and, as a result, the same insertion trajectory could not be duplicated.

Restrictions also limited the study to being performed in a cadaver laboratory, and the environmental constraints produced in the tactical setting could not be completely replicated. Although cadavers could not be transported onto the helicopter, over 3 years of field experience have illustrated that PJs can position themselves on the side of a patient and place the IO in the HH even under the limitations imposed by and experienced in the back of a Pavehawk helicopter. We are confident that the skills and procedures demonstrated in the training environment are easily transferable and can be replicated with the same degree of success in the tactical setting.

DISCUSSION

Although less common in the civilian sector, IO access has tremendous importance and application in the tactical setting and can be successfully trained predeployment. The use of a cadaver as a teaching tool for human anatomy and the ability to get precise, human tissue tactile feedback cannot be understated.

The ability to gain vascular access is the *sine qua non* for shock management after initial hemorrhage control. It is expected that many patients in various states of hemorrhagic shock have collapsed veins. IO access was first adopted during World War II, but has since fallen out of favor with the advent of plastic IV catheters. In civilian settings, venous cutdowns, and central venous line insertions, are used when peripheral IV access is not possible or contraindicated.

In the tactical setting, the sternum and tibial tuberosity have been the most popular sites for IO access. Although the success rate for sternal and tibial IO placement is relatively high, issues specific to the tactical setting may make access to these insertion sites difficult or impossible. The presence of body armor and the difficulty to perform high quality chest compressions during CPR are significant barriers to sternal IO placement. Also, the use of a spring-loaded device is technically cumbersome and can often be difficult. Environmental issues may also be a limiting factor to the success of sternal IO placement, as providers may not be able to position themselves above the patient's head. The loss of lower limbs caused by explosions and IEDs represent the majority of injuries experienced by tactical personnel, and makes tibial IO insertion impossible.

HH IO access has tactical advantages over peripheral IV placement, even when peripheral access is readily accessible. There are many steps to successfully place an IV peripherally, including preparing the tape, acquiring and placing a tourniquet, waiting to visualize and palpate a vein, preparing the insertion site, inserting the catheter, and taping the catheter to secure it in place. In addition, the tactical helicopter environment may have a direct effect on the success rate and ease of placement; the vibration and banking of the helicopter, as well as difficult provider position, may make it difficult to successfully place a peripheral IV.

We believe that the HH is a more efficient IO access site and is the most appropriate within the tactical setting. HH IO placement involves acquiring the drill and needle, prepping the insertion site, palpating the anatomy, drilling, withdrawing the stylet, aspirating marrow and attaching the line. Also, the needle can be held securely in the humeral head. Provider positioning, light, movement, and fine motor skills are less of a concern, and in tactical settings with unstable patients, the HH IO approach is an easier, faster, simpler, and more reliable method for obtaining IV access.

With regard to HH IO insertion, we recommend an anterior approach for two reasons. First, we have previously studied optimal placement of the needle using magnetic resonance imaging and have concluded that the anterior trajectory represents the shortest distance to the humeral head, and there is less soft tissue anteriorly.[22] Second, we believe the line would be more stable if it is placed anteriorly as opposed to laterally, as a lateral placement may lead to an increased risk of inadvertent dislodgement.

As the HH approach is adopted as the standard IO route of administration, it will be necessary to adequately train respective military personnel. We believe that the results of this study have successfully illustrated that a human cadaver model is an appropriate method for the procedural training of PJs and combat medics as demonstrated by the high first pass success rates of HH IO placement. The fresh frozen and thawed cadavers allow the same tactile feedback as a live human. Additionally, the ability for the operator to learn to aspirate

bone marrow to confirm placement is critical. The cadaver model provides a controlled environment for learning the procedure under supervision. It also allows procedural repetition and the introduction of stressors to improve tactical readiness. Most importantly, it allows the medical educator to observe, correct, and sign off on the operator for this procedure.

CONCLUSION

(1) There is a high first pass success rate for both the drill and the manual driver.
(2) There is 100% success by the second pass.
(3) The cadaver lab allows a controlled environment for a medical educator to train an operator and observe competence with repetition.
(4) It is impossible to use any other model in the absence of access to clinical training (where this is an uncommon procedure) to replicate the actual human anatomy and tactile feedback of thawed, unfixed human cadavers.
(5) The ability to document proper placement is not possible in other training models.
(6) The minimal nature of the gear, ease, and speed of use are conducive to tactical field operations.

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Bactericidal Micron-Thin Sol–Gel Films Prevent Pin Tract and Periprosthetic Infection

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ABSTRACT Orthopedic injuries constitute the majority of wounds sustained by U.S. soldiers in recent conflicts. The risk of infection is considerable with fracture fixation devices. In this pilot study, we examined the use of unique bactericidal micron-thin sol–gel films on fracture fixation devices and their ability to prevent and eradicate infections. External fixation was studied with micron-thin sol–gel coated percutaneous pins releasing triclosan and inserted medially into rabbit tibiae. A total of 11 rabbits received percutaneous pins that were either uncoated or sol–gel/triclosan coated. Internal fracture fixation was also studied using sol–gel coated intramedullary (IM) nails releasing vancomycin in the intramedullary tibiae. Six sheep received IM nails that were coated with a sol–gel film that either contained vancomycin or did not contain vancomycin. All animals were challenged with *Staphylococcus aureus* around the implant. Animals were euthanized at 1 month postoperative. Rabbits receiving triclosan/sol–gel coated percutaneous pins did not show signs of infection. Uncoated percutaneous pins had a significantly higher infection rate. In the sheep study, there were no radiographic signs of osteomyelitis with vancomycin/sol–gel coated IM nails, in contrast to the observations in the control cohort. Hence, the nanostructured sol–gel controlled release technology offers the promise of a reliable and continuous delivery system of bactericidals from orthopedic devices to prevent and treat infection.

INTRODUCTION

During combat operations in Iraq and Afghanistan in support of Operation Iraqi Freedom and Operation Enduring Freedom, extremity injuries have accounted for the majority of wounds (65%).[1] One of the lessons learned during these wars was that infections associated with combat-related injuries can have a significant impact on morbidity and mortality. Among the extremity injuries in U.S. casualties, orthopedic injuries constituted the majority of wounds.[2,3] Typically, these included a large percentage of fractures, the majority of which were open, complex injuries prone to infection and other complications. Approximately 5% to 15% of these injuries developed osteomyelitis.[4]

Depending on the nature, condition and location of the fracture, surgeons may choose internal or external fixation devices to provide stability during the healing process. These orthopedic implants are most commonly made from stainless steel or titanium and its alloys. A vexing issue is that in the presence of bacteria, a biofilm is prone to form on these metallic implant surfaces. Once such a biofilm forms, treatment with systemic antimicrobials rarely eradicates infection because bacteria are protected within this extracellular matrix. As a result, the adherent bacteria can then cause a chronic infection that has been reported to persist for months, years, or even a lifetime.[5] Biofilm infections are very difficult to treat. Once formed, high doses of very potent antibiotics are needed, which exacerbates the risk of fostering bacterial resistance. The use of these systemically administered antibiotics also creates the risk of irreversible damage to organs. Furthermore, the failure of systemic antibiotic treatment to eradicate biofilm-associated infection typically necessitates additional surgeries.

Fracture fixation devices, which include both internal and external devices, incur a postoperative infection rate of 5% overall.[6] In the specific case where external fixation of bone fragments is the treatment of choice for achieving bone stability, the incidence of deep infection is high, namely 16.2% overall, with 4.2% of the cases developing chronic osteomyelitis. A rate of infection, up to 32.2%, has been reported for the external fixation of femoral fractures.[7]

As the care of combat casualties continues to improve, thereby achieving enhanced survival after initial injury, infectious complications will remain a major cause of short- and long-term morbidity. A major hurdle to overcome in the treatment of orthopedic-related infections is that bacterial adhesion and biofilm formation on the orthopedic implant may result in decreased antibiotic sensitivity. One emerging method attracting attention is the coating or impregnating antimicrobial agents onto the surface of these implants to inhibit biofilm formation.

Our laboratory has developed room-temperature-processed, biocompatible, nanostructured silica sol–gels that can release bactericidals in a controlled fashion for weeks and months.[8–10] These include a wide variety of molecules ranging in size from

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500 to 70,000 Daltons.[8–10] The release properties can be varied extensively by modifying the nanostructure of the sol–gels as a result of understanding the property relationships as they relate to the sol–gel processing variables.[8–10]

In the studies reported here, micron-thin sol–gel films were applied onto 2 types of orthopedic implants: percutaneous pin of external fixators and intramedullary (IM) nails. A broad-spectrum antimicrobial agent, triclosan (2,4,4'-trichloro-2'-hydroxydiphenylether), was incorporated into the sol–gel film on percutaneous stainless steel pins. The broad-spectrum antibiotic drug, vancomycin, was incorporated into the sol–gel films on IM nails made of titanium alloy (Ti6Al4V).

The current studies were formulated to verify the hypothesis that, using a rabbit tibia model, the infection arising from bacterial ingress along the percutaneous pin surfaces can be prevented by the triclosan/sol–gel films and, using a sheep osteomyelitis tibia model, osteomyelitis can be treated and biofilm formation on the surface of IM nails can be prevented by vancomycin/sol–gel films.

MATERIALS AND METHODS

Synthesis of Sol–Gel Coatings

Sol–gel coatings containing 20 wt% triclosan were used for the study with percutaneous pins. Triclosan solutions in ethanol were used for incorporation of triclosan during the sol synthesis. TEOS (tetraethoxysilane, Sigma-Aldrich, St. Louis, Missouri), ethanol, deionized water, and 1N HCl were mixed to form an acid-catalyzed silica sol. The H_2O/TEOS molar ratio and the ethanol/TEOS volume ratio were equal to 5 and 1.8, respectively. The coatings were applied on percutaneous pins (AISI 316L stainless steel, diameter of 2 mm and length of 14 mm) by dipping at a withdrawal speed of 100 mm/min. The number of applied sol–gel layers was 8 to arrive at films with a total thickness of about 2 μm.

Sols with nominal vancomycin concentrations of 5 wt% or 20 wt% were used for the sol–gel coatings on IM nails (Ti6Al4V titanium alloy, length of 140 mm and diameter of 6 mm). The sol–gel coatings comprised 15 layers (5 layers of 5% vancomycin and 10 layers of 20% vancomycin).

All applied sol–gel compositions resulted in the formation of uniform films.

Surgeries and Outcome Measures

The 2 animal study protocols were approved by the Institutional Animal Care and Use Committee of the University of Pennsylvania.

Rabbit Tibia Percutaneous Pin Study

Eleven adult male New Zealand White rabbits (Charles River Laboratories) between 4 and 18 months of age and weighing between 3.0 and 4.5 kg at the time of surgery were used for the experiments. The implants, with or without sol–gel coating, were placed from the medial side into the tibia, engaged and then screwed tightly into the lateral side of the cortex; the pins protruded approximately 5 to 6 mm from the skin. An aliquot of 0.1 mL of *S. aureus* solution (1.5×10^7 cfu/mL, ATCC™ 25923) was inoculated around the implant using a sharp injection needle. Six of the 11 rabbits received triclosan containing sol–gel coated pins and the remaining 5 received uncoated percutaneous pins. The rabbits were sacrificed 4 weeks after surgery. A scoring system was used to quantify pin tract infection as follows (grading from least to most severe): 0, no sign of infection; 1, marginal inflammation without drainage; 2, serous-type discharge; 3, purulent discharge; or 4, seropurulent drainage with redness and/or osteolysis.[11]

Sheep Tibia IM Nail Study

Skeletally mature (2.5–3.5 years) Dorset-cross ewes were used for the experiment. Sol–gel coated IM nails, with and without vancomycin, were implanted into the IM tibial canal of sheep via the tibial plateau. Using a percutaneous stab incision to gain access to the proximal tibial diaphysis, 3 mL of bacterial inoculum (10^8 cfu/mL, *S. aureus*) was slowly injected into the medullary space via a drill hole that was sealed afterward. Six sheep were operated on with 3 receiving vancomycin-containing sol–gel coated IM nails and 3 receiving nails coated with a control sol–gel film, this is, a film without the antibiotic. After surgery, radiographs were taken to monitor the status of the indwelling implants and to record any evidence of infection and osteolytic changes. One month after surgery and implantation, the animals were sacrificed and the tibiae were dissected using an autopsy saw. To determine bacterial presence, swabs were taken around the cortex screw, the IM nail head, and in the medullary cavity, and analyzed.

RESULTS

Rabbit Tibia Percutaneous Pin Study

Results showed that the 5 rabbits implanted with percutaneous pins without a triclosan/sol–gel coating had a significantly higher infection rate as determined clinically 4 weeks post implantation. Four of the 5 rabbits showed the signs of infection with 3 demonstrating a serous-type discharge and 1 showing a purulent discharge around the percutaneous pins. By way of contrast, none of the 6 rabbits receiving triclosan/sol–gel coated percutaneous pin showed any signs of infection at 4 weeks (Table I). The difference between

TABLE I. Infection Rates of Rabbits Receiving Different Percutaneous Pins

Percutaneous Pin	Animals for Evaluation	Animals With Clinical Signs of Infection[a]
Stainless Steel	5	4
Triclosan/Sol–Gel	6	0

The difference between animals receiving triclosan/sol–gel coated and uncoated pins was statistically significant ($p < 0.001$, Fisher's test). [a]An animal showing discharge, cellulitis, and/or deep infection at the time of sacrifice was checked as infected.

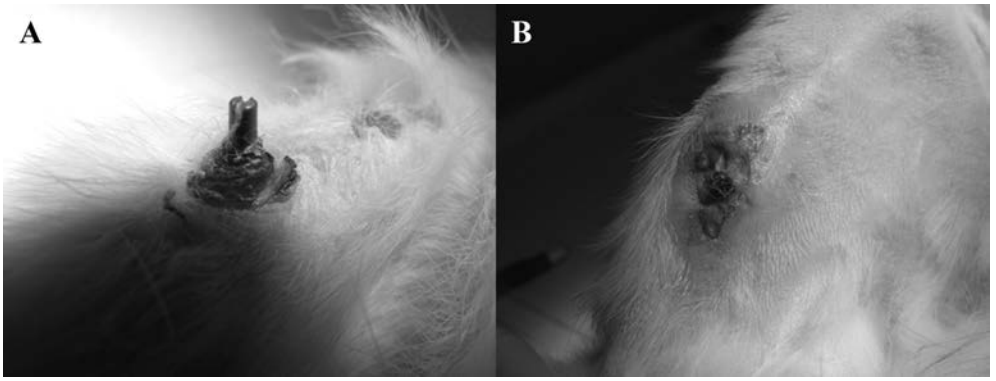

FIGURE 1. Clinical observation of (A) sol–gel coated and (B) control percutaneous pin 4 weeks after implantation. Note the strong signs of infection (purulent discharge) around the control implant, but not around the triclosan/sol–gel coated pin.

rabbits receiving a coated versus uncoated pin was statistically significant ($p < 0.001$, Fisher's test). Clinical photos of the implants taken 4 weeks after implantation are shown in Figure 1. No signs of infection were around the triclosan/sol–gel coated implant (Fig. 1A). However, strong signs of infection (purulent discharge) were visible around the control implant (Fig. 1B).

Sheep Tibia IM Nail Study

No radiographic signs of infection were observed in animals that received vancomycin/sol–gel IM nails (Fig. 2A). All 3 animals that received IM nails coated with sol–gel films without vancomycin showed radiographic signs of osteomyelitis (endosteal lysis). In addition, 1 sheep showed both periosteal reaction and endosteal lysis (Fig. 2B). The periosteal proliferation was this animal's reaction to the infection in its tibia. Generally, a periosteal proliferation is considered a positive marker for osteomyelitis.[12] The radiographic results differ significantly between treatment and control groups ($p < 0.05$, Fisher's test). Bacterial culture was used to detect the presence of bacteria on 2 implant sites (the cortex screw head and the IM nail head) and within the *medullary* cavity 4 weeks after implantation. All animals that received a control IM nail had positive culture results, whereas the animals that received a treatment IM nail had negative culture results. Table II summarizes these postsacrifice results.

FIGURE 2. Radiographic images showing progressive signs of periosteal proliferation (arrow with a solid line) and intramedullary bone matrix response (arrow with a dotted line) in control sheep at 4 weeks post implantation (B); such responses are not seen in the sheep treated with vancomycin/sol–gel coated IM nails (A).

DISCUSSION

The concept of endowing orthopedic devices with antimicrobial properties, such as by coating them with an antibiotic drug containing film, has been widely pursued.[13–15] Various methodologies have been tested. These include tobramycin-laden poly(methylmethacrylate) coatings,[16] hydroxyapatite/chlorhexidine coatings,[13] and silver coatings.[17–19] The antimicrobial properties of silver have been utilized to limit microbial colonization, and silver-coated pins have been tried in clinical applications. However, concerns have been raised related to elevated blood levels of silver in these cases.[17,19] Polymer coatings have also been studied, but such coatings typically exhibit burst release profiles, followed by a relatively slow release phase.[20] Both the use of silver and polymer coatings create concerns. With a slow release subsequent to the

TABLE II. Summary of Postsacrifice Evaluation After 4 Weeks Implantation

IM Nail	Animals for Evaluation	Animals With Positive Culture of Bacteria[a]	Animals With Radiographic Signs of Osteomyelitis
Treatment (Vancomycin/ Sol–Gel Coated)	3	0	0
Control (Sol–Gel Coated)	3	3	3

The results in animals receiving treatment with vancomycin sol–gel coated nails differ significantly in terms of radiographic and bacterial culture outcomes ($p < 0.05$, Fisher's test). [a]Swab cultures with presence of bacteria at either the cortex screw, the IM nail head, or in the medullary cavity.

burst, minimum inhibitory concentrations for inhibiting bacterial growth or biofilm formation may not be achieved.

The controlled release and local delivery of antibiotics from a room-temperature-processed sol–gel film has been studied in our laboratory.[21] Using such films, it was demonstrated that antibiotic-containing sol–gel films can significantly inhibit *S. aureus* viability and growth in vitro and in vivo.[22]

In this *in vivo* study, we performed a pilot study to examine the feasibility of using micron-thin, adherent,[23] antibiotic-containing sol–gel films for conventional trauma hardware (percutaneous pins and IM nails) to prevent bacterial infection. Inoculation with *S. aureus* was chosen because this bacteria is commonly identified as the pathogenic organism in infected bone and joint replacement cases.[24,25]

External fixation (percutaneous pin) is especially prone to infection because the percutaneous passage of the pins creates a gateway for bacterial ingress. In this study, *S. aureus* inoculation around the implant led to distinct outcomes. Without the treatment pins, the bacteria settled and populated tissue pockets and triggered their breakdown. As a result, 4 weeks after implantation, rabbits receiving control percutaneous fixation pin had developed infections with unambiguous clinical signs (Fig. 1A). This outcome was unlike that observed in animals implanted with the percutaneous treatment pins (triclosan/sol–gel coated pins). Here, bacterial adhesion, growth, and migration along the external fixator pins and into the tissues were prevented.

IM nailing is another commonly used orthopedic technique that is associated with a high rate of infection. In the second study of this report, bacteria were injected into the intramedullary cavity after implantation. The bacterial swab culture results of the control animals suggest that bacteria continued to grow with the bacteria being ubiquitous within the tibia medullary cavity and on the surface of the IM nail. Such pervasive bacterial presence leads to osteomyelitis, as revealed by the radiographic results at 4 weeks after implantation of the non-vancomycin-containing IM nails (control nails). On the contrary, the vancomycin/sol–gel coated IM nail inhibited the growth of the bacteria injected into the tibial cavity with no signs of osteomyelitis being observed.

Postoperative bone and joint infections are usually caused by Gram-positive organisms, especially *S. aureus*. Vancomycin is commonly used in the treatment of infections caused by Gram-positive bacteria. Triclosan is an antimicrobial agent, which is active against a wide range of Gram-positive and Gram-negative bacteria. In 1998, triclosan was recommended for the control of methicillin-resistant *S. aureus*.[26] To date, resistance levels among *S. aureus* remain low.[27] However, the extensive use in household and consumer products has resulted in elevated concentrations of triclosan in surface waters,[28] leading to concerns that high environmental concentrations may trigger bacterial resistance. In an external fixation setting, the percutaneous pins containing triclosan are only intended for use up to 3 months. The few in situ studies investigating long-term triclosan exposure did not indicate changes in resistance after 6 to 12 months of exposure.[29] Although no study has reported bacterial resistance to triclosan, reducing the usage of triclosan in household or consumer products is desirable by virtue of maintaining the bactericidal benefit of triclosan in important medical applications. The use of triclosan on percutaneous pins clearly falls into this category as a 30% infection rate with external fixator pins in femoral fractures and the prevention thereof is a significant clinical issue that needs a solution.

CONCLUSION

In this study, micron-thin sol–gel films on orthopedic devices successfully prevented bacterial adhesion, osteomyelitis, and device failure as a result of infection. This sol–gel micron-thin film technology can be used to coat surfaces of orthopedic devices made of various metallic materials (stainless steel and titanium alloy), and for various trauma devices (external fixation systems and IM nails). The sol–gel micron-thin film methodology described here opens up promising perspectives for reducing infections associated with orthopedic devices.

ACKNOWLEDGMENTS

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Pathophysiology of Blast-Induced Ocular Trauma With Apoptosis in the Retina and Optic Nerve

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ABSTRACT Background: Blast-induced ocular trauma is a frequent cause of morbidity for survivors of improvised explosive devices. Blast overpressure (BOP) of 120 ± 7 KPa has been shown to cause damage to lungs, brain, and gut in a rat model; however, the effects of BOP on ocular tissues have not been characterized. To elucidate the pathophysiology of blast-induced ocular trauma, ocular tissues from rats subjected to blast were examined for evidence of apoptosis by the detection of activated caspase 3 and TUNEL assay in their ocular tissues. Methods: A compressed air shock tube was used to deliver 120 ± 7 KPa of BOP for duration of 2 msec to the right side of the rats. Rats were then euthanized at specific time points after blast exposure (3 hours, 24 hours, 48 hours). Ocular tissues were processed for immunohistochemistry to detect activated caspase 3 and TUNEL assay. Tissues were evaluated for relative levels of positive signal as compared to nonblast exposed controls. Results: Activated caspase 3 was detected in the optic nerve, ganglion layer, and inner nuclear layer post blast exposure. At 24 and 48 hours, the inner nuclear layer from the right side had more cells with activated caspase 3. In the optic nerve, the highest levels of activated caspase 3 were detected on the right side at 24 hours post blast. Conclusion: BOP of 120 ± 7 KPa induces optic neuropathy and retinal damage. In both the optic nerve and retina, caspase 3 was activated in the right and left sides following blast exposure. The results of this study reveal that blast exposure induces apoptosis in both the optic nerve and retinal tissues.

INTRODUCTION

Current military conflicts in Iraq and Afghanistan have led to a dramatic increase in the numbers of military personnel experiencing blast-induced trauma, particularly to the brain. Although receiving less attention than traumatic brain injury, a high percentage of blast-injured personnel have been found to also have some degree of damage to the visual system.[1] The precise mechanisms that underlie blast-induced ocular trauma remain unknown; consequently, therapeutic intervention to prevent or repair these injuries is not possible. A sentinel study published in 2011 revealed that 20% of military personnel injured by explosion exhibited signs of ocular trauma, from 2 weeks to 7 years after the event.[1] Although more obvious injuries such as globe rupture and penetrating injuries are quickly diagnosed and treated, the long-term effects of ocular exposure to sublethal blast pressure may not be recognized.

In recent years, explosive devices have become the preferred weapon in the majority of terrorist attacks in war zones. The relative ease of manufacturing and portability of improvised explosive devices make them the weapon of choice for terrorists and insurgents.[2] Murray et al[3] documented that 78% of military personnel wounded in action and treated at medical units in Iraq had been injured by explosive devices. Polytrauma induced by blast exposure includes tympanic membrane rupture, abdominal, lung, and brain injury.[4,5] However, a recent study reported that ocular injuries were often concomitant with cranial injuries occurring during Operation Iraqi Freedom, with over 80% of warriors suffering from mild traumatic brain injury also exhibiting symptoms of visual dysfunction.[6] On the battlefield, the warriors' eyes are the most important sensors, and good vision is essential for optimal performance on the battlefield, in support functions, and in later life as a civilian. Nevertheless, few studies have been conducted on animal models to evaluate the pathology underlying blast-induced ocular trauma. Apoptosis is a cell death program initiated in response to stress, biochemical, or physical damage. We hypothesize that exposure of rats to moderate levels of blast overpressure (BOP) will result in ocular tissue damage, leading to apoptosis of specific cell types required for visual function, as described in laser-induced ocular injury.[7]

To test our hypothesis and to better understand the pathological mechanisms that underlie blast-induced ocular trauma, we have conducted a study in which a compressed air-driven shock tube was used to deliver a sublethal dose of blast pressure to rats. Ocular tissues were collected after blast exposure and examined by immunohistochemistry for

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This study has been conducted in compliance with the Animal Welfare Act, the implementing Animal Welfare Regulations, and the principles of the Guide for the Care and Use of Laboratory Animals.

The opinions or assertions contained herein are the private views of the author and are not to be construed as official or as reflecting the views of the Department of the Army or the Department of Defense.

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markers of tissue damage. This is the first study to precisely identify the specific cell types damaged by blast exposure and cellular pathways that are involved in the pathology of blast-induced ocular trauma.

METHODS

Subjects

Sprague–Dawley rats were purchased from Charles River (Wilmington, Massachusetts). All experiments were performed according to the regulations in the Association for Research in Vision and Ophthalmology Statement for the Use of Animals in Ophthalmic and Vision Research and all experimental procedures were approved by the local Institutional Animal Care and Use Committee. A total of 26 adult, virus-free Sprague–Dawley rats (300–350 g) were randomly divided into a blast-exposed group and a control group. Male rats were used for this study to eliminate the confounding effects of hormonal fluctuations that occur during the estrous cycle of female rats. Animals were anesthetized with isoflurane and positioned in a holder that prevented secondary and tertiary blast injuries.[8] As shown in Figure 1, animals were placed into the end of the expansion chamber of an air-driven shock tube housed at Navy Medical Research Center (Silver Spring, Maryland),[8] with their right side perpendicular to the direction of BOP. Animals assigned to exposures were subjected to a peak overpressure of 120 ± 7KPa with duration of 2 msec directed to the right side of the animal. Previous studies have demonstrated that 120 ± 7 KPa results in moderate tissue damage and is not lethal to rats.[9] Control animals received anesthesia and were treated the same way except for the exposure to BOP. Rats were sacrificed at 3 hours (n = 7), 24 hours (n = 5), and 48 hours (n = 6) after exposure to blast. Rats not exposed to blast were used for controls (n = 8).

Immunohistochemistry

Retinas and optic nerves were collected at 3, 24, and 48 hours post blast exposure. Five μm paraffin-embedded sections were deparaffinized and quenched with hydrogen peroxide to block endogenous peroxidase activity. Antigen retrieval was achieved by heating the sections in 10 mM citrate buffer. Tissue sections were blocked in phosphate buffer saline containing 3% normal serum and incubated with cleaved caspase 3 antibody (1:300) (Cell Signaling Technology, Boston, Massachusetts) for 1 hour at room temperature. Primary antibody was removed by washing the tissue sections with phosphate buffer saline. Biotinylated secondary antibody (1:200) was added and incubated for 1 hour at room temperature. A standard immunohistochemical avidin–biotin–peroxidase complex technique, Elite ABC kits (Vector Laboratories, Burlingame, California) was then applied to visualize protein expression using 0.02% of 3-diaminobenzidine tetrahydrochloride substrate. Sections were counterstained with methyl green.

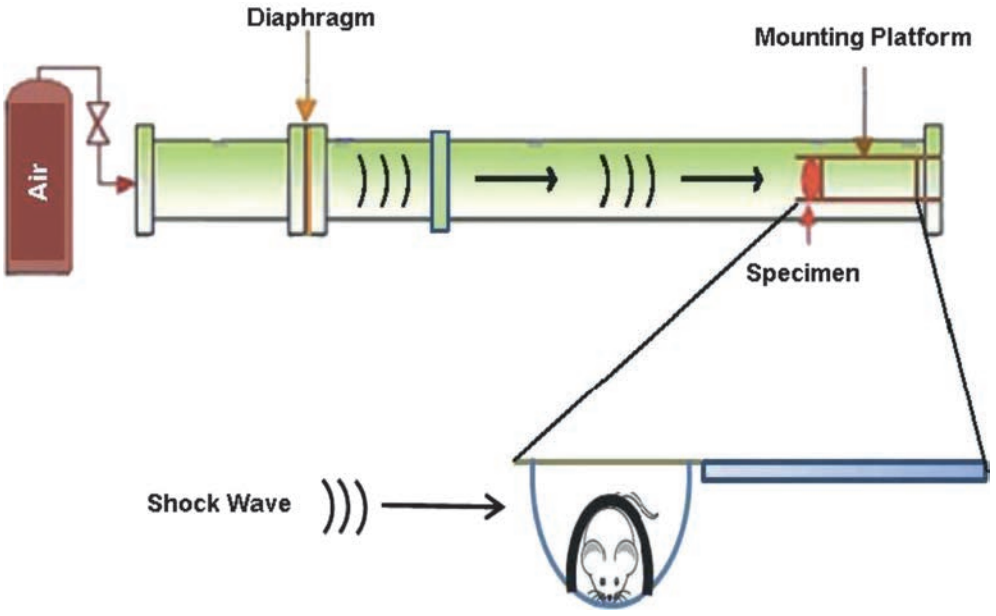

FIGURE 1. A compressed air-driven shock tube was used to deliver 120 ± 7KPa of BOP to rats. Anesthetized rats were positioned in a holder that prevented secondary and tertiary blast injuries. Animals were subjected to a BOP of 120 ± 7KPa with duration of 2 msec directed at the right side of the animal.

TUNEL Analysis

A biotin-streptavidin–based TUNEL kit (R&D systems, Minneapolis, Minnesota) was used. Deparaffinized tissue sections were permeabilized with proteinase K, quenched with 3% hydrogen peroxide, and then incubated at 37°C with a mixture deoxyribonucleotide triphosphates conjugated to biotin, Mn^{2+}, and terminal deoxynucleotidyl transferase (TdT) reaction buffer for 1 hour. After stopping the TdT reaction, the tissues were incubated for 30 minutes at room temperature with streptavidin-conjugated horseradish peroxidase, washed, and developed with 3-diaminobenzidine tetrahydrochloride. Sections were counterstained with methyl green.

Microscopy

Bright-field images were acquired at 400× for retinal sections and 200× for optic nerve sections with an Olympus CK2 microscope (Olympus, Center Valley, Pennsylvania).

Quantification of Caspase 3 Activation

Tissue sections were examined by bright-field microscopy at 400× magnification. The number of caspase 3+ cells per field of view was quantified by a human rater blinded to the groups.

Statistical Analysis

Data are expressed as mean ± standard error. The medians of the actual numbers of caspase 3+ cells were compared using the Wilcoxon test. $p < 0.05$ was considered statistically significant.

RESULTS

Blast Exposure Causes Increased Caspase 3 Activation in the Retina

Retinal tissues from rats exposed to 120 ± 7KPa blast pressure on the right side were processed for immunohistochemistry to detect activated caspase 3, which is the final executioner of the apoptotic sequence.[10] The antibody used in this study only recognizes activated caspase 3,[11] enabling identification of apoptotic cells. As shown in Figure 2, retinal tissues from rats exposed to blast pressure had increased levels of activated caspase 3 as indicated by the brown staining. Although the rats were exposed to blast pressure on the right side, caspase 3 activation was also detected in retinal tissues from the left side. The retina is composed of several distinct layers of tissues, including the ganglion layer, the inner nuclear layer, and the outer nuclear layer. At 3 hours post blast, low levels of activated caspase 3 were detected in the ganglion layer and inner nuclear layer in retinal tissues from both the left and right sides. At 24 hours post blast exposure, activated caspase 3 remained detectable at low levels in the ganglion layer and inner nuclear layer from the left side, but increasing numbers of activated caspase 3+ cells were detected in the ganglion layer and inner nuclear layer from the right side. At 48 hours post blast exposure, cells with activated caspase 3 increased in the ganglion layer from the left side, with a modest reduction of activated caspase 3+ cells in the inner nuclear layer. However, in the tissues from the right side, high levels of activated caspase 3 were detected in the ganglion layer, whereas levels decreased in the inner nuclear layer. Activated caspase 3 was not detected in the outer nuclear layer at any time post blast exposure, whether from the left or right sides. Activated caspase 3 was low or undetectable in the tissues from rats not exposed to BOP.

Blast Exposure Causes Increased Caspase 3 Activation in the Optic Nerve

Optic nerve sections from left and right sides of rats exposed to 120 ± 7KPa of BOP were processed for immunohistochemistry as described above to detect activated caspase 3. As shown in Figure 3, activated caspase 3 was detectable in the optic nerves from both left and right sides. At 3 hours post blast exposure, low levels of activated caspase 3 were detectable in both right and left sides. However, by 24 hours post blast, the number of cells with activated caspase 3 had increased dramatically in the right side, whereas the number of cells with activated caspase 3 showed a modest increase in the left side. At 48 hours post blast exposure, the number of cells with activated caspase 3 had increased on the right side, but decreased on the left side. Activated caspase 3 remained low or undetectable in optic nerve tissues from control animals not exposed to BOP.

Blast Exposure Causes Increased Apoptosis in the Retina

The TUNEL assay is a well-established method for the detection of cells in the final stage of apoptosis. To further confirm that blast exposure causes apoptosis of retinal cells, the retinal tissues from rats exposed to 120 ± 7KPa of BOP were examined by TUNEL assay. As shown in Figure 4, at 48 hours post blast exposure, a significant level of apoptosis was detected in both the ganglion layer and inner nuclear layer obtained from right side retinal tissues as indicated by TUNEL, whereas no apoptotic cells were detected in retinal tissues from control animals not exposed to blast pressure. Importantly, cells in the outer nuclear layer were also negative for TUNEL, confirming the activated caspase 3 results from Figures 2 and 3.

DISCUSSION

We report here the results of experiments in which rats were exposed to sublethal doses of blast pressure on the right side. Examination of ocular tissues from the

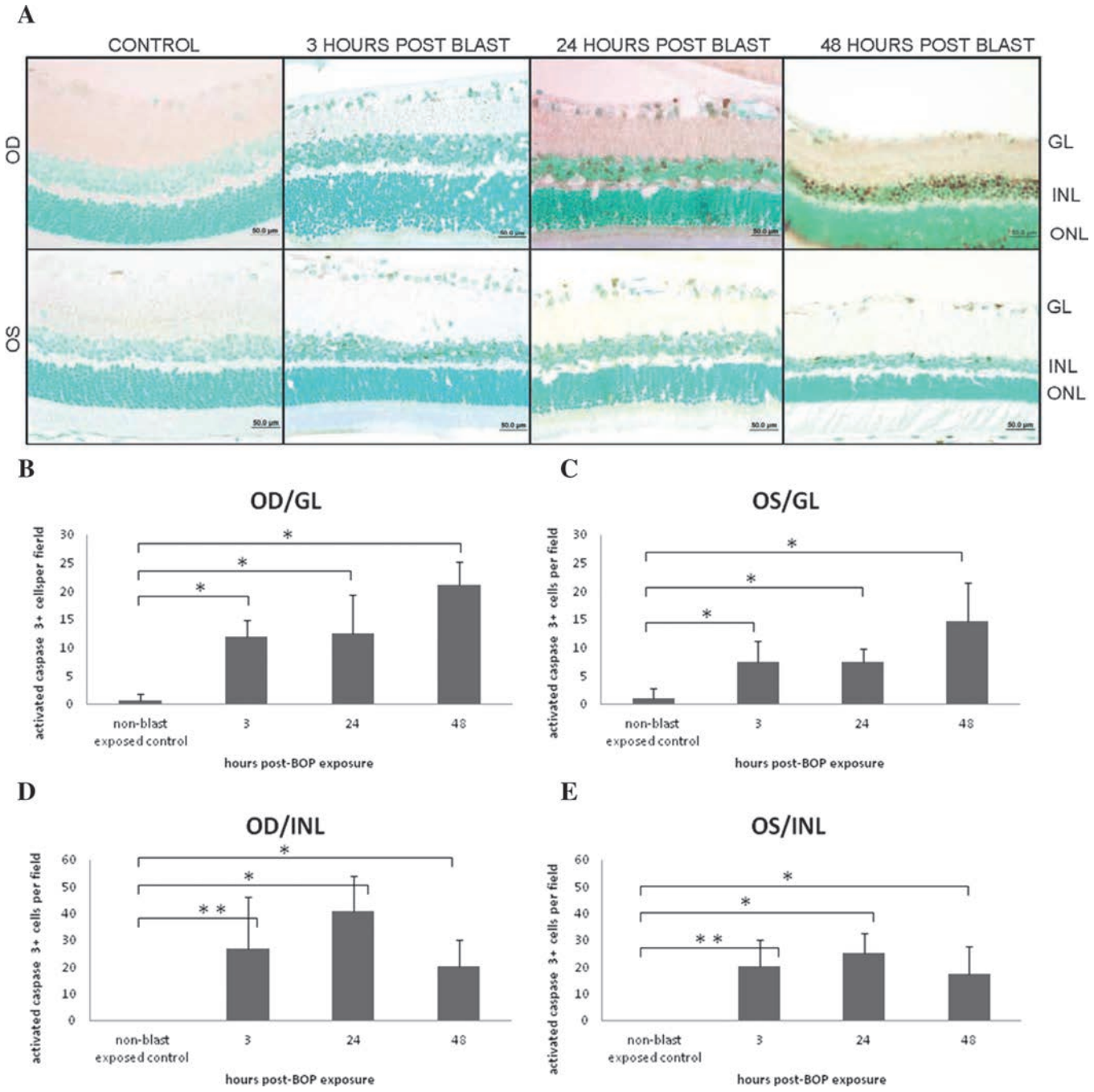

FIGURE 2. Caspase 3 activation in retina following blast exposure. Retinas were collected at 3, 24, and 48 hours post blast exposure. Tissues were examined for expression of activated caspase 3 (brown staining). (A) Retinal tissues from the right side (OD) of the rats exposed to BOP are shown in the upper panel. Retinal tissues from the left side (OS) of the rats exposed to BOP are shown in the lower panel. (B–E) The number of caspase 3+ cells in each field of view was quantified. The number of caspase 3+ cells in the ganglion layer (GL) and inner nuclear layer (INL) was compared to the same cell type in tissues from rats not exposed to BOP. Activated caspase 3 was not detected in outer nuclear layer (ONL) at any time point. Statistical significance is indicated, with * = $p < 0.05$ and ** = $p < 0.0$l.

blast-exposed rats revealed increased levels of activated caspase 3 in tissues collected from both left and right sides. Although caspase 3 activation was lower on the left side, these results indicate that even the eye not directly exposed to blast pressure remains vulnerable to damage. Since caspase 3 is the final executioner caspase in apoptosis, the detection of activated caspase 3 is a positive indicator for apoptosis. In accordance with this data, TUNEL assay

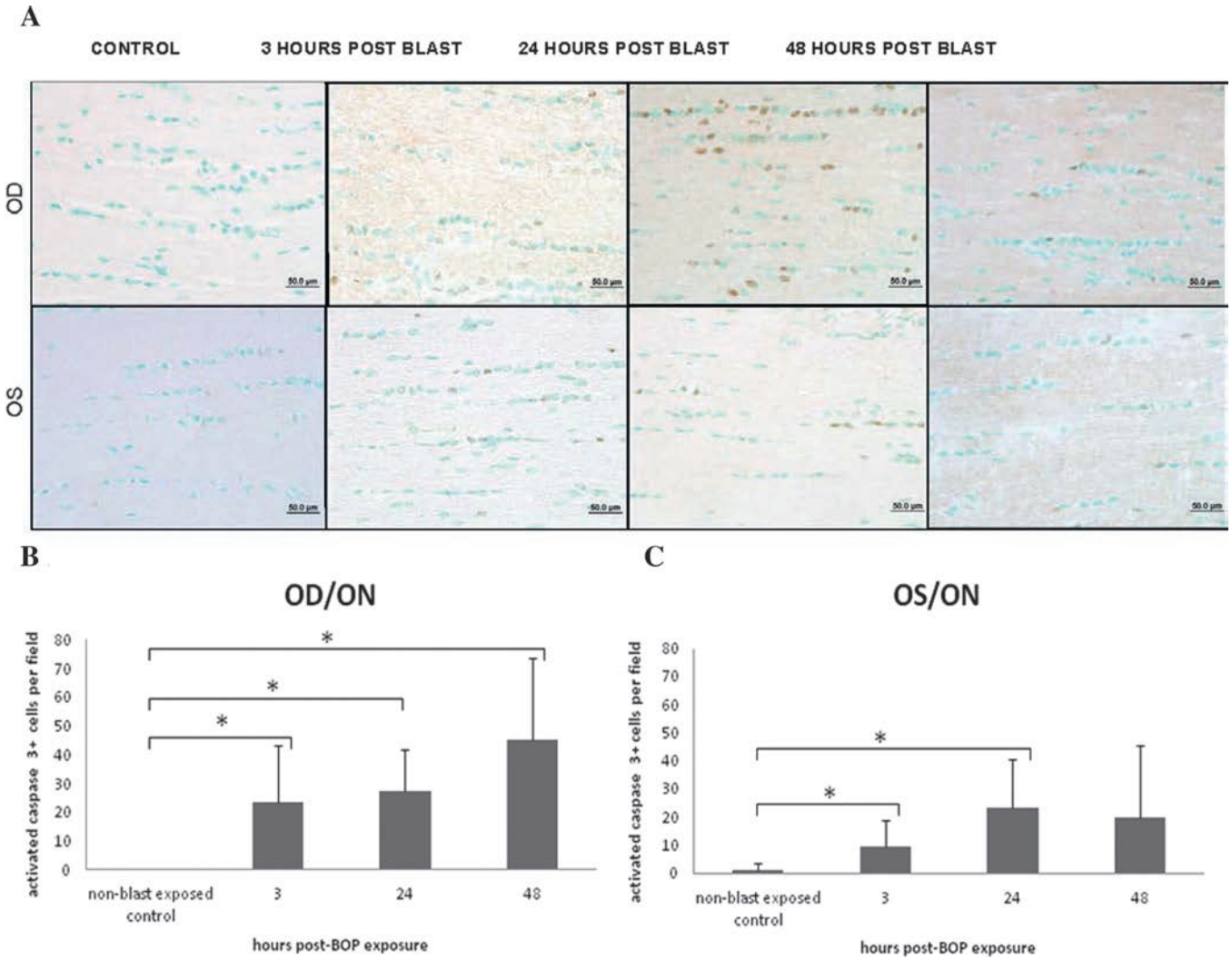

FIGURE 3. Caspase 3 activation in the optic nerve following blast exposure. Optic nerves were collected at 3, 24, and 48 hours post blast exposure. Tissues were examined for expression of activated caspase 3 (brown staining). (A) Optic nerve (ON) tissues from the right side (OD) of the rats exposed to BOP are shown in the upper panel. Optic nerve tissues from the left side (OS) of the rats exposed to BOP are shown in the lower panel. (B and C) The number of caspase 3+ cells in each field of view was quantified. The number of caspase 3+ cells in the optic nerve sections was compared to optic nerve tissues from rats not exposed to BOP. Statistical significance is indicated by *, with $p < 0.05$ considered to be significant.

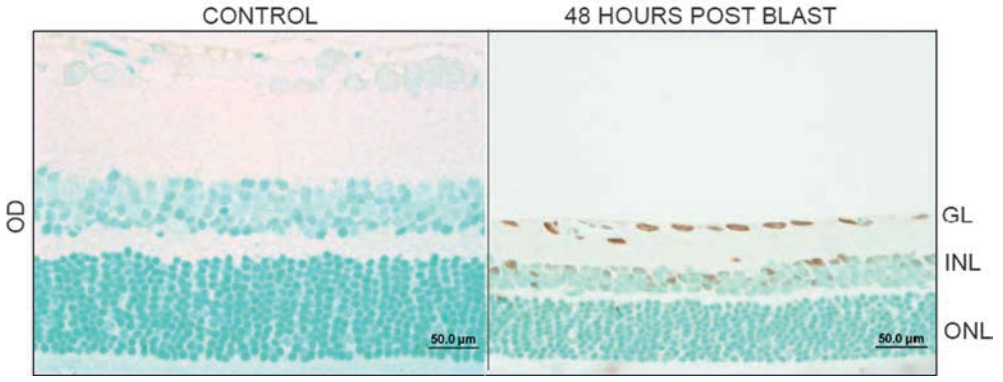

FIGURE 4. TUNEL assay to detect apoptosis in the retina following blast exposure. Retinal tissues collected at 48 hours post blast exposure were examined for DNA damage by TUNEL assay, a positive marker of apoptosis (brown staining). Retinal tissue from rats not exposed to BOP (left panel) was negative for TUNEL. Apoptosis was detected in the ganglion layer (GL) and inner nuclear layer (INL) at 48 hours post blast exposure, whereas the outer nuclear layer (ONL) remained negative in retinal tissue from rats exposed to 120 ± 7 KPa BOP.

results revealed significant levels of DNA damage and apoptosis at 48 hours post blast in the ganglion layer and inner nuclear layer.

The retina is a very thin layer of light-sensitive neural tissue lining the back of the eye. It is a part of central nerve system; once the cells undergo cell death, they cannot be regenerated. The multiple layers of the retina function in an integrated fashion to both capture external light and process the resultant stimuli. Photoreceptors in the outer nuclear layer capture photons of light, become hyperpolarized, and convert the photon energy into electrical signals in a process known as phototransduction. Second-order information processing occurs in the inner nuclear layer where the bipolar and horizontal cells communicate with the photoreceptors via the exchange of chemical neurotransmitters. Higher order processing occurs in the ganglion layer where the ganglion cells collect all visual information and transmit it to the brain via the optic nerve. The ganglion cell axons converge at the optic disk to form the optic nerve that terminates at the lateral geniculate body. The optic nerve is composed of the ganglion cell axons and oligodendrocytes and is the only part of the central nervous system that is exterior to the cranial cavity. The optic nerve is myelinated by oligodendrocytes rather than Schwann cells, which explains why the optic nerve cannot regenerate following injury.[12,13]

This study has revealed that exposure to moderate levels of BOP induces damage leading to apoptosis in both the eye directly receiving the blast as well as the contralateral eye. Furthermore, the cells most sensitive to blast-induced damage were in the ganglion layer, the inner nuclear layer, and the optic nerve. Exposure to blast pressure that induces apoptosis of ganglion cells, inner nuclear cells, and in the optic nerve would disrupt signal transduction from photoreceptors through the optic nerve, and have profound effects upon visual function.

The results of this study were obtained from an animal model in which rats were exposed to moderate levels of BOP. The architecture of the rat skull and the anatomy of the rat eye are clearly different from that of humans; however, the data can be extrapolated to humans who are exposed to blast from explosions. Importantly, although the right eye was directly exposed to BOP, our results indicate that both eyes sustained damage. As reported by Cockerham et al,[1] many troops exposed to blast suffered damage to both eyes, although orientation to the explosion was not indicated. In addition, these results indicate a short period of time after blast exposure during which therapeutic intervention may be most effective before the onset of apoptosis of damaged cells. The length of this critical time period may differ between human and rat, nevertheless, this concept is clinically relevant. Despite the limitations inherent to the use of animal models of human injury, this study provides important insight into the impact of BOP on ocular tissues and the visual system.

In conclusion, this is the first study to identify apoptosis as a cellular pathway activated in ocular tissues following exposure to sublethal blast pressure. The specific ocular tissues of the visual system that are most sensitive to blast exposure have been identified, specifically the cells in the ganglion layer and inner nuclear layer of the retina, and cells of the optic nerve. The damaging effects of BOP were observed in tissues from the side exposed to BOP as well as the contralateral side. Finally, this study characterizes an initial temporal profile of blast injury to ocular tissue suggesting that injury may peak at 24 hours following trauma. Using this study as a foundation, further investigation is needed to understand injury mechanisms, targets, and timing which will allow identification of potential protective or therapeutic measures to mitigate blast-related visual injury.

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The Intraoperative Administration of Ketamine to Burned U.S. Service Members Does Not Increase the Incidence of Post-Traumatic Stress Disorder

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ABSTRACT Aim: Patients with severe burns typically undergo multiple surgeries, and ketamine is often used as part of the multimodal anesthetic regimen during such surgeries. The anesthetic ketamine is an *N*-methyl-D-aspartate receptor antagonist that also provides analgesia at subanesthetic doses, but the psychoactive side effects of ketamine have caused concern about its potential psychological effects on a combat-wounded population. Post-traumatic stress disorder (PTSD) affects approximately 30% of burned U.S. service members injured in Operation Iraqi Freedom/ Operation Enduring Freedom. A preliminary analysis by our research group reported that patients who received perioperative ketamine had a significantly lower prevalence of PTSD than those injured service members who did not receive ketamine. We have now expanded this research to examine the relationship between ketamine and PTSD development in a much larger population. Methods: A retrospective analysis on data from service members being treated for burns at the San Antonio Military Medical Center was conducted. Collected data included drugs received, injury severity score (ISS), total body surface area (TBSA) burned, length of hospital stay (LOS), number of intensive care unit days, number of surgeries, and PTSD Checklist-Military (PCL-M) scores and administration dates. Subjects were grouped based on intraoperative receipt of ketamine, and the groups were compared. The groups were binary for ketamine (yes or no), and dose of ketamine administered was not included in data analyses. Propensity score matching based on ISS and TBSA was performed to control for individual differences in burn severity. Results: Two hundred eighty-nine burned U.S. service members received the PCL-M at least 30 days after injury. Of these subjects, 189 received intraoperative ketamine, and 100 did not. Despite significantly greater injuries, as evidenced by significantly higher TBSA burned and ISS ($p < 0.01$), patients who received ketamine did not screen positive for PTSD at a different rate than those patients who did not (24% vs. 26.98%, $p = 0.582$). Patients receiving intraoperative ketamine also underwent a significantly greater number of surgeries, spent more time in the hospital, spent more days in the ICU, and received more morphine equivalent units ($p < 0.0001$). Propensity score matching based on ISS and TBSA resulted in a total subject number of 130. In the matched samples, subjects who received ketamine still underwent significantly more surgeries and experienced longer hospital stays ($p < 0.0001$). Again, there was no statistically significant difference in the incidence of a positive screen for PTSD based upon the receipt of ketamine (28% vs. 26.15%, $p = 0.843$). Conclusions: Ketamine is often used in burn patients to reduce opioid usage and decrease the hemodynamic and respiratory side effects. Although this study does not show a benefit of ketamine on PTSD development that was identified in previous work with a smaller sample number, it does support the conclusion that ketamine does not increase PTSD development in burned service members.

INTRODUCTION

Pain is a significant problem in the military, from basic training to the battlefield and home again.[1] The most common medications given for severe pain, both on the battlefield and in definitive care facilities, are opioids. However, the widespread use of opioids had led to significant problems in the health system. First, initial use of intramuscular morphine on the battlefield is not very effective at providing analgesia.[2] Although opioids are the most commonly prescribed medication for severe pain, there are numerous side effects that must be considered when administering these drugs. Opioids can cause nausea, vomiting, constipation, respiratory depression, sedation, hemodynamic depression, and itching.[3,4] Additionally, opioids carry the risk of tolerance, dependence, addiction, and opioid-induced hyperalgesia.[5,6] Other alternatives to pain management must be considered.

Pain is a particularly challenging problem in burn patients.[7–9] These patients are already severely injured because of the significant tissue damage produced by a burn; a severe burn can also alter coagulation, inflammation, and metabolic pathways.[10] These alterations to normal physiology have to be considered when medications are being administered, particularly those that can negatively affect hemodynamic stability. The burn also impacts peripheral neurons that send pain signals to the central nervous system. Burn pain has multiple components, making it especially hard to treat.[11] Burn patients

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frequently suffer from unrelieved pain and receive a complex pharmacopeia to attempt to control the pain.[9,12] The basis of pain management is opioids, which have the aforementioned side effects.

Ketamine is an *N*-methyl-D-aspartate receptor antagonist that is commonly used as part of balanced anesthesia, particularly in burn and pediatric patients. Ketamine has a rapid onset of action and allows for stable cardiovascular and respiratory physiology. It produces sedation, analgesia, and dissociative anesthesia, but is also capable of producing profound analgesia even at subanesthetic doses.[13–15] However, ketamine is associated with the psychomimetic effects, including emergence delirium and hallucinations.[16] These negative side effects can be mitigated through benzodiazepine coadministration and pretreatment counseling. However, these dissociative properties of ketamine raised the concern that ketamine may increase the prevalence of post-traumatic stress disorder (PTSD) or other mental health sequelae[17] in combat-wounded service members.

PTSD is a psychological disorder characterized by recurrent flashbacks, nightmares, emotional disturbances, social withdrawal, and forgetfulness.[18] It often arises after a traumatic experience where the participant is threatened with harm and/or death. Experiencing a traumatic event, threat of injury or death, and threat to one's physical integrity, such as untreated pain are predisposing factors for PTSD. PTSD affects almost one-third of the burn patient population, with civilian burn centers reporting a prevalence of 8% to 45%.[19–22]

PTSD is a concern for U.S. service members returning from theater. Approximately 20% of returning injured Operation Iraqi Freedom/Operation Enduring Freedom Service members reported symptoms consistent with PTSD.[23] Pain is a stressor that may contribute to PTSD development and frequently, pain is comorbid with PTSD in veterans.[19,24,25] A previous study conducted at our facility suggested that ketamine administration in the operating room did not increase the risk of PTSD in burned service members; indeed, there was a statistically significant decrease in the prevalence of PTSD among the cohort that received ketamine as compared to those that did not receive ketamine.[26] However, there were a very small number of subjects, particularly in the no ketamine group, and there was an extremely high prevalence of positive screens for PTSD in the no ketamine group. Therefore, this retrospective study revisits the relationship between PTSD and ketamine in population of burned U.S. service members. We compared the prevalence of PTSD in patients who received intraoperative ketamine versus those that did not.

MATERIALS AND METHODS

This retrospective chart review study was conducted under a protocol reviewed and approved by the U.S. Army Brook Army Medical Center Institutional Review Board, and in accordance with the approved protocol. The population analyzed was burned U.S. service members treated at the U.S. Army Institute of Surgical Research (USAISR) burn unit between 2004 and 2011. Inclusion criteria were any active duty service member admitted to the USAISR burn unit who completed the PCL-M screening tool for PTSD. Only those subjects who received screening for PTSD at least 30 days after the burn were included in this study.

Data on age, date of injury, intraoperative medications, opioids received, Injury Severity Score (ISS), percent total body surface area burned (% TBSA), length of hospital stay (LOS), number of days spent in the intensive care unit (ICU days), and number of surgeries were collected from patient charts. Chart data from all military patients admitted to the USAISR burn unit was extracted to a password-protected Microsoft Excel database stored on in-house servers; data included patient demographics, drugs administered, and PTSD Checklist-Military (PCL-M) scores. Morphine equivalent units (MEUs, mg/day) were calculated by adding opioid dosages received both intraoperatively and on the wards and dividing by the LOS. Opioid dosages were converted to intravenous morphine equivalents using standard conversion tables.[27–29] The most recent PCL-M screening results were also collected for each subject. The variability in time frame of when the patient received the PCL-M, postburn, was not analyzed, nor were other drugs or treatments administered. We also did not evaluate subjects based upon the presence of additional mental health disorders.

Multiple screening tools for assessing PTSD are available and are currently used in civilian trauma centers. However, the PCL-M is a screening tool for PTSD that is authorized for use by the U.S. military. It consists of 17 questions rated on a scale of 1 to 5, indicating the presence, frequency, and severity of PTSD symptoms. A score of 44 or higher yields a diagnostic efficiency of 0.900,[30] and thus was the cutoff used for a positive screen in this study. The complete diagnostic criteria for PTSD are described in the "Diagnostic and Statistical Manual of Mental Disorders," third (1980) and fourth (1994) editions.[18] All subjects received the PCL-M immediately before discharge from the USAISR burn unit.

Subjects were stratified into two groups. One group received intraoperative ketamine during their initial operations, and the other group did not receive intraoperative ketamine during their initial operations. The groups were binary for ketamine (yes or no), and dose of ketamine administered was not included in data analyses. The two groups were then compared to determine if there was a difference in incidence of a positive screen on the PCL-M or on frequency/severity of PTSD symptoms, as indicated by the PCL-M Score.

Continuous data was tested for normality and a Student's *t*-test and Wilcoxon two-sample test was performed accordingly. Categorical data was tested using a χ^2 test. Propensity score matching based on ISS and TBSA was performed to control for individual differences in burn severity. A logistic regression was conducted using ketamine as the dependent variable and ISS and TBSA as the independent variables. The

probability index generated from the Logistic Regression was used by a matching algorithm to pair ketamine (yes/no). ISS and TBSA with then compared by univariate analysis to ensure there was no statistical difference between the groups (ketamine yes/no) on these variables after matching. A p value of $p < 0.05$ was considered significant in this study.

RESULTS

Between 2004 and 2011, 785 burned service members were treated at the USAISR burn unit. Of these, 290 received the PCL-M at least 30 days after injury. Of these subjects, 189 received intraoperative ketamine, and 100 did not (Fig. 1). Because inclusion criteria required PCL-M data from at least 30 days after injury, no subjects were lost to follow-up.

Analysis of patient demographics demonstrated that the subjects in both groups were similar in age (Table I). However, those patients who received intraoperative ketamine had significantly higher ISS, %TBSA, and number of surgeries ($p < 0.0001$). Patients receiving intraoperative ketamine also spent more days in the ICU, had longer overall hospital stays, and received more opioids than those patients who did not receive intraoperative ketamine ($p < 0.0001$, Table II). Despite these significantly greater injuries, patients who received ketamine did not screen positive for PTSD at a different rate than those patients who did not ($p = 0.582$, Table II). Patients who received ketamine also did not exhibit increased PTSD symptoms and had similar PCL-M scores to those patients that did not receive ketamine ($p = 0.370$). Because the comparison could be confounded by the significantly greater injuries received by those patients who were administered intraoperative ketamine (Table I), propensity score matching based on ISS and TBSA was done, resulting in a total subject number of 130, 65 in each group. Table III shows the demographics of the patients in the matched groups. The matched groups were similar in age, ISS, % TBSA, days spent in the ICU, and opioids received (Table III). Those patients who received intraoperative ketamine still spent more time in the hospital and experienced more surgeries than those patients who did not receive intraoperative ketamine ($p < 0.0001$, Table III). Again, there was no statistically significant difference in the incidence of a positive screen for PTSD based upon the receipt of ketamine ($p = 0.843$, Table IV). There was also no difference between

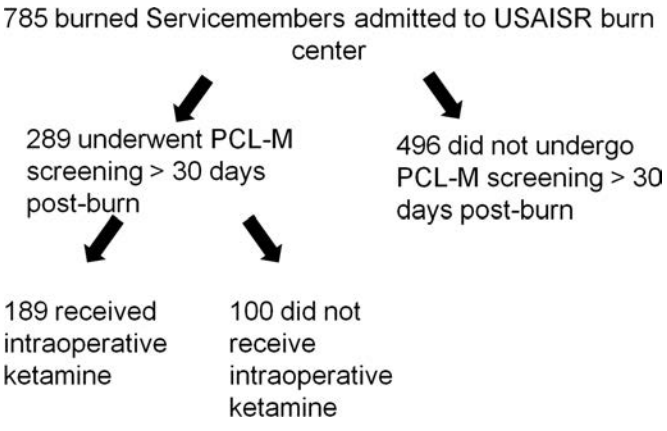

FIGURE 1. Patient population. Between 2004 and 2010, the U.S. Army Institute of Surgical Research admitted 785 burned service members. Of these, 289 received PTSD screening at least 30 days after their injury. One hundred eighty-nine of these subjects received intraoperative ketamine, and 100 did not receive intraoperative ketamine.

TABLE I. Patient Demographics, Injury Severity Parameters, and Intravenous Morphine Equivalents Received

After Matching	No Intraoperative Ketamine ($n = 65$)	Intraoperative Ketamine ($n = 65$)	p Value
Age	24.97 ± 6.35	25.67 ± 6.40	0.577
ISS	9.51 ± 7.01	9.51 ± 7.01	1
Percent TBSA	11.30 ± 10.94	13.09 ± 12.09	0.218
Number of Surgeries	0.95 ± 1.68	3.38 ± 4.35	<0.0001
ICU Days	1.85 ± 4.58	5.55 ± 15.31	0.033
Length of Stay	15.96 ± 22.34	22.05 ± 21.13	<0.0001
MEQ (mg/day)	91.52 ± 107.60	89.26 ± 74.45	0.645

Subjects receiving intraoperative ketamine had greater ISS, higher percent TBSA burned, underwent more surgeries, spent more time in the ICU and in the hospital, and received more intravenous morphine equivalents per inpatient day (MEQ [mg/day]). There was no difference in age between the two groups.

TABLE II. The Relationship Between Intraoperative Ketamine Receipt and PTSD

	No Intraoperative Ketamine ($n = 100$)	Intraoperative Ketamine ($n = 189$)	p Value
PCLM Score	32.98 ± 15.62	34.57 ± 15.64	0.37
PTSD Prevalence	24%	26.98%	0.582

There is no difference between PCL-M scores and PTSD incidence in patients that received intraoperative ketamine versus those that did not.

TABLE III. Propensity Score-Matched Patient Demographics, Injury Severity Parameters, and Intravenous Morphine Equivalents Received

	No Intraoperative Ketamine ($n = 65$)	Intraoperative Ketamine ($n = 65$)	p Value
PCLM Score	33.98 ± 16.10	35.06 ± 15.91	0.663
PTSD Prevalence	28%	26.15%	0.843

After propensity score matching based upon percent TBSA burned and ISS scores, subjects receiving intraoperative ketamine experienced a greater number of surgeries and spent more time in the hospital. There was no significant difference between the two groups in age, ISS, % TBSA, days spent in the ICU, or intravenous morphine equivalents received per day (MEQ [mg/day]).

TABLE IV. Propensity Score-Matched Analysis of the Relationship Between Intraoperative Ketamine and PTSD

Before Matching	No Intraoperative Ketamine (n = 100)	Intraoperative Ketamine (n = 189)	p Value
Age	25.41 ± 6.72	25.65 ± 5.73	0.495
ISS	6.82 ± 6.87	20.66 ± 13.12	<0.0001
Percent TBSA	9.03 ± 9.52	26.57 ± 20.26	<0.0001
Number of Surgeries	0.71 ± 1.52	5.53 ± 5.71	<0.0001
ICU Days	1.33 ± 3.86	18.99 ± 30.24	<0.0001
Length of Stay	12.06 ± 19.03	49.54 ± 57.14	<0.0001
MEQ (mg/day)	80.04 ± 96.59	115.67 ± 116.87	<0.0001

Following propensity score matching based on % TBSA and ISS. There is no difference between PCL-M scores and PTSD incidence in patients that received intraoperative ketamine versus those that did not.

the groups in the incidence/severity of PTSD symptoms as determined by PCL-M scores (p = 0.663, Table IV).

DISCUSSION

Pain is a common and often severe problem for burn patients. Providers balance the impact of pain compared to the potential side effects of anesthetic and analgesic agents.[8] Although opioids are the most common analgesic and anesthetic agents, they have significant risk for respiratory depression, hemodynamic depression, decreased cardiac output, suppression of the immune system, and constipation.[3] These side effects are particularly alarming for burned patients who already suffer from alterations in coagulation, immune suppression, and are at significant risk for multiorgan failure. Effective alternatives to opioids are few, but include ketamine. Ketamine is an effective anesthetic and analgesic agent.[14,15,31,32] However, there are concerns that ketamine might increase psychological problems. However, we found no evidence for an association between ketamine and increased PTSD. For this study, the prevalence of PTSD in 289 burned soldiers (26.1%) is similar to the prevalence found in civilian burn populations (8% to 45%). Our data indicate that intraoperative ketamine administration does not affect the rate of PTSD in burned U.S. service members. These findings identified that ketamine does not increase the prevalence of PTSD.

Ketamine is used as part of a multimodal anesthetic plan that usually includes an opioid component. Ketamine is a multifunctional drug affecting multiple receptors including N-methyl-D-aspartate receptors and opioid receptors.[13,33–35] Ketamine is a potent analgesic, which has opioid sparing properties.[14,36,37] It is used in total intravenous anesthesia where it functions as both an analgesic and anesthetic depending on plasma concentration.[38,39] Our data suggest that intraoperative ketamine can be used in burned service members without affecting the prevalence of PTSD in this population. These data do not provide evidence that ketamine might be effective for the treatment for PTSD. Previous studies by our group found an association between ketamine and decreased PTSD development in service members.[26] However, this study did not find a similar association.

To date, there are no consistent correlations between PTSD in a combat-wounded population and medications received on the battlefield or in the hospital. Multiple retrospective studies have identified correlations between individual drugs and the subsequent development of PTSD. For example, a study of Marines showed that those subjects who received the most morphine within 24 hours following injury had a decreased incidence of PTSD in comparison to those Marines who did not receive morphine. This suggests that morphine reduces PTSD incidence, but does not address the possibility that the decreased PTSD development may be related to effective pain control, or to effects on memory, rather than to an intrinsic property of the drug.[40]

Limitations

This is a retrospective study with significant limitations. The study has a small sample size, and subjects were evaluated over a 7-year period. Many changes in practice and personnel likely occurred over this time frame and may contribute to differences in individual subjects or subsets of subjects that we were unable to identify when grouping all subjects together in this study. To qualify for inclusion in the study, the subject must have been screened for PTSD at least 30 days after burn; this would eliminate many patients with less severe burns as they may not have been available for in-person evaluation and PCL-M screening. There was little consistency in the time postburn at which the patient was screened using the PCL-M, leading to the possibility of underreporting the incidence of PTSD in patients who may have been successfully treated for PTSD before their final PCL-M screen. The presence of other mental health disorders that may contribute to PTSD or be associated with PTSD were not evaluated, and other medications or treatments that may affect PTSD or the manifestation of PTSD symptoms were not included in this study. Each patient also received multiple other drugs and treatments during their hospital stays that may have affected their outcomes. Additionally, there is limited applicability of these findings from an active duty military population, most of whom were burned in a combat zone, to the civilian burn population. Finally, and importantly, the dose of ketamine each patient received was not included in the analysis. Thus, the effects of ketamine were likely not completely explained when evaluated on a binary, yes/no basis.

CONCLUSION

Ketamine is often used in burn patients to reduce opioid usage and decrease the hemodynamic and respiratory side effects of such usage. These data suggest that ketamine administration does not affect PTSD development in burned service members. However, those patients who received

intraoperative ketamine also spent longer in the hospital, underwent more procedures, received more MEUs, and were more severely injured. It is likely that these sicker patients required a more aggressive and comprehensive pain management strategy and thus were more likely to receive ketamine in addition to opioids. Although this study does not show a benefit of ketamine on PTSD development that was identified in previous work with a smaller sample number, it does support the conclusion that ketamine does not increase PTSD development in burned service members. There was no statistical difference in PTSD prevalence in patients that received ketamine versus those that did not. Data from this study and others support the conclusion that ketamine remains a good option for use in a balanced anesthesia regimen the severely burned population.

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The Challenge of Undiagnosed Sleep Apnea in Low-Risk Populations: A Decision Analysis

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ABSTRACT Objectives: Obstructive sleep apnea (OSA) may contribute to impaired performance among otherwise healthy active duty military personnel. We used decision analysis to evaluate three approaches to identifying and treating OSA in low-risk populations, which may differ from current standard practice for high-risk populations. Methods: We developed a decision tree to compare two simple strategies for diagnosis and management of sleep apnea in a low-risk population. In one strategy, a simple screening inventory was followed by conventional laboratory polysomnography (split-night), whereas the alternative strategy involved performing home testing in all individuals. This allowed us to weigh the costs associated with large-scale diagnostic approaches against the costs of untreated OSA in a small fraction of the population. Results: We found that the home testing approach was less expensive than the screen-then-test approach across a broad range of other important parameters, including the annual performance cost associated with untreated OSA, the prevalence of OSA, and the duration of active duty. Conclusions: Assuming even modest annual performance costs associated with untreated OSA, a population strategy involving large-scale home testing is less expensive than a screening inventory approach. These results may inform either targeted or large-scale investigation of undiagnosed OSA in low-risk populations such as active duty military.

INTRODUCTION

Obstructive sleep apnea (OSA) is a prevalent disorder associated with morbidity and mortality, as well as impaired work performance and motor vehicle accidents[1–3] with annual cost burden estimates in the range of $50 billion in the United States.[4] OSA is traditionally diagnosed by laboratory polysomnogram (PSG), according to the frequency of apneas and hypopneas observed during sleep. According to recent guidelines from the American Academy of Sleep Medicine, OSA is diagnosed by having either an apnea–hypopnea index (AHI) > 15 regardless of symptoms, or an AHI > 5 if accompanied by snoring, sleepiness, or related symptoms.[5]

Despite the health and performance consequences of OSA, and the variety of available treatments, most individuals remain undiagnosed.[6,7] Identifying OSA is particularly challenging in low-risk populations, such as young healthy active duty military personnel. The prevalence of OSA depends on the definitions used with more strict definitions yielding 2% to 4% prevalence in adults, whereas more modern definitions yielding 10% to 15% prevalence.[8] In healthy younger populations, the values may be lower than typically reported in epidemiological studies, but occult OSA can still occur in 5% even after extensive screening.[9] The challenge involves imperfect screening tools[10] that are vulnerable to false positive findings when applied in low-prevalence populations, as is the case for modern OSA screening tools.[11] Although PSG is the gold standard diagnostic test, using PSG to screen for OSA in large populations with low disease prevalence may not be feasible due to limitations of cost and availability. The growing availability of validated home sleep devices has offered an alternative approach,[12,13] but the assumption that a home diagnostic framework is necessarily cost-saving has been questioned.[14,15]

Another important challenge is that the standard Epworth Sleepiness Scale correlates poorly with the severity of OSA,[16,17] or with objective sleepiness measured by multiple sleep latency testing.[18] The consequence of this disease–symptom dissociation is that one cannot expect individuals with OSA to "declare themselves" clinically on the basis of symptoms, even when those symptoms are elicited in the structured context of a medical evaluation. In recognition of this challenge, various inventories have been developed to improve the yield of clinical screening in order to triage at-risk individuals for formal testing.[10] However, these tools demonstrate only modest performance characteristics, making them particularly vulnerable from a Bayesian standpoint when applied to either high- or low-risk populations. Specifically, the challenges of interpreting unexpectedly positive results in low-prevalence populations (in which there is an increased risk of false positives), or unexpectedly negative results in high-risk populations (in which there is an increased risk of false negatives), are not straightforward.[19]

Here, we performed a decision analysis to evaluate two approaches to undiagnosed OSA in low-risk populations. Although we recognize many health-related motivations for diagnosis and treatment of OSA, our model is intended

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to emphasize the performance impairments that might accompany OSA in a healthy population. Thus, the overarching goal is to provide a framework for balancing the performance related costs against the costs associated with diagnosis and treatment of OSA in the special setting of a low-risk active duty population.

METHODS

Modeling was performed using TreeAge Pro 2011 (TreeAge Software, Williamstown, Massachusetts). Unlike many models presented in the literature, our model considers only the cost of each decision. Given our intention of offering a framework for approaching diagnostics in a healthy, low-risk population, the main considerations are the costs associated with decreased performance among those with undiagnosed OSA weighed against the costs associated with diagnostic evaluation and treatment. We did not therefore explicitly consider quality of life or health outcomes, which undoubtedly will impact a cost–benefit analysis as one considers older and less healthy military personnel and veterans. However, for modeling purposes in this presumed healthy population, performance-related costs may outweigh health considerations (although health risks are expected to improve the cost–benefit favorability of identifying and treating occult OSA).

Model Structure

The tree consists of a decision node and three main branches representing strategies to approach undiagnosed OSA in a low-risk population. Every branch after the decision node is a chance node, that is, each binary pathway option is determined by a probability. Names of pathways are given above the lines, whereas the probability values associated with the path are given below the lines. The "#" sign indicates the complement of the probability value given on the upper branch of each chance node. The triangles indicate terminal nodes, where the costs of each step in the corresponding pathway are collected.

Model Parameter Estimates and Assumptions

We used model parameter values from the decision analysis of Pietzsch et al.[20] The cost of OSA testing with a typical "level 3" home monitor was $210 per person for a single-night test; we included a 10% failure rate, requiring repeat testing, such that the cost was adjusted upward by 10% to $231 per person. The cost of c*ontinuous positive airway pressure* (CPAP) treatment per year includes regular replacement of disposable equipment such as tubes and filters ($114 per year), and two office visits per year ($180 per year). We estimated the cost of a machine at $1,200, assumed to be spread over 10 years (assuming it would need to be replaced every 10 years). Thus, the total CPAP cost per person per year was thus the sum of these: $114 + $180 + $120 = $414 per year. The cost associated with rejecting CPAP after a trial period of home use was assumed to be the cost of a 3-month rental ($112 × 3 = $336) plus a single clinic visit ($90), for a total one-time cost of $426 per person. The cost of PSG, which was assumed to be a single split-night study, was $891. We did not discount costs over time, nor did we model the possibility of individuals initially accepting CPAP rejecting it at a later date, or of those rejecting it initially reconsidering it at a later date. We did not model the human cost of durable medical equipment company staff performing an initial setup. The sensitivity and specificity values for split-night PSG and for home monitor are shown in Table I. The baseline values for sensitivity and specificity of the screening inventory is taken from Chung et al,[21] as determined for the binary detection of OSA when defined by the cutoff value of AHI > 5.

Estimating the performance cost associated with untreated OSA is not straightforward. There is likely to be a distribution of potential costs associated with the spectrum of performance consequences, such as risk for motor vehicle or on-the-job accidents, the costs associated with such accidents, and the impact of poor performance on different types of work-systems. We simplified this complex problem by assuming as a baseline estimate that untreated OSA conferred a 20% reduction in work efficiency. Assuming an annual salary of $50,000, the reduction in work efficiency would amount to $10,000 per year. We performed several sensitivity analyses involving this variable, not only because it is the most uncertain of the model, but also because the plots allow one to see how this value alters the optimal decision. The duration of service no doubt involves many factors and accordingly was subjected to sensitivity analyses.

TABLE I. Parameter Estimates for the Baseline Model

Parameter	Base Value	Parameter	Base Value
Sensitivity Home Monitor	0.91[a]	Cost Screen	$10[c]
Specificity Home Monitor	0.83[a]	Cost Home Monitor	$231[a]
Sensitivity PSG	0.89[a]	Cost PSG	$891[a]
Specificity PSG	0.94[a]	Cost CPAP	$414/Year[a]
Sensitivity Screen	0.84[b]	Cost CPAP Reject	$426[a]
Specificity Screen	0.56[b]	Cost UnTx OSA	$10,000/Year[c]
Pretest OSA	0.05[c]	p(Accept CPAP if OSA)	0.70[c]
Duty Years	20[c]	p(Accept CPAP if no OSA)	0.25[c]

[a]Pietzsch et al.[20] [b]Chung et al.[21] [c]Estimated.

We estimated the cost associated with administering a simple screening test as $10, the probability of accepting CPAP as 70%. We made the conservative assumption that the probability of continuing with CPAP in the absence of OSA as 25% (the true value is not known, and may be much lower).

At the terminal nodes of each pathway, the costs are calculated in a weighted fashion according to the probabilities at each chance node and are evaluated from the perspective of an individual across the time horizon of the duration of active duty. The costs for the "do nothing" branch include only the costs of untreated OSA per year, multiplied by duty years. For the Screen branch, the one-time costs include administering the screen, the PSG for those testing positive, and the cost of rejecting CPAP. Accumulated costs per year of active duty include the cost of CPAP treatment per year, and the cost of untreated OSA per year. For the Home testing branch, the one-time costs include administering the home monitor (adjusted for the 10% chance of needing to repeat this one more time), and the cost of rejecting CPAP after a brief home trial of treatment. Accumulated yearly costs for this branch, like the others, include the costs of untreated OSA and the cost of ongoing CPAP treatment.

RESULTS

Model Structure

In this decision analysis, we assumed three strategies for approaching undiagnosed OSA (Fig. 1). Each strategy, represented by the first branches of the tree stemming from the decision node, will be evaluated in terms of the expected cost of the decision, which incorporates costs downstream of the decision path. The "do nothing" branch simply reports the cost associated with untreated OSA in the subset of the population defined by the pretest probability of OSA. The "screen" branch employs a screening test to determine who will undergo laboratory PSG, which in this model is assumed to be conducted as a split-night study. This is a conservative estimate of cost, by avoiding the expense associated with a two-PSG approach (one diagnostic and one titration). The "home monitor" branch employs a device used in the home to detect OSA.

For the screen and home monitor branches, the probability of each possible outcome of testing is given by chance nodes, and include true positive and false positive (for each positive test result) and true negative and false negative (for each

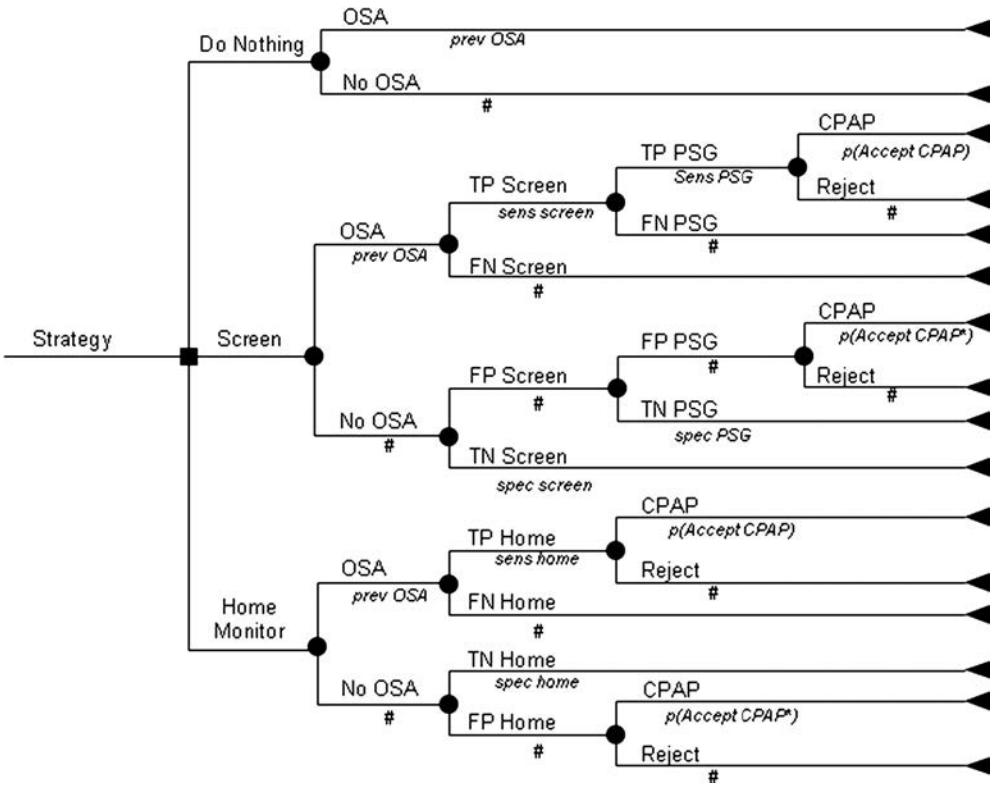

FIGURE 1. Model structure. The Decision Node (square) is shown at the left ("Strategy"). Each chance node is given by a circle from which two branches project, each with a probability under the path line (italics), and a descriptive name above the path line. The "#" sign indicates the complement of the probability given on the other path line of each pair. The terminal nodes, indicated by triangles aligned on the right side, indicate the final step in the model. Costs are accumulated at these nodes (see Methods). "OSA" and "No OSA" refer to the true disease status of an individual; note that it is placed at the first chance node to simplify the tree structure, but would not be known clinically. TP, True Positive; FP, false positive; TN, true negative; FN, false negative; PSG, polosomnogram (split-night); prev, prevalence; sens, sensitivity; spec, specificity. The probability of accepting CPAP given true OSA is *p(AcceptCPAP)*, While the probability of accepting CPAP given no OSA is *p(AcceptCPAP*)*.

negative test result). The tree simplifies the clinical approach to OSA as follows. For the screening branch, one administers a simple screening test, and only those with positive results are sent for laboratory PSG. Those testing positive in this setting are given CPAP. For the home monitoring branch, one administers a device to quantify OSA in the home setting, and only those with positive test results are given CPAP. Those receiving CPAP may or may not accept the treatment after a trial period. Note that the pretest probability in this model refers to the prevalence of undiagnosed OSA; we do not consider costs associated with the diagnosis and management of OSA in the course of routine clinical care. Thus, the model is meant to provide insight into how to approach the problem of occult OSA in a large population with presumably low OSA risk. We note that considering whether AHI > 5 or AHI > 15 is the pertinent cutoff is contained in the pretest probability parameter. That is, if the prevalence of AHI > 5 is 5%, then the prevalence of AHI > 15 might be, say, 2%. Thus, one can perform sensitivity analysis of the prevalence of undiagnosed OSA as a proxy to also consider what severity of OSA is relevant to treat.

The baseline parameter values are shown in Figure 1 and also listed in Table I. A detailed description of the assumptions underlying each parameter is given in the Methods section. Analysis of the model using the baseline parameter values indicated that the home testing arm was favored in terms of cost. Specifically, over the 20-year time horizon, doing nothing costs $10,000 per person, whereas the screen option costs $5,468 per person, and the home testing option costs $4,516 per person. Note that these values are per person over 20 years, as time is included as a variable in the model; the per year cost is 10,000/20, or $500 per person per year. Considering there are approximately 1,000,000 active duty military personnel, this would amount to an expected cost savings between doing nothing and the favored approach of population home testing of approximately $5,000 × 1,000,000 or $5 billion ($250 million per year).

We emphasize that the process of decision modeling necessarily involves uncertainty with regards to the model parameters. This can be as a result of uncertainties in the published literature, or in whether a particular patient is sufficiently similar to those enrolled in clinical trials to extrapolate the results to clinical care. Performing sensitivity analyses addresses uncertainty in particular parameters by systematically varying them and re-evaluating the model results. In the subsequent sections, we will perform one-way and two-way sensitivity analysis to evaluate the impact of uncertainty in key parameters on the preferred approach using our model.

One-Way Sensitivity Analysis

To determine how uncertainty in key parameters will influence the costs associated with each branch of the initial decision node, we conducted a series of one-way sensitivity analyses, in which a single variable was evaluated across a range of possible values, while holding all other parameter values constant. In each case, the outcome is expressed as the expected value of cost, across the active duty duration, per individual.

Varying the cost of untreated OSA revealed that doing nothing was the most expensive option, even for a very low annual cost of untreated OSA of approximately $1,000 (Fig. 2A). The crossover point was approximately $1,500 when the duty years value was set at 10 (data not shown). Although we used a 20-year service duration for the base case above, here and subsequently we used a 10-year time horizon that may be more realistic of the spectrum of service durations throughout the population, and will be a more conservative measure of cost (i.e., favoring do-nothing).

Varying the pretest probability of undiagnosed OSA revealed that doing nothing was the most expensive option for prevalence values above 0.5% (Fig. 2B). The crossover point was approximately 0.8% when the duty years value was set to 10 (data not shown).

Varying the duration of service (duty years) revealed that doing nothing was the most expensive option for durations of service greater than 1 year (Fig. 2C). The crossover point increased to 2 years when the annual cost of untreated OSA was decreased to $5,000 (data not shown).

Varying the cost of home testing (Fig. 2D), the probability of accepting CPAP given the presence of OSA (Fig. 2E), or the probability of accepting CPAP given the absence of OSA (i.e., false positive individuals), each showed that doing nothing remains clearly more expensive across a range of values. Additionally, varying the annual cost of CPAP from $200 to $800 showed continued preference for the home monitor pathway (data not shown), similar to the results of home testing analysis (Fig. 2D).

In all of the one-way analyses (including those indicated as not shown), the screen branch was somewhat more expensive than the home monitor branch.

Two-Way Sensitivity Analysis

In a series of two-way sensitivity analyses, we evaluated how variation in the values of pairs of parameters might alter the preferred strategy. These analyses revealed several interesting findings of practical relevance to approaching OSA in low-risk populations.

Varying service duration and cost of untreated OSA revealed a strong preference for the home monitor branch over doing nothing (Fig. 3A). The contour border between these two strategies indicates that the minimum cost of untreated OSA required to favor the home monitor branch rapidly decreases as service duration increases. In other words, doing nothing is favored from a cost standpoint mainly when service duration is short.

Varying pretest probability of undiagnosed OSA and cost of untreated OSA similarly revealed a strong preference for the home monitoring strategy over doing nothing (Fig. 3B). The contour border between these two strategies indicates

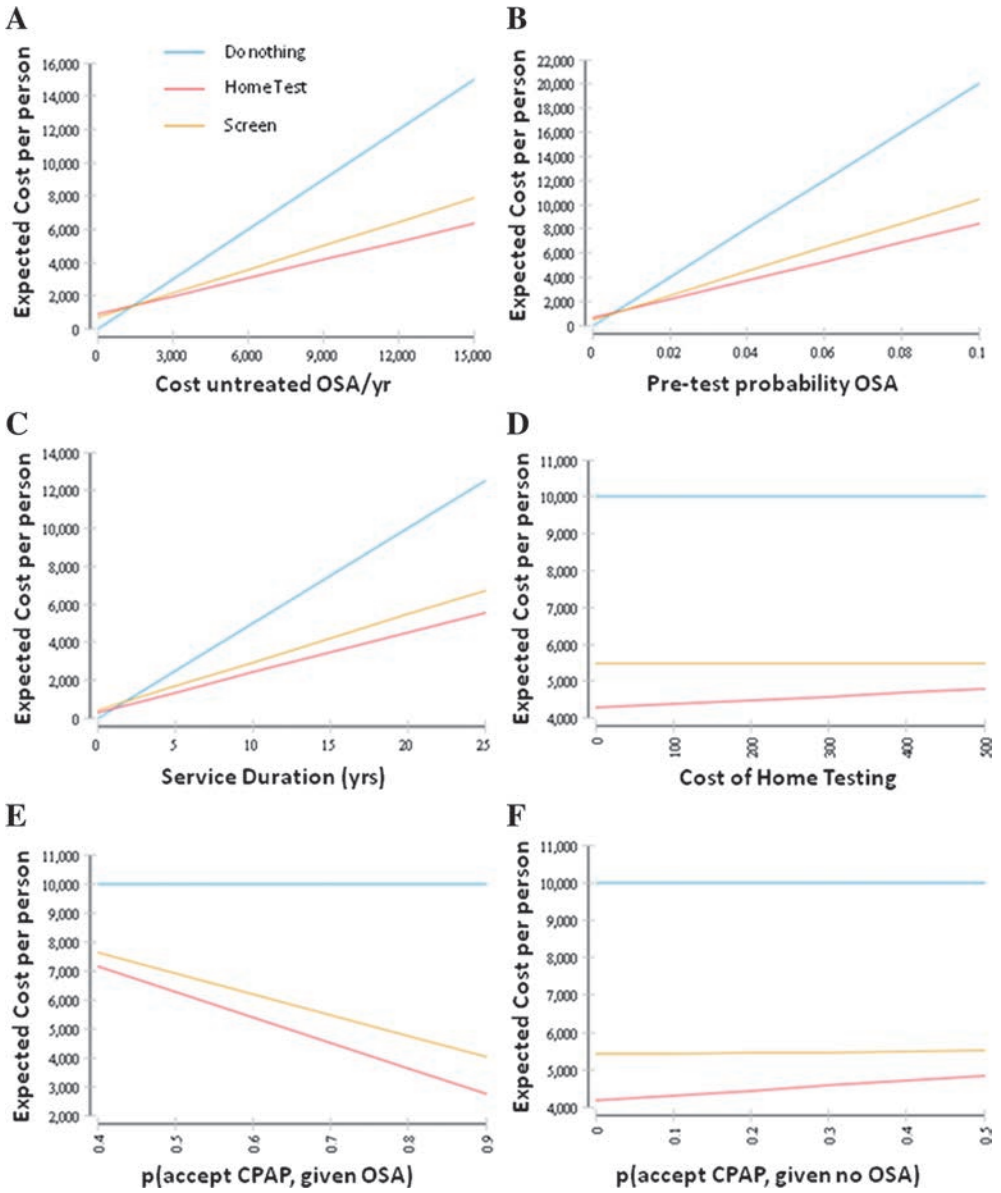

FIGURE 2. One-way sensitivity analyses. The expected costs incurred, per person, is shown across variation of several parameters, including (A) the cost of untreated OSA per year, (B) the pre-test probability or prevalence of untreated OSA, (C) the duration of active duty in years, (D) the cost of home testing per person, (E) the probability of accepting CPAP among those individuals with OSA, and (F) the probability of accepting CPAP among those individuals without OSA. In each panel, the plots include the costs associated with the do nothing branch (blue), the screen branch (red), and the home monitor branch (yellow).

that the minimum cost of untreated OSA required to favor the home monitor branch rapidly decreases as the pretest probability of undiagnosed OSA increases. Repeating these two-way analyses assuming marked improvement in the screening test specificity to 84%, which would make the screen superior to any current validated inventory, increased the parameter space favoring the screen strategy, but home testing remained the optimal choice for the majority of the parameter space (data not shown).

Given that the performance of the screen branch depends on the performance characteristics, and to allow for the potential for improved (yet inexpensive) screens to be developed in the future, we conducted two-way analyses on the sensitivity and specificity of the screen when the pretest probability of undiagnosed OSA was either 2.5% (Fig. 3C) or 5% (Fig. 3D). We fixed the service duration at 10 years, and the cost of untreated OSA at $5,000 per year, as more conservative estimates that occurred near the "elbow" of the contours shown in the one-way sensitivity analysis (Fig. 2). The results show that an improved hypothetical screening test must be considerably more accurate than currently available screens in order to favor the screen branch in terms of cost. Note that the higher pretest probability (5%) of undiagnosed OSA is shown to require better screen performance in order to favor the

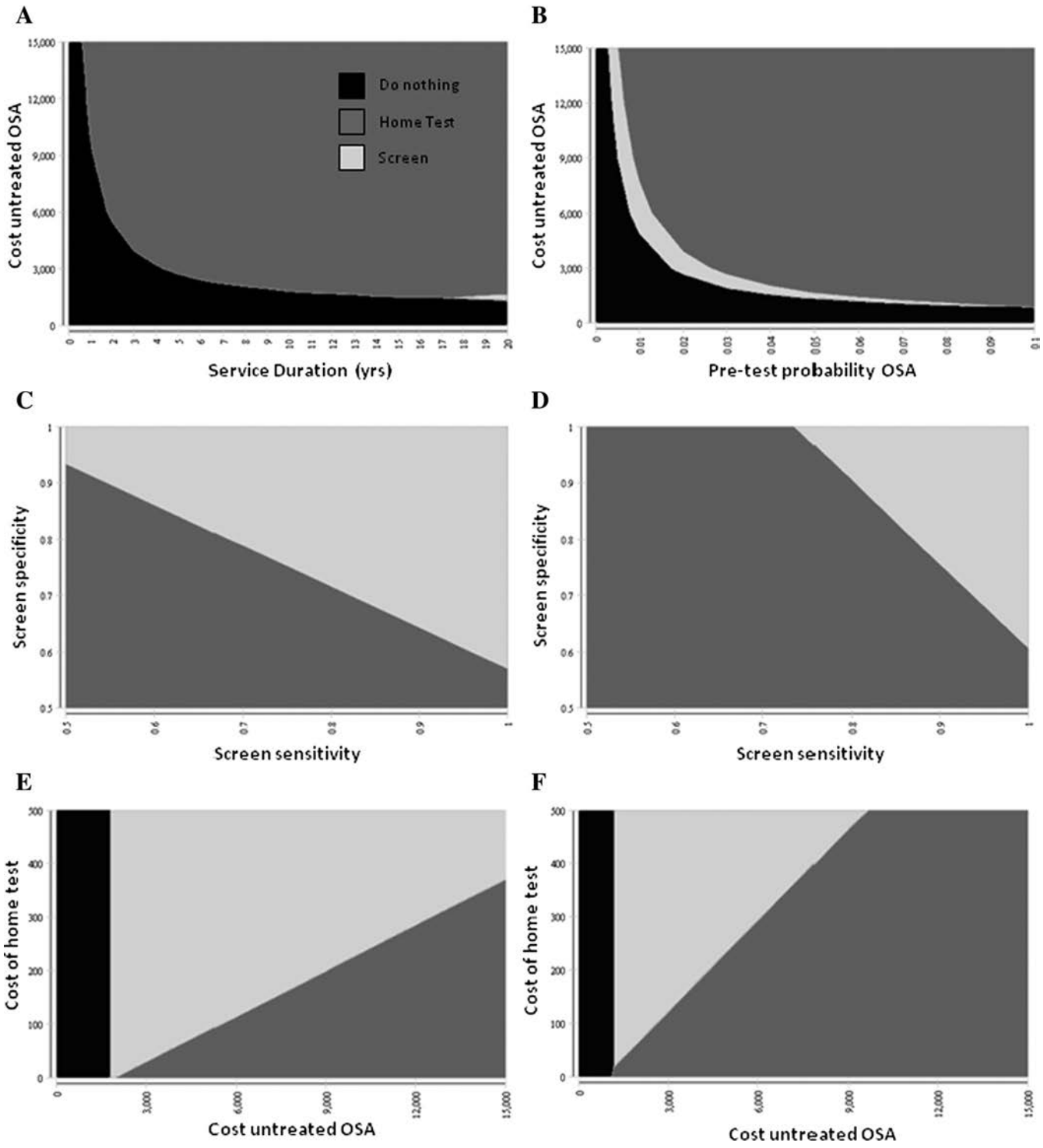

FIGURE 3. Two-way sensitivity analyses. (A) When varying the cost of untreated OSA and the service duration, the home monitor branch (red) is favored over doing nothing (blue) for most of the parameter space. The screen branch is a thin line at the interface of these two options, and is not well visualized. (B) Similarly, when varying the cost of untreated OSA and the pretest probability of undiagnosed OSA, the home monitor branch (red) is favored over doing nothing (blue) for most of the parameter space (and again the screen option is poorly visualized in between these options. When varying the sensitivity and specificity of the screen tool, the screen (yellow) is favored for a larger parameter space when the pre-test probability of undiagnosed OSA is 2.5% (C) than when it is 5% (D). Conservative estimates of the cost of untreated OSA ($5,000 per year) and duty duration (10 years) were implemented in panels (C) and (D). When varying the cost of home monitor administration and the cost of untreated OSA, the home monitor branch is favored for most of the parameter space when the pre-test probability of OSA is 2.5% (E) and more so if it is 5% (F). In panels (E) and (F), conservative estimates were implemented for screen performance (84% sensitivity and 84% specificity) and active duty duration of 10 years.

screening strategy. This is a consequence of the false negative risk incurring progressively larger cost burden of untreated OSA as the prevalence increases.

Next, we varied the cost of home testing and the cost of untreated OSA, when the pre-test probability of undiagnosed OSA was either 2.5% (Fig. 3E) or 5% (Fig. 3F). For these plots, we made conservative assumptions regarding the screening test performance improving to 84% sensitivity and 84% specificity, and service duration of 10 years (each of which would be expected to favor screening). These plots show the tendency to favor the home monitor branch as cost of untreated OSA increases. However, certain combinations of low cost of untreated OSA and high cost of home monitor use will favor screening with a tool that has superior sensitivity and specificity than those currently available.

DISCUSSION

Our decision model addresses the important question of balancing the costs of untreated OSA against those associated with large-scale diagnostics and disease management. Our model differs from typical decision analyses of involving OSA in that we focused on costs associated with performance impairments related to untreated OSA, rather than the morbidity and mortality linked to OSA. This model provides a framework for answering key questions, including (1) what range of performance costs attributable to OSA warrant large-scale screening?, (2) what range of expected service time maintains the cost favorability of screening?, and (3) should the diagnostic approach begin with simple screening inventories before PSG, or should large-scale home testing be undertaken? This latter question is of special interest, given that the current American Academy of Sleep Medicine guidelines indicate that home sleep devices should only be used in those at high risk of OSA.[13] The recommendations of this guideline were based on available evidence for diagnostic accuracy (which was felt to be limited), and focused on the use of home devices to target the confirmation of OSA in patients with high clinical suspicion, rather than using the home monitors for screening. In contrast, our results indicate that in certain settings, even modest costs attributable to untreated OSA outweigh the cost of large-scale screening, even for very low OSA prevalence (≤5%). Our results also indicate that screening inventories can theoretically be less expensive than large-scale home testing, though this would require considerable improvements over currently available screening tools.[13]

The Performance Cost of Untreated OSA

This is arguably the most important and also most uncertain parameter in our model. Performance impairment may have consequences spanning work and automobile accidents, as well as general decreased work efficiency. Although the spectrum of potential costs is vast, this is precisely the setting in which sensitivity analyses can prove most useful. Here, we see that the cost of large-scale home testing is less than the cost of untreated OSA even when the performance-associated costs are modest (under $5,000 per year). When considering implementation of OSA testing, a targeted approach to focus on those military personnel serving roles predicted to be most sensitive to sleepiness or attention could further optimize the potential cost savings.

The Role of Risk Stratification With Screening Tools

Ideally, one could use easily acquired demographic or symptom data to risk stratify large populations without incurring substantial cost, such as administering the STOP-BANG inventory to all active duty members. However, our results suggest that the performance of such a screen must have substantially higher performance characteristics (sensitivity and specificity) than currently available tools. Even assuming better performance of the screen strategy in our modeling, the cost of performing home testing on all service members was balanced by even modest costs associated with untreated OSA.

Limitations and Future Directions

Our model has several limitations. We implemented simplifying assumptions to provide a general framework to approach OSA in low-risk populations. For example, we assumed that individuals accepting CPAP continue to use it, and those who reject it do not have the opportunity to reconsider or to pursue CPAP alternatives. We also do not model the infrastructure costs that might be incurred in population screening or capital investment in leasing home monitors. Those who reject CPAP in our scenario might come from either true OSA cases or from false positive cases without OSA—a model incorporating further investigation of CPAP rejection could more closely approximate clinical workflow. Future models may include the long-term costs and treatment benefits associated with OSA, as well as alternatives to CPAP in those who are intolerant but warrant treatment. We limited ourselves here to young healthy population with low OSA prevalence, but as the military population ages, important health problems may accumulate for which OSA is a risk factor (such as hypertension, heart attacks, stroke, and diabetes). Several groups have published cost–benefit decision analyses in this regard.[22–25]

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Mental Health, Help Seeking, and Stigma and Barriers to Care Among 3- and 12-Month Postdeployed and Never Deployed U.S. Army Combat Medics

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ABSTRACT U.S. Army Combat Medic serves as both Soldier and provider of combat casualty care, often in the heat of battle and with limited resources. Yet little is known about their help-seeking behavior and perceived stigma and barriers to care. Participants were three groups of U.S. Army Combat Medics surveyed at 3- and 12-months postdeployment from assignment with line units vs. those Medics who had never deployed to combat. The primary data source was surveys of mental health service utilization, perceived stigma and barriers to care, and depression and post-traumatic stress disorder screens. Medics who received help in the past year from a mental health professional ranged from 18% to 30%, with 18% to 30% seeking mental health assistance from other sources. Previously deployed Medics were more likely to obtain assistance than those who never deployed. Those meeting a mental health screening criteria were more likely to report associated stigma and barriers to care. Findings indicate that Medics in need of assistance report greater perceived barriers to mental health care, as well as stigma from seeking treatment, and that depression may be a salient issue for Medics. The longitudinal nature of the ongoing study will help determine the actual trajectory and onset of depression and post-traumatic stress disorder.

INTRODUCTION

"Sixty-Eight Whiskey" (68W) is the Military Occupational Specialty for the U.S. Army's health care specialist, also known as the Combat Medic. Combat Medics are one of the largest Military Occupational Specialty within the Army, second only to the Infantry. Medics are an integral part of the Army's combat mission, serving in maneuvering or sustainment units, military treatment facilities and clinics. Those serving in maneuvering units are more likely to directly engage the enemy in combat, whereas Medics serving with sustainment units or in military treatment facilities or clinics provide medical support to logistics and personnel services units required to maintain combat operations. This article focuses specifically on U.S. Army Combat Medics who deployed with maneuvering units, particularly Brigade Combat Teams.

Because the U.S. Army relies heavily upon the Combat Medic during war, all Army Medics receive training in Tactical Casualty Combat Care for treating Soldiers directly on the battlefield. Combat Medics are an integral part of the combat mission. During warfare, they deploy with other Soldiers on the front lines, where they provide frontline trauma care, often in the heat of battle, with limited resources, and under enormous stress. They are considered a special subpopulation because of their dual role of both warfighter and health care provider, carefully balancing the emotional burden associated with the responsibility of maintaining the health and well-being of all Soldiers, while facing the potentially life-threatening traumas of war experienced by most Soldiers. Because of their limited numbers and increased rotation on patrols/missions, Medics are likely to report more combat experiences than other Soldiers deployed outside operating bases (Poster presented at the U.S. Army Force Health Protection; "Comparing Combat Medics 3 months postdeployment with MHAT findings: Preliminary analysis of a 3-year mixed methods study designed to build a model of resiliency)." This is important insight, as combat is considered a primary risk factor for post-traumatic stress disorder (PTSD) and comorbid psychopathologies. Although operations in Iraq and Afghanistan have resulted in a steady stream of information on the health behaviors of U.S. service members, there is little research assessing Army Combat Medic behavioral health or their help-seeking behavior following deployment.

Within the military culture, individuals seeking help for behavioral health problems may be stigmatized.[1] This stigmatization may lead those experiencing behavioral health problems to underutilize mental health care. In 2004, Hoge et al reported that of Soldiers who screened positive for a mental health problem, only 23% to 40% sought assistance and of those, only 13% to 27% sought help from a behavioral health provider. Additionally, Soldiers who screened positive for a mental health problem were twice as likely to report

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concerns about possible stigmatization and barriers to seeking mental health care compared to those who screened negative.[2] This lack of health-seeking behavior may continue upon separation from military service. In 2005, the Veterans Administration began expanding mental health service capacity in response to the Operation Enduring Freedom/Operation Iraqi Freedom (OEF/OIF) conflicts.[3] However, fewer than 10% of Veterans with newly diagnosed PTSD received the recommended number and intensity of mental health treatment sessions within the first year of diagnosis. Thus, it appears that a substantial proportion of those suffering from mental health problems either do not access, delay, or fail to complete an adequate course of mental health treatment.[3]

This study presents novel findings associated with mental health and help-seeking behaviors among U.S. Army Combat Medics. Although other studies have examined samples consisting of various health care providers (e.g., medics, nurses, techs, doctors, radiologists),[4–6] this is the first study to utilize a homogenous sample of health care providers who served in combat units and experienced war firsthand. This article presents the perceptions of Combat Medics in terms of help-seeking behavior and stigma and barriers to care. Based on previous research on the developmental trend of PTSD among service members, it was expected that Medics 12 months postdeployment would report higher levels of depression and PTSD compared to Medics 3 months postdeployment and Medics who had never deployed to combat.[7] In accordance with past research with military populations, it was also hypothesized that Medics who screened positive for a mental health issue would also endorse more issues with stigma and barriers to care than those who screened negative.[2] Lastly, we explored the help-seeking behavior of Soldiers who screen positive for mental health issues.

METHODS

Sample Design and Participants

Data were drawn from the first year of an ongoing 3-year longitudinal study on behavioral health among U.S. Army Combat Medics. Complete sampling techniques and sample descriptive characteristics are available elsewhere.[8]

Participation was open to all European and Fort Hood, Texas, U.S. Army Combat Medics, and consisted of 799 Medics. All participants were enlisted Soldiers, in one of two groups: E1–E4 (no leadership responsibilities) and E5–E9 (Non-Commissioned Officers). Those with combat-related physical injuries requiring overnight hospitalization and those under the age of 18 were excluded. The main study excluded Soldiers with combat-related physical injuries requiring overnight hospitalization during their most recent deployment because of (a) the high correlation of physical injury and mental health issues and (b) time out of theater. Eligible participants attended a briefing where they were informed about the study and written informed consent was obtained.

For this article, Medics were categorized into three groups: 347 Combat Medics surveyed 3 months after returning from a 12-month deployment to Iraq or Afghanistan and assigned to maneuver units; 196 Combat Medics who were surveyed 12 months after completing a yearlong deployment with maneuvering units; and 256 Combat Medics who had never been deployed to a theater of operations. This latter group served as a comparison group to which the others are compared. The nondeployed group, while not deployed to a theater of operations within the past 12 months, provided medical support across Europe. Most had deployed to Iraqi theater of operations, and all had been assigned to Brigade Combat Teams.

Data Collection

Initial data were collected by the research team in person between November 2009 and May 2010. The Europe Regional Medical Command structure approved this study and identified elements meeting our criteria and our time frame, and coordinated with the local command structure for our visit. Research team members then visited each installation across Europe and then at Fort Hood to recruit participants. Eligible participants attended a briefing where they were informed about the study and provided time to ask questions regarding the study. An ombudsman was utilized. Written informed consent containing statements about the purpose of the survey, the voluntary nature of participation, and methods used to ensure participant confidentiality and anonymity was obtained. No members of the command structure were present.

The combined response rate among Soldiers who were briefed was 96%. The rates of missing values for individual items in the survey were generally less than 10%. Because the amount of missing data was so small, listwise deletion of missing data was utilized in analyses, leaving us with more than 20 cases per independent variable. The high response rate was probably due to a number of factors, including the use of both active duty and civilian researchers as well as the overwhelming Command support for this research. The study was conducted under a protocol approved by the Institutional Review Board of the Brooke Army Medical Center.

Measures

Validated measures used in larger military population health samples were utilized in this study and originated from the previous Mental Health Advisory Team[9] studies of the U.S. Army and the "Manual for the Deployment Risk and Resilience Inventory (DRRI): A Collection of Measures for Studying Deployment-Related Experiences of Military Veterans."[10] Psychometric properties for the Mental Health Advisory Team measures are provided elsewhere.[9] For this study, participants responded to a survey questionnaire containing demographic items and measures of mental health service utilization, perceived stigma and barriers to care, and depression and stress symptoms.

TABLE I. Perceived Stigma and Barriers to Seeking Mental Health Services Among Study Participants

	Total Sample (N = 799)		Met Screening Criteria (n = 117)		Did Not Meet Screening Criteria (n = 679)	
	f	%	f	%	f	%
Perceived Barrier						
1. It is difficult to schedule an appointment.***	187	23	50	43	137	20
2. There would be difficulty getting time off for treatment.***	180	23	49	42	131	19
3. I don't have adequate transportation.**	48	6	14	12	34	5
4. My leaders discourage the use of mental health services.*	35	4	10	9	25	4
5. I don't know where to get help.	25	3	7	6	18	3
Perceived Stigma						
1. My unit leadership might treat me differently.***	291	36	73	62	217	32
2. I would be seen as weak.***	244	31	62	53	181	27
3. Members of my unit might have less confidence in me.***	263	33	58	50	203	30
4. My visit would not remain confidential.***	194	24	43	37	151	22
5. It would harm my career.***	168	21	40	34	126	19

Summary statistics exclude missing data. Asterisks for a given item indicate a significant difference between those who met and did not meet the screening criteria for some mental health issue (depression and/or PTSD). *$p < 0.05$, **$p < 0.01$, ***$p < 0.001$.

The 9-item Patient Health Questionnaire[11] was utilized to screen for major depression. Instructions were to indicate how bothersome each symptom had been in the past 2 weeks using a 4-point scale. Responses were "not at all," "several days," "more than half the days," or "nearly every day." Spitzer et al[12] recommend using a cutoff score of 10 or greater, which has sensitivity for major depression of 88%, a specificity of 88%, and a positive likelihood ratio of 7.1. For this study, the measure yielded a Cronbach's α of 0.88.

Post-traumatic stress symptoms were measured with the PTSD Checklist (PCL).[12] The PCL is a 17-item self-report rating scale designed by the Department of Veterans Affairs' National Center for PTSD to evaluate PTSD symptom categories. Two versions of the PCL were utilized, although the differences are slight. The PCL-M is a military version and questions refer to "a stressful military experience." The PCL-C is a general civilian version that is not linked to a specific event; the questions refer to "a stressful experience from the past." Because of the lack of military exposure, the Medics who had not deployed—the comparison group—were administered the PCL-C. The response structure and scoring of the two versions is identical. Respondents indicated how bothered they had been in the past month utilizing a 5-point scale ranging from "Not at all" to "Extremely." Results were scored in accordance with DSM-IV-TR critera,[13] as positive if participants reported at least one intrusion symptom, three avoidance symptoms, and two hyperarousal symptoms that were categorized at the moderate level or higher and had a sum score greater than 50.[14] The psychometric properties of this measure are well-established in the literature.[15–17] The Cronbach's α obtained for this sample was 0.95 for each of the checklists.

Mental health service utilization was measured by asking participants if they had received counseling/mental health services for a stress, emotional, alcohol, or family problem within the past year from a mental health professional, combat stress control professional, general medical doctor, military chaplain, Medic in your unit, or another Soldier (other than a Medic). Responses were dichotomized into a yes/no format and reported as "mental health professional" or "any other help." This is similar to work on military populations presented by Hoge et al.[2]

Perceived stigma and barriers to care were measured with five items each originally developed by Hoge et al.[2] Participants rated concerns that might affect the decision to receive mental health services. Responses ranged from "strongly disagree" to "strongly agree." A positive response was considered an endorsement of either "agree" or "strongly agree." Cronbach's α of 0.84 and 0.79 were observed for stigma and barriers to care, respectively. Items are available in Table I.

Quality Control and Statistical Analysis

Analyses were performed using SPSS Version 20. Analyses were conducted with listwise deletion of missing data and consisted of calculating frequencies for demographic characteristics and χ^2 tests to determine if deployment status was significantly associated with demographic characteristics. Proportions were calculated for individuals meeting the screening criteria for PTSD or depression, participants engaging in health-seeking behaviors in the past year, and individuals who positively endorsed stigma and barrier to care items. χ^2 tests were conducted to determine if screening outcomes (positive vs. negative) were significantly associated with the endorsement of stigma and barriers to care. Lastly, sequential logistic regressions were conducted to determine if deployment status would predict behavioral health outcomes.

RESULTS

Demographic Characteristics

Demographic characteristics for groups are provided in Table II. Differences in groups were noted for demographics to include gender, ($\chi^2(1, N = 795) = 53.68$, $p < 0.001$),

TABLE II. Demographic Characteristics by Deployment Group

Characteristic	Total Sample (N = 799)		Never Deployed (n = 256)		3 Months Postdeployment (n = 347)		12 Months Postdeployment (n = 196)	
	f	%	f	%	f	%	f	%
Rank/Grade***								
E1–E4	495	62	202_a	79	222_b	64	71_c	36
E5–E9	303	38	54	21	124	36	125	64
Sex***								
Male	587	74	146_a	57	285_b	82	156_b	80
Female	208	26	109	43	61	18	38	20
Race/Ethnicity								
White	539	69	164_a	65	248_b	73	127_{ab}	66
Black	123	16	38	15	49	14	36	19
Other	122	15	50	20	43	13	29	15
Education*								
High-School or Less	200	25	67_{ab}	26	97_a	29	36_b	19
Some College	526	67	173	68	209	61	144	75
College Graduate	59	8	14	6	34	10	11	6
Marital Status**								
Not Married	303	38	110_a	43	138_a	40	55_b	28
Married	489	62	144	57	205	60	140	72
Deployment								
OIF	511	66	0	0	336	98	175	93
OEF	61	11	0	0	20	11	41	39
	M	SD	*M*	SD	*M*	SD	*M*	SD
Age***	28.11	6.48	25.86_a	6.01	27.97_b	6.16	31.32_c	6.36

Summary statistics exclude missing data. Means/frequencies sharing a common subscript are not statistically different at $\alpha = 0.05$ according to the Tukey HSD/χ^2 test procedure. *$p < 0.05$, **$p < 0.01$, ***$p < 0.001$.

age ($t(792) = 43.54$, $p < 0.001$), marital status ($\chi^2(1, N = 792) = 11.65$, $p = 0.003$), education ($\chi^2(1, N = 785) = 13.16$, $p = 0.01$), and rank ($\chi^2(1, N = 798) = 87.04$, $p < 0.001$). Because the passage of time is known to influence these variables by inducing artifactual differences, pairwise analyses between subgroups were not pursued.

Help Seeking

As depicted in Table III, approximately 18% to 30% of all Medics received help in the past year from a mental health professional, with another 18% to 30% of Medics seeking mental health assistance from someone other than a mental health professional (e.g., combat stress control professional, general medical doctor, military chaplain, unit Medic, or other Soldier). Although approximately 25% to 39% of all Medics received some assistance, both groups of previously deployed Medics were significantly more likely to obtain assistance than those who had never deployed with a line unit to a combat zone. Specifically, Soldiers 12 months postdeployment were 1.67 times more likely to have sought assistance from a mental health professional ($\chi^2(1, N = 452) = 9.11$, $p = 0.003$) and 1.70 times more likely to seek mental health assistance from another source ($\chi^2(1, N = 446) = 6.86$, $p = 0.009$) compared to those who had never deployed. Soldiers 3 months postdeployment were 2.35 times more likely to have sought assistance from a mental health professional ($\chi^2(1, N = 603) = 7.10$, $p = 0.01$) and 2.42 times more likely to seek this assistance from another source ($\chi^2(1, N = 600) = 12.46$, $p < 0.001$) compared to those who had never deployed. There were no differences between Soldiers 3 and 12 months

TABLE III. Help-Seeking and Mental Health Issues by Deployment Group

	Never Deployed (n = 256)		Months Postdeployment (n = 347)				12 Months Postdeployment (n = 196)			
	f	%	*f*	%	OR	95% CI	*f*	%	OR	95% CI
Type of Help										
Mental Health Professional	45	18	93	27	2.35***	1.50–3.68	58	30	1.67***	1.26–2.20
Any Other Help	45	18	105	30	2.42***	1.56–3.77	54	28	1.70***	1.28–2.25
Mental Health Issue										
Depression	22	9	57	16	2.47**	1.41–4.31	30	15	2.72**	1.43–5.18
PTSD	10	4	30	9	ns	—	13	7	ns	—

Summary statistics exclude missing data. OR = odds ratio; CI = confidence interval. Multiple binary logistic regression was used to control for demographics characteristics. *$p < 0.05$, **$p < 0.01$, ***$p < 0.001$.

postdeployment for seeking mental health assistance from either a mental health professional ($\chi^2(1, N = 543) = 0.049$, $p = 0.48$) or others, ($\chi^2(1, N = 538) = 0.29$, $p = 0.59$).

Depression and PTSD

Surprisingly, significant associations were not found between deployment status and PTSD screening outcomes ($\chi^2(1, N = 450) = 1.66$, $p = 0.198$). To further investigate these findings, hierarchical binary logistic regressions were conducted to determine the relation between deployment group and positive depression and PTSD screenings, after controlling for variance attributed to participant demographics. The minimum ration of valid cases to the independent variable for logistic regression is 10 to 1, with a preferred ratio of 20 to 1. In this analysis, there were 760 valid cases and 6 independent variables, making the ratio of cases to independent variables 126.67 to 1, which satisfied the sample size requirement.[18] Demographic variables of age, marital status, education, race, and rank were entered in the first step, with deployment group entered into the second step (Table IV). The Omnibus χ^2 for the second block was significant ($\chi^2(2, N = 667) = 13.17$, $p = 0.001$). The Wald criterion demonstrated that deployment status made a significant contribution to prediction (W(2) = 11.83, $p = 0.003$). Specifically, Soldiers 12 months postdeployment were 2.55 times more likely to screen positive for depression than Soldiers who had never deployed ($B = 0.94$, SE = 0.34, Walds χ^2 (1)= 7.47, $p = 0.006$, 95% OR CI [1.30-5.00]). Soldiers 3 months postdeployment were 2.70 times more likely to screen positive for depression, $\chi^2(1) = 11.26$, $p = 0.001$, OR [1.51, 4.82], compared to those who had never deployed. The likelihood of screening positive for depression was not significantly different for Soldiers 3 and 12 months postdeployment ($\chi^2(1) = 0.04$, $p = 0.84$).

A second hierarchical logistic regression was conducted similarly as above for PTSD screening outcomes (Table V). Again, deployment group was entered into the second step after accounting for demographics. The Step 2 block was significant, ($\chi^2(2, N = 769) = 8.80$, $p = 0.01$), indicating a statistically -significant relationship between PTSD screening outcome and the independent variable deployment group after controlling for demographics. The Wald criterion demonstrated that deployment status made a significant contribution to prediction of PTSD (W(2) = 8.10, $p = 0.017$). Specifically, Soldiers 3 months postdeployment were 2.59 times more likely to screen positive for PTSD than Soldiers who had

TABLE IV. Hierarchical Logistic Regression Model for Positive Depression Screen After Controlling for Demographic Variables

Predictors	*B*	*SE B*	Wald's χ^2	df	*p*	OR	95% CI
Step 1: 21.10**, $p = 0.007$							
Gender							
Males	−0.01	0.25	0.001	1	0.98	0.99	0.61–1.63
Grade/Rank							
E1–E4	0.83**	0.27	9.22	1	0.01	2.29	1.34–3.91
Race			5.52	2	0.06		
Black	−0.06	0.33	0.03	1	0.86	0.94	0.49–1.81
Other	0.61	0.27	5.09	1	0.02	1.85	1.08–3.15
Marital Status							
Married	−0.17	0.23	0.54	1	0.46	0.85	0.55–1.32
Age	0.05*	0.02	6.14		0.01	1.05	1.01–1.09
Education			5.85	2	0.06		
Some College	0.54	0.29	3.45	1	0.06	1.71	0.97–3.01
College Graduate	−0.31	0.55	0.31	1	0.58	0.74	0.25–2.18
Step 2: 13.17**, $p = 0.001$							
Gender							
Males	−0.28	0.27	1.07	1	0.3	0.76	0.45–1.28
Grade/Rank							
E1–E4	0.97***	0.28	12.14	1	<0.001	2.64	1.53–4.55
Race			7.46	2	0.02		
Black	−0.01	0.34	0.002	1	0.97	0.99	0.51–1.91
Other	0.74	0.28	7.08	1	0.01	2.10**	1.22–3.62
Marital Status							
Married	−0.17	0.23	0.56	1	0.46	0.85	0.54–1.32
Age	0.04	0.02	3.81	1	0.05	1.04	1.00–1.08
Education			7.27	2	0.03		
Some College	0.62	0.29	4.5	1	0.03	1.87*	1.05–3.32
College Graduate	−0.31	0.57	0.3	1	0.58	0.73	0.24–2.22
Postdeployment Group			11.83	2	0.003		
3 Months	0.99	0.3	11.26	1	0.001	2.70**	1.51–4.82
12 Months	0.94	0.34	7.47	1	0.006	2.55**	1.30–5.00

*$p < 0.05$; **$p < 0.01$; ***$p < 0.001$.

TABLE V. Hierarchical Logistic Regression Model for Positive PTSD Screen After Controlling for Demographic Variables

Predictors	*B*	*SE B*	Wald $\chi 2$	df	*p*	OR	95% CI
Step 1: 5.53, $p = 0.70$							
Gender							
Males	0.05	0.29				1.06	0.60–1.85
Grade/Rank							
E1–E4	0.34	0.3				1.41	0.79–2.52
Race			0.09	2	0.96		
White	–0.1	0.34	0.08	1	0.78	0.91	0.47–1.77
Black	–0.1	0.45	0.05	1	0.82	0.9	0.38–2.17
Marital Status							
Married	0.12	0.26	0.22	1	0.64	1.13	0.68–1.89
Age	0.01	0.02	0.22	1	0.64	1.01	0.97–1.06
Education			3.71	2	0.16		
High School or Less	–0.33	0.58	0.32	1	0.57	0.72	0.23–2.24
Some College	0.32	0.5	0.4	1	0.53	1.37	0.52–3.63
Step 2: 8.80*, $p = 0.01$							
Gender							
Males	–0.18	0.3	0.38	1	0.54	0.83	0.46–1.50
Grade/Rank							
E1–E4	0.44	0.3	2.1	1	0.15	1.55	0.86–2.80
Race			0.4	2	0.82		
White	–0.22	0.35	0.4	1	0.53	0.81	0.41–1.58
Black	–0.17	0.45	0.14	1	0.71	0.84	0.35–2.04
Marital Status							
Married	0.14	0.26	0.28	1	0.6	1.15	0.69–1.93
Age	0.01	0.02	0.05	1	0.82	1	0.96–1.05
Education			4.66	2	0.1		
High School or Less	–0.3	0.59	0.26	1	0.61	0.74	0.23–2.36
Some College	0.42	0.51	0.7	1	0.4	1.52	0.57–4.10
Postdeployment Group			8.1	2	0.02		
3 Months Postdeployment	0.95	0.34	8.04	1	0.005	2.59**	1.34–5.01
12 Months Postdeployment	0.66	0.4	2.73	1	0.1	1.93	0.88–4.22

*$p < 0.05$; **$p < 0.01$; ***$p < 0.001$.

never deployed (B = 0.95, SE = 0.34, Walds χ^2 (1) = 8.04, $p = 0.005$, 95% OR CI [1.34–5.01]). Soldiers 12-months postdeployment were no more likely to screen positive for PTSD than Soldiers who had never deployed, $\chi^2(1) = 2.72$, $p = 0.10$. Further analysis also indicated that Soldiers 3 months postdeployment were no more likely to screen positive for PTSD than Soldiers 12 months postdeployment, ($\chi^2(1) = 0.88$, $p = 0.349$).

Stigma and Barriers to Care

The reported perceptions of stigma and barriers to care between those who screened positive vs. negative for mental health problems were also compared using chi squares (Table I). All perceived barriers and stigmas were significantly different at the $p < 0.05$ level based on meeting psychological screening criteria, with the exception of "I don't know where to get help." Soldiers who meet the screening criteria for any psychological issue were more likely to report issues with stigmas or barriers to care compared to Medics who did not meet screening criteria for any psychological issue. Generally, those who met the screening criteria were two to three time more likely to report concerns about being stigmatized and about other barriers to accessing and receiving mental health services than Soldiers who did not screen positive.

The most frequently reported barriers to care were "difficulty getting time off for treatment" and "difficulty scheduling an appointment." This was the same regardless of screening criteria outcome. The most frequently cited stigmas differed by screening group. Medics who did not meet the screening criteria for any psychological issues most frequently reported "my unit leadership might treat me differently" (36%), and "members of my unit would have less confidence in me" (33%), whereas those who did meet the screening criteria for any psychological more frequently reported "my unit leadership might treat me differently" (62%) and "I would be seen as weak" (53%).

DISCUSSION

To summarize, Combat Medics who deployed with maneuvering units were more likely than their never deployed peers to have needed and sought care for mental health issues. Additionally, those who screened positive for mental health issues were more likely to report concerns regarding stigma and barriers to care than those who screened negative. Participant

responses indicated that stigma was a more salient issue among Combat Medics than barriers to care. Lastly, both groups of deployed Medics were more likely to screen positive for depression than the never deployed comparison group, but there were no statistical differences between Medics 3 and12 months postdeployment after controlling for demographic characteristics. Hierarchical regressions revealed that Soldiers 3 months postdeployment were more likely to screen positive for PTSD than their never deployed peers. However, there was no significant difference in PTSD screenings between Soldiers 12 months postdeployment and the never deployed comparison group of peers. Although findings are novel and beckon for further research to be conducted, these results may have important implications for Medics and other health care professionals who deploy with maneuvering units. Although these findings are novel and require follow up to ascertain issues of delayed onset,[18,19] these results may have important implications for Medics and other health care professionals who deploy with maneuvering units.

Compared to other studies utilizing military samples, findings from this study indicate that Medics may be more inclined to seek mental health assistance (28% to 30%). compared to other studies (Hickling: 1.7% to 14.1%; Hoge: 21% to 27%).[2,6] Although Hickling's study was conducted on health care providers, it should be noted that the study utilized a dataset from the initial years of the OEF/OIF/OND conflicts with a mix of health care providers, to include Medics.

Though Medics may have better access to care because of their close proximity and relationships to health care resources and providers, Medics deployed to the front lines with maneuvering units reported being plagued by the same stigmas as the never deployed baseline comparison group. Combat Medics who need the most assistance appear to be the ones who report greater perceived barriers to mental health care, as well as stigma from seeking treatment. These findings are consistent with previous studies examining the relationship between psychological symptomatology and perceived treatment barriers among service members and suggest that perceptions of and willingness to use care could be negatively impacted by the presence of psychological symptoms.[2,20–23] Likewise, it could be that those service members needing care have actually initiated help-seeking activities in the past, only to realize the difficulty due to barriers and stigma. Although the Army has taken steps to reduce stigma across its ranks,[23–25] it is still very influential among Soldiers, including Medics, who are trained in the identification of Soldiers who may need assistance, as well as where to obtain such services. Certainly, additional research is needed to more fully comprehend the underpinnings of these issues.

Stigma is still influential in decisions to seek care despite Army efforts to reduce it.[23–25] Developing strategies to change the stigma associated with seeking mental health care may be a long and difficult journey. In the short term, leadership could enact change in how services are delivered to and received by service members. Tele mental health has made strides over the years. This technology may be a short-term avenue for military leadership to endorse rather than fighting an uphill battle to change the mindset that is so deeply rooted in the military culture. Findings from this study compared samples of deployed and never deployed U.S. Army Medics screening positive for depression and PTSD. The deployed sample was postdeployed from Iraq. In this study, the proportion of deployed U.S. Army Medics who screened positive for PTSD was higher compared to the sample of U.S. Army Soldier Medics who had never deployed. However, using the same scoring algorithm and cutpoint of 50 as those utilized in this study, Hoge et al[2] reported 12.9% of U.S. Army Soldiers postdeployed from Iraq screened positive for PTSD, a number somewhat larger than the 7% of postdeployed Medics in this study.

In terms of depression, deployed Medics were more likely to screen positive for major depression than fellow Soldier Medics who had never deployed. However, non-Medic Soldiers have reported lower proportions of depression. Using the same cutpoints as those utilized in this, Hoge et al[2] reported 7.9% of US Army Soldiers screened positive for depression compared to 15% of U.S. Army Soldier Medics in the current sample. This is a timely finding, considering the increases in suicide rates among service members, particularly the Army. However, it should be noted that individuals may experience different trajectories of depression, with symptoms occurring before, concurrent with, or after symptoms of PTSD. The longitudinal nature of the ongoing study will help determine the trajectory and onset of depression and PTSD, yielding important research and clinical implications.

This study makes several important contributions. From a clinical perspective, a one-size-fits-all approach to postdeployment mental health care may not apply to all Soldier subpopulations. From a policy perspective, it is important that military leadership accommodate service members so they can access mental health services. Currently, the focus appears to be on developing strategies to change the stigma associated with seeking mental health care. Because of the military culture, this will be a long and difficult journey. A more direct route might be for military leadership to enact change in how services are delivered and received by service members rather than changing the minds of others. Telemental health technologies are more accommodating to Soldier schedules and would eliminate barriers such as the need for excessive travel time and transportation issues. Additionally, allowing former military personnel who are trained clinicians to anonymously provide care may result in more Soldiers seeking needed assistance. The use of former military personnel as trained clinicians may serve to swiftly develop the rapport and trust required to dutifully face one's demons, whereas anonymity can serve to provide a safe environment without repercussion for seeking mental health services. Admittedly, this may not remove the stigma associated with mental health care, but it may ease the anxiety associated with worrying that others will find out about one's help seeking.

With the current high rates of suicide within the military, it is even more important that Soldiers seeking mental health care have access to it. Likewise, those who need the care should not be afraid to seek it.

There are several limitations to this study. First, data were drawn from the first year of a longitudinal study. Additional data will allow for developmental trajectories to be examined. Second, PTSD and depression were based on screening measures and do not provide a definitive diagnosis. Additionally, both the civilian and military versions of the PCL were utilized in this study. Finally, it is unclear if self-reported behaviors generalize to actual care seeking.

To conclude, the results support the notion that Combat Medics who have deployed may be more resilient to the effects of post-traumatic stress 12-months postdeployment, but that depression may be a more lingering issue. Our findings extend the literature examining the relationship between psychological symptomatology and perceived treatment barriers, specifically within a homogenous sample of health care providers, namely Combat Medics. Reducing the perception of stigma and the barriers to care among military personnel is a priority for research, policymakers, clinicians, and leaders who are involved in providing care to those who have served in the armed forces. Future research efforts should continue to evaluate the relationships among psychological symptoms, barriers to care, and mental health care utilization, but should include a sample of Navy Corpsman. Navy Corpsmen are the equivalent of the Army Combat Medic, but serve alongside U.S. Marines rather than U.S. Army Soldiers. Therefore, Navy Corpsmen may be vulnerable to the same risks as Army Combat Medics.

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Symptoms of Psychological Distress and Post-Traumatic Stress Disorder in United States Air Force "Drone" Operators

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ABSTRACT The goal of this study is to repeat a survey administered in 2010 to assess for changes in mental health among United States Air Force aircrew operating Predator/Reaper remotely piloted aircraft, also commonly referred to as "drones." Participants were assessed for self-reported sources of occupational stress, levels of clinical distress using the Outcome Questionnaire-45.2, and symptoms of post-traumatic stress disorder (PTSD) using the PTSD Checklist-Military Version. A total of 1,094 aircrew responded to the web-based survey composed of the commercially available standardized instruments mentioned above. The survey also contained nonstandardized items asking participants to report the main sources of their occupational stress, as well as questions addressing demographics and work-related characteristics. The estimated response rate to the survey was 49%. Study results reveal the most problematic self-reported stressors are operational: low manning, extra duties/administrative tasks, rotating shift work, and long hours. The results also reveal 10.72% of operators self-reported experiencing high levels of distress and 1.57% reported high levels of PTSD symptomology. The results are lower than findings from the 2010 survey and from soldiers returning from Iraq and Afghanistan. Implications of the study and recommendations for United States Air Force line leadership and mental health providers are discussed.

INTRODUCTION

Since the onset of Operations Enduring and Iraqi Freedom, United States Air Force (USAF) Predator/Reaper remotely piloted aircraft (RPA) (commonly referred to as "drones") emerged as critical assets to intelligence, surveillance, reconnaissance (ISR), and close air support operations. Although advancements in satellite communication technology allow Predator/Reaper operators to remain stationed within the nation's borders, the bases are tasked to provide 24-hour support 7 days a week to military missions on the other side of the globe. The increased requirement for mission support has created a rapidly expanding need for Predator/Reaper operators (pilots, sensor operators, and mission intelligence coordinators) to keep pace with the surge in drone operations and the evolving paradigm of this modernized form of warfare.

Previous research identified several potential operational and combat-related stressors routine to the Predator/Reaper drone work environment affecting the health and well-being of operators.[1,2] Operational stressors are those associated with available manpower, equipment, training, schedules, and general resources to accomplish occupational tasks and objectives. Such stressors include, but are not limited to, long hours, rotating shift work, ergonomic design of the work station, sustaining vigilance, and processing continuous auditory and visual data during aerial missions.[3] Combat-related stressors are those associated with direct participation in ISR and weapons deployment missions and include the use of high-definition video feeds to track, target, and destroy enemy combatants and assets; provide force protection to ground troops; and provide surveys of postbattle damage. Although such drone operators are not "deployed" in hand-to-hand combat and are usually protected from direct threat, they are often involved in operations where they witness and make decisions that lead to the destruction of enemy combatants and assets. They can still become attached to people they track, experience grief from the loss of allied members on the ground, and experience grief/remorse when missions create collateral damage or cause fratricide.[1]

The increasing demand for Predator/Reaper drone operations has led to a significant increase in work hours, shift changes, and virtual exposure to streaming data and images of combat operations. However, there is limited research on the impact of this unique form of modern warfare and high operational tempo on the mental health of operators. There is also limited research in assessing if continuously balancing warfighter roles with domestic/personal lives and intermittent (and virtual) exposure to combat elevates their risk for clinical distress and post-traumatic stress disorder (PTSD). It is widely accepted that exposure to combat heightens the risk for emotional problems (e.g., depression, anxiety, PTSD) as well as behavioral problems (e.g., increased alcohol and substance use) in military personnel who have been deployed.[4–10]

Although the media focus on exposure to combat operations as a major problem among Predator/Reaper drone operators,

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recent research found operational stressors to be their primary concern. Chappelle et al[11] surveyed 670 USAF Predator/Reaper drone operators in 2010 from several different squadrons within the United States. The survey asked participants to self-report the main sources of occupational stress affecting their performance and general health. The results revealed the most prominent stressors were (a) long work hours and low manning, (b) rotating shift work, (c) balancing domestic roles and responsibilities with their warfighter role, (d) the ergonomic design of ground control work stations and inefficient computer-based procedures, and (e) sustaining vigilance to continuously monitor high levels of auditory and visual streaming data. Such stressors are not unlike those faced by other USAF "virtual warriors" sustaining around-the-clock operations such as USAF image analysts and intelligence operators,[12] as well as cyber warfare operations.[13] The results of their studies were consistent with an earlier study finding elevated levels of fatigue among USAF Predator drone operators having to sustain around-the-clock shift work.[14]

The term "distress" is used to refer to an unpleasant state characterized by negative emotional (e.g., feelings of anger, agitation, sadness), behavioral (e.g., trouble getting along with others), physical (e.g., difficulty sleeping, fatigue, muscle tension, headaches), and cognitive (e.g., difficulty concentrating, sustaining attention) symptoms. The study by Chappelle et al of Predator/Reaper drone operators surveyed in 2010[11] included a standardized measure of distress (Outcome Questionnaire-45.2[15]) commonly used within USAF mental health clinics. The results of their study revealed approximately 20% of survey participants reported high levels of distress, which may be reasonably perceived to elevate the risk for human factor contributions in USAF drone mishaps.[14,16,17] Elevated distress scores have also been found among those seeking outpatient mental health care.[15] Although there is no published research linking elevated distress scores (as measured by the OQ-45) with a specific mental health diagnoses in civilian or military populations, USAF mental health providers use the instrument and elevations in self-reported distress for augmenting mental health evaluations and monitoring treatment progress for various conditions (i.e., adjustment, anxiety, and mood-related disorders).

In addition to general distress, PTSD is a well-known psychological condition that may develop after exposure to a traumatic event (witness or experience events that lead to actual or threatened death, injury to others) where the individual experienced intense feelings of fear, helplessness, or horror. The exposure is followed by a month-long bout of symptoms that fall within the categories of (a) a sense of re-experiencing the event (e.g., recurrent and intrusive recollections of the event, distressing dreams of the event, acting or feeling as if the traumatic event were recurring, physiological reactivity to cues that resemble an aspect of the event); (b) persistent avoidance of stimuli associated with the event or numbing of general responsiveness (e.g., avoidance of activities that arouse recollections of the event; feeling of detachment from others; restricted range of affect); as well as (c) increased arousal (e.g., difficulty falling or staying asleep, increase in outbursts of anger, hyper-vigilance, exaggerated startle response). It is the clustering, severity, and persistence (i.e., greater than 1 month) of such symptoms accompanied by significant distress and/or impairment in an important area of functioning (e.g., social or occupational) that is required for the diagnosis of PTSD.[18]

Evaluating for symptoms of general psychological distress and PTSD among deployed military personnel supporting combat operations in theater is a standard practice. It is reasonable to consider the same precautions with Predator/Reaper drone operators providing continuous support to battlefield operations. Maguen et al,[19] in a study of over 2,700 U.S. Army service members, found that the soldiers' perception of their role in "killing" and "being responsible for killing" was associated with PTSD symptoms and other emotional problems. The results of the study by Chappelle et al[11] of Predator/Reaper drone operators surveyed in 2010 also included the Post-Traumatic Stress Checklist-Military Version (PCL-M). The authors of the study used a cutoff score of 50 for the PCL-M for identifying those at high risk of PTSD based on the accuracy rates of such scores reported in previous research.[20–23] The results of their study revealed Predator/Reaper drone operators were at higher risk for PTSD (5%) than noncombatant airmen at the same installation (2%). This percentage is significantly less than the estimated 12% to 17% of soldiers returning to the United States following deployment to Iraq or Afghanistan with self-reported high levels of PTSD symptomology.[24]

The survey conducted by Chappelle et al[11] elevated situational awareness to the sources of stress and the mental health of RPA drone operators to their commanders, but it had several shortcomings. The researchers travelled to each unit's location and distributed paper versions of the survey to operators. They arranged to meet with operators in large groups and during pre-/postmission debriefings. The methodology was costly in terms of researcher time, as well as disruptive to the schedule of those already engaged in operational missions. The requirements made the survey difficult to repeat or sustain over prolonged periods of time. As a result, a web-based version of the survey was developed so participants could complete the survey from their work station and researchers were not required to travel.

The goal of this study is to re-administer the mental health survey used in 2010[11] utilizing a more efficient web-based platform to compare results on (a) main self-reported sources of occupational stress and (b) the levels and prevalence of clinical distress and PTSD among operators to those from 2010.

METHODS

Participants

A total of 1,094 Predator/Reaper drone operators participated in the survey across 17 different squadrons based in the

United States. Participants were from Air Combat Command, Air National Guard, and Air Force Special Operations Command squadrons. Based on numbers of assigned personnel, the overall estimated response rate was 49%. The total number of Predator/Reaper drone operators assigned to each unit based in the continental United States was obtained from Air Force operational leadership. This number was then compared with the number of drone operators that participated in the study to obtain an overall estimated response rate. See Table I for demographics of participants in comparison to 2010 study participants.

Instruments

Participants were given a demographics questionnaire to complete, which was composed of items that assessed duty position, rank, gender, age range, marital status, length of time serving in their duty position, average number of hours worked in a typical week, and current shift they were working (day, swing, night). Participants were also asked to report their top occupational stressors that lead to high occupational stress. The demographics questionnaire was developed to ensure anonymity to support self-disclosure in a community where there may be stigma associated with mental health problems.

Outcome Questionnaire (OQ-45.2)

The OQ-45.2 is a self-report instrument assessing symptoms of psychological distress over the last week including difficulties in interpersonal relationships, social roles, and general quality of life and has reasonable reliability and high concurrent validity.[15,25,26] The instrument consists of 45 items, all of which are based on a 5-point Likert-type frequency scale with the values of 0 (never), 1 (rarely), 2 (sometimes), 3 (frequently), and 4 (almost always). Several items are reverse-scored to reduce random responding. The total score on the OQ-45.2 ranges from 0 to 180, with higher scores representing higher levels of psychological distress.[15] A total score of 63 or more may be considered indicative of high levels of distress.[15,26] Concurrent validity estimates for the total score range from 0.64 to 0.88, and test–retest reliability and internal consistency values range from 0.84 to 0.93. The OQ-45.2 is commonly used at mental health clinics on USAF installations to assess psychological

TABLE I. Drone Operator Participant Demographics by Year

Demographic	2010 Survey (N = 670; Estimated Response Rate: 39%)		2012 Survey (N = 1094; Estimated Response Rate: 49%)	
	n	%	*n*	%
Gender				
Male	533	80	965	88
Female	130	19	125	12
No. That Declined to Report Gender	7	1	4	<1
Age				
18–25	259	39	222	20
26–30	202	30	367	34
31–34	101	15	184	17
35–39	60	9	151	14
40+	48	7	168	15
No. That Declined to Report Age	N/A		2	<1
Rank and Duty Position				
Enlisted (Sensor Operator and MIC[a])	453	68	562	51
Officer (Pilot)	217	32	523	48
No. That Declined to Report Duty Position	N/A		9	<1
Marital Status				
Single	298	45	398	36
Married	372	55	692	63
Time on Station				
Less Than or Equal to 24 Months	242	36	637	58
Greater Than 24 Months	428	64	456	42
No. That Declined to Report Time on Station	N/A		1	<1
Shift Schedule				
Standard Day Shift	379	57	195	18
Swing or Night Shift	291	43	893	82
No. That Declined to Report Shift Schedule	N/A		6	<1
Hours Worked Per Week				
Less Than or Equal to 50 Hours	430	65	668	61
Greater Than 50 Hours	240	35	425	39
No. That Declined to Report Hours Worked	N/A		1	<1

[a]Mission Intelligence Coordinator.

distress and track progress among USAF personnel seeking mental health care.

PTSD Checklist-Military Version

The PCL-M is a 17-item self-report screening instrument based on the Diagnostic and Statistical Manual of Mental Disorders-4th Edition criteria for PTSD.[27] The PCL-M is commonly used in the Department of Defense and Department of Veterans Affairs and has excellent reliability, validity, and diagnostic utility.[20,27,28] Participants are asked to rate a list of PTSD-related problems and complaints on a 5-point scale, with each item being scored on a 1 ("not at all") to 5 ("extreme") rating scale. A total symptom severity score ranges from 17 to 85 and can be obtained by summing the scores from each of the 17 items. A cutoff score of 50 was used for identifying those at high risk of PTSD based on previous research evaluating specificity, sensitivity, and accuracy of PCL cutoff scores.[20–23] When conducting research with the goal of population prevalence estimates (e.g., excluding individuals who do not meet diagnostic criteria for PTSD), utilization of higher cutoff scores (i.e., 50 and above) with the PCL-M is recommended.[22,23] Research with the PCL-M indicates a total cutoff score of 50 correctly identifies 90% or more of those diagnosed with PTSD while minimizing false positive error rates.[23]

Procedure

Requests for participation was sent by USAF group commanders via a mass e-mail to all drone operators assigned to operational units in the United States. The request to participate came from USAF group commanders to validate line operational endorsement and encourage participation. However, to mitigate the potential for coercion, the group e-mail request to participate informed drone operators that participation was voluntary and responses were anonymous. The voluntary and anonymous nature of the survey was to promote participation and self-disclosure. The group e-mail request for participation had an Internet link to the USAF School of Aerospace Medicine (USAFSAM) web-based survey that contained an opening page with an introductory script further explaining the study was conducted by independent researchers and participation was voluntary and anonymous.

Furthermore, before proceeding, participants were asked to respond to a question asking if they understood the nature, purpose, instructions of the survey, and were voluntarily consenting to participate. Those who endorsed "yes" were then allowed to proceed and take the survey. Those who endorsed "no" were not given the survey and redirected to another web page that instructed them on how to contact the independent researchers of the study for additional information. A total of two drone operators, who endorsed "no," contacted the researchers to clarify the purpose of the study.

Additionally, it was stated in the group e-mail request to participate that the results of the survey would be used to help line operator leadership understand the sources and current levels of distress among drone operators. The introductory script on the opening page of the USAFSAM survey further explained to potential participants the nature, purpose, and instructions of the study. The introductory page also informed participants that operational leadership would not have access to individual responses and that results were presented in a summarized format. Potential participants were informed the results would also be utilized by medical leadership to consult with USAF commanders on areas of concern and for developing strategies to mitigate stressful working conditions. The introductory script informed participants they could withdraw at any time without negative repercussions.

The survey was distributed electronically via a Department of Defense-approved electronic survey tool. The survey was open to USAF Predator/Reaper drone operators across the United States over a 4-week period and re-advertised during the second week. In general, it took participants 20 minutes to complete the survey. Participants who completed the survey were instructed on how to obtain the results of the study and when information would be available. Results were aggregated at the squadron level without any identification of individual responses.

Data Analysis

Total scores for the OQ-45.2 and PTSD measures were obtained by summing item responses that corresponded to each scale. Group means and standard deviations were calculated, as well as logistic regression and χ^2 analyses, to identify occupational and demographic predictors of self-reported clinical distress and PTSD symptomology.

RESULTS

Sources of High Occupational Stress

Participants' responses to the item asking them to identify and/or write and rate their top three occupational stressors were analyzed. Three behavioral science researchers performed a qualitative analysis on the content of responses. The notes from each research team member were cross-validated and consolidated into a list of stressors reported to lead to high levels of stress (rated 8 and above on the 0–10 scale) among the drone operators (Table II). Responses appearing to label similar stressors were consolidated under a single category. For example, terms such as "rotating shift schedule every 30 days" and "switching from day to swing shift" were categorized under the main stressor of shift work.

Clinical Distress

The average OQ-45.2 total score was 36.41 (standard deviation [SD] = 20.00) for survey participants. Individuals were separated according to those with OQ-45.2 total scores at and above 63 and those below 63. A total of 116 (11%) participants had high total distress scores at or above 63. The percentage of individuals meeting the OQ-45.2 total score cutoff

TABLE II. Top Self-Reported Occupational Stressors Leading to High Levels of Stress

2010 Survey (n = 670; Estimated Response Rate 39%)	2012 Survey (n = 1094; Estimated Response Rate 49%)
Low Unit Manning Not enough manning to cover required shifts and tasking requirements, cancelled vacation time/work leave to sustain high operational tempo	Low Unit Manning Not enough manning to cover all shifts and tasking requirements, cancelled vacation time/work leave to sustain high operational tempo
Long Hours Working 50+ hours a week to sustain operational mission requirements, 6-day work weeks, 12-hour shifts 4 days in a row	Long Hours Working 50+ hours a week to sustain operational mission requirements, 6-day work weeks, 12-hour shifts 4 days in a row
Rotating Shift Work Rotating every 30 days between day, swing, and night shift to sustain around the clock operations; uncertain predictability of shift rotation schedule	Rotating Shift Work Rotating between day, swing, and night shift to sustain around the clock operations; uncertain shift rotation schedule
Deployed In-Garrison Status Daily balance of warfighter role with domestic tasks and duties, access to base resources during swing/night shift, juggling family obligations and relationships	Extra Duties/Administrative Tasks Assignment of additional supervisory, training, or administrative tasks in addition to standard operational duties; line-of-sight taskings without consideration of equitable workload distribution

Combat operations and/or participation in ISR and weapons deployment were not listed as top stressors by any RPA or intelligence operators participating in this study.

(63 or more) as compared with 2010 survey results is shown in Figure 1. Logistic regression revealed shift work (swing/night shift), working 51 or more hours a week, and being assigned to duties for 24 or more months were significant predictors of total distress scores (χ^2 [11] = 21.03, $p < 0.05$).

Subsequent odds ratios indicated those working more than 50 hours a week were approximately twice as likely (95% CI = 1.09–2.42), those working swing/night shift were approximately twice as likely (95% CI = 1.04–3.53), and those working in their current duties for greater than 24 months were also approximately twice as likely (95% CI = 1.07–2.46) to report OQ-45.2 total scores at or above 63.

Post-Traumatic Stress

The average PCL-M total score was 22.91 (SD = 8.29) for survey participants. Individuals in each group were separated according to those with PCL-M total scores at and above 50 and those below 50. A total of 17 (2%) participants had PCL-M total scores of 50 or higher. The percentage of individuals meeting the discretionary PCL-M cutoff (50 or more) as compared with 2010 survey results is also included in Figure 1. The number of participants with high symptomology was too small to perform logistic regression analyses. However, c^2 analyses were significant (c^2 [11] = 7.46, $p < 0.01$), and subsequent odds ratios indicated those working more than 50 hours a week were approximately four times more likely (95% CI = 1.36–11.16) to report PCL-M scores at or above 50.

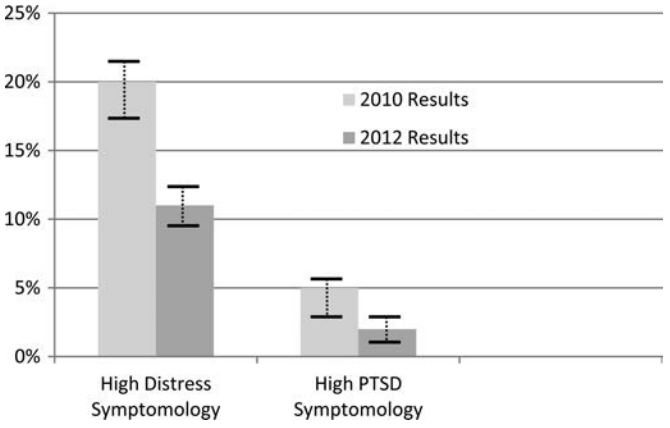

FIGURE 1. Percentage of survey participants endorsing high levels of distress and PTSD symptomology. A total of 95% CI rates for clinical distress range from 17% to 22% (2010) and 9% to 12% (2012), and high-PTSD symptomology ranges from 3% to 6% (2010) and 1% to 3% (2012).

DISCUSSION

The results of the study suggest the most problematic stressors among Predator/Reaper drone operators are operational and include low unit manning, rotating shift work, extra duties/administrative tasks, and long hours. The results of the study are similar to the occupational stressors reported by Predator/Reaper drone operators in 2010,[11] as well as other USAF "virtual warriors" sustaining around-the-clock intelligence exploitation[12] and cyber warfare.[13] The repeated finding of operational stressors, as opposed to combat stressors, as the most problematic self-reported sources of stress is helpful for line commanders and medical personnel in developing interventions for mitigating stress and promoting performance.

Although combat-related stressors were not reported to be a top source of occupational stress, such a finding is interpreted cautiously when evaluating an individual operator. It is possible there are drone operators who perceive the deployment of weapons and exposure to live video feed of combat (i.e., destruction/death of enemy combatants and ground forces) as highly stressful events. As a result, it is recommended military mental health providers continue to monitor the impact of virtual exposure to combat operations and the impact on the emotional well-being of operators.

Given the sensitive, high-demand nature of USAF Predator/Reaper drone operations,[29,30] it is important military commanders gauge the prevalence rates of distress among officer and enlisted airmen engaged in such operations. Results of the

study indicate 1 out of every 10 Predator/Reaper drone operators self-reported high levels of distress. To reach the high distress threshold in this study, such operators needed to endorse a variety of symptoms (e.g., difficulty concentrating and sustaining attention; increased thoughts of worry; difficulty falling and staying asleep, increased feelings of anger, sadness, anxiety; increased alcohol usage; trouble getting along with peers) tied to a decline in their general health and well-being. This includes negative changes in social and interpersonal functioning that increases the difficulty for Predator/Reaper drone operators having to juggle the daily duties of their war fighter roles with their domestic/personal life obligations (and vice-versa). It stands to reason that such distress (whether temporary or chronic) elevates the risk for problems with performance, mishaps, and force sustainment.

Data analyses did not find duty position, gender, marital status, age, or rank to be predictive of higher distress scores. However, the results of the study found those who work more than 50 hours a week, swing or night shift, and have been in their current duties for longer than 2 years are at increased risk for high levels of distress. The results suggest operators sustaining a high operational tempo for long periods of time, especially if performing shift duty, are at elevated risk for the development of emotional difficulties. This group of operators would likely benefit from closer monitoring by commanders, as well as outreach efforts by medical and mental health providers assigned to such units.

The results of the study reveal a low rate of operators (1.57%) endorsing high levels of PTSD symptomology (frequency and severity of symptoms over a 1-month period). This finding suggests the vast majority of Predator/Reaper drone operators within the nation's borders supporting ISR and weapons deployment operations are not experiencing elevated PTSD symptomology. This is consistent with the finding that exposure to combat was not reported a top source of occupational stress. Although prevalence rates were low, data analysis revealed drone operators working more than 50 hours a week are more vulnerable to reporting symptoms of PTSD. It is possible the longer hours may elevate risk via increased levels of vicarious exposure to traumatizing visual images and combat-related events. Data analyses did not find shift work, duty position, length of time performing operational duties, marital status, gender, age, or rank to be predictive of higher PCL-M scores.

The rates of those reporting PTSD in this study were lower than those reported in the 2010 study among Predator/Reaper drone operators using the same instruments and similar methodology.[11] Since the original survey study in 2010,[11] USAF line and aeromedical leadership have implemented changes to address operational stressors and increase access to medical and mental health care. Although an exhaustive list of USAF-wide and unit-specific changes is beyond the scope of this study, some of those changes contributing to lower rates may include (a) active duty installations assigning field-grade, doctoral-level psychologists with top secret security clearances to line units to provide outreach and consultant support on a daily basis to both line operators and flight medicine personnel; (b) Air National Guard units assigning directors of psychological health to develop initiatives that target medical and mental health needs of operators; and (c) line leadership from several units adjusting workload distributions and shift work rotational schedules to increase predictability to allow drone operators advanced planning for balancing work roles with their domestic/personal life obligations. It is possible the reduction in distress may be, in part, due to such changes.

Considerations Regarding Self-Disclosure

Capturing an exact estimate of the rates of distress and PTSD symptomology is difficult and centered on genuine self-disclosure. The reluctance to disclose mental health problems (or any condition impacting duty or retention status) is a phenomenon not unique to aircrew. When studying mental health problems among military members, a methodology that mitigates obstacles to self-disclosure is important, especially when gathering data on those who must adhere to strict medical standards and whose competition for promotion may be affected by an untimely and prolonged period of illness (whether physical or psychological). Additional obstacles to obtaining genuine disclosure may include concerns regarding how disclosure may affect security clearances or participation in sensitive operations and limit career opportunities. However, the anonymous nature of the survey helps mitigate problems with self-disclosure.

A total of 9 drone operators (out of 1,094 participants) did not complete (or only partially completed) the demographic items (i.e., age, gender, rank range, marital status, duty position, shift schedule, hours worked per week). Despite the design of the study and reassurances from the independent researchers and USAF operational leadership, it is possible some respondents remained concerned regarding anonymity. However, the number of respondents was small (less than 1% of the total sample) and data analyses (e.g., logistical regression assessing for demographic and operational predictors of distress) were not likely impacted.

Recommendations

First, as indicated in the analysis, the sources of stress most associated with high stress are operational (and not necessarily exposure to combat). Developing a collaborative line leadership, flight medicine, and mental health provider management strategy to mitigate the impact of long hours, low manning, shift work, and other operational issues appears needed. Second, additional surveillance of occupational stressors and impact of emotional well-being among this unique group of operators appears warranted. The rapidly evolving technology comprising weapon-deploying drone operations along with shifting conflicts across the globe may result in a continuously changing operational environment leading to fluctuations in the sources

and rates of distress relevant to the provision of mental health care. Third, imbedding military mental health providers with top secret security clearances would likely facilitate communication and awareness of the impact of operational and combat-related stressors as well as access to mental health care for those supporting operations on an around-the-clock basis.

Limitations of the Study

This study has several limitations that bear consideration: (a) self-report surveys are prone to response bias from a self-selected sample that might affect generalization of results; (b) the descriptive nature of the study does not warrant definitive cause-effect conclusions between sources and levels of distress; (c) although conservative thresholds were developed for identifying folks with high levels of distress and PTSD symptomology, it is difficult to determine which operators are experiencing chronic versus situational-specific conditions; (d) results should not be generalized to other drone platforms (such as Global Hawk) within the Air Force or across the armed services because of the differences in platforms, missions, and operational requirements; and (e) caution should be taken when comparing 2010 with 2012 results because of differences in methodology and time periods the surveys were administered. Despite these limitations, this study provides descriptive data on rates of distress and PTSD symptomology using an anonymous survey to increase participation and disclosure rates.

CONCLUSION

The findings have implications for future studies and raise awareness to salient sources of stress, rates of distress, and PTSD symptomology within a unique group of airmen who are increasingly relied upon to carry out a wide range of ISR and combat-related weapons strikes in support of joint armed forces operations.

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Chimeric Autologous/Allogeneic Constructs for Skin Regeneration

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ABSTRACT The ideal treatment for severe cutaneous injuries would eliminate the need for autografts and promote fully functional, aesthetically pleasing autologous skin regeneration. NIKS progenitor cell-based skin tissues have been developed to promote healing by providing barrier function and delivering wound healing factors. Independently, a device has recently been created to "copy" skin by harvesting full-thickness microscopic tissue columns (MTCs) in lieu of autografts traditionally harvested as sheets. We evaluated the feasibility of combining these two technologies by embedding MTCs in NIKS-based skin tissues to generate chimeric autologous/allogeneic constructs. Chimeric constructs have the potential to provide immediate wound coverage, eliminate painful donor site wounds, and promote restoration of a pigmented skin tissue possessing hair follicles, sweat glands, and sebaceous glands. After MTC insertion, chimeric constructs and controls were reintroduced into air-interface culture and maintained *in vitro* for several weeks. Tissue viability, proliferative capacity, and morphology were evaluated after long-term culture. Our results confirmed successful MTC insertion and integration, and demonstrated the feasibility of generating chimeric autologous/allogeneic constructs that preserved the viability, proliferative capacity, and structure of autologous pigmented skin. These feasibility studies established the proof-of-principle necessary to further develop chimeric autologous/allogeneic constructs for the treatment of complex skin defects.

INTRODUCTION

Treatment of complex skin injuries resulting from burns or trauma poses a significant medical challenge to both military and civilian populations. Historically, burns have accounted for up to 20% of combat casualties.[1] Similarly, during the initial combat phase of Operation Iraqi Freedom, open skin wounds constituted 42% of the reported injuries.[2] The challenges encountered treating complex skin defects resulting from injury or illness is no less severe in the civilian population. Approximately 50,000 people are hospitalized annually for burns, with 13,000 requiring skin grafts,[3] whereas roughly 1.25 million Americans require medical attention for complex skin defects each year.[4] Extensive burns and severe skin injuries that disrupt the epidermal permeability barrier must be addressed promptly to prevent life-threatening complications. Treatment of complex skin defects typically consists of surgical excision followed by temporary coverage of the wound site to reduce fluid loss and infection[5] and maintain a moist wound environment to promote wound healing[6,7] until the wound can be definitively closed by autograft. Autograft tissue contains complex skin structures (such as hair follicles, sebaceous and eccrine glands) and possesses pigmentation; however, autograft is often meshed and expanded to reduce the size of the donor site. The resultant autografted area often contracts, leading to scarring and negatively impacting cosmetic and functional outcomes.[8] Moreover, autograft harvesting creates painful donor site wounds that contribute to the morbidity associated with major skin trauma. Currently, no therapeutic approach addresses both the immediate need for wound coverage and the restoration of fully functional autologous skin, namely regeneration of the interfollicular epidermis and the cutaneous appendages with appropriate pigmentation to match the patient's skin coloration.

As an alternative to the traditional standard of care for these devastating injuries, we have proposed combining two unique technologies currently in development: allogeneic NIKS progenitor cell-based bioengineered skin tissues and a device designed to "copy" autologous tissue at a microscopic scale. The lack of an abundant and consistent source of pathogen-free allogeneic human keratinocytes is the limiting factor when considering the clinical use of chimeric autologous/allogeneic constructs. The safe, reliable sourcing of human cells for use in biological therapies is a well-recognized problem.[9] NIKS epidermal progenitors provide an abundant, consistent source of genetically uniform, nontumorigenic, and pathogen-free human keratinocytes ideally suited for tissue engineering applications.[10] NIKS cells are unique in that they retain the ability to proliferate in submerged culture but undergo normal epidermal differentiation and generate a fully stratified epithelium when exposed to the appropriate environmental signals. StrataGraft skin substitute tissue, generated using NIKS progenitor cells, has been designed to promote wound healing

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In the conduct of research where humans are the subjects, the investigator(s) adhered to the policies regarding the protection of human subjects as prescribed by Code of Federal Regulations (CFR) Title 45, Volume 1, Part 46; Title 32, Chapter 1, Part 219; and Title 21, Chapter 1, Part 50 (Protection of Human Subjects). In conducting work involving the use of recombinant DNA the investigators adhered to the current version of the National Institutes of Health (NIH) Guidelines for Research Involving Recombinant DNA Molecules.

The views, opinions, and/or findings contained in this report are those of the author(s) and should not be construed as an official Department of the Army position, policy, or decision unless so designated by other documentation.

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through provision of barrier function and delivery of factors known to play a role in wound healing. Initial clinical evaluation of StrataGraft skin tissue, generated using NIKS keratinocytes, demonstrated this skin substitute to be comparable to cadaver skin, the standard-of-care, in the temporary management of traumatic skin wounds.[11] StrataGraft skin tissues were well tolerated, did not elicit an acute allogeneic immune response to NIKS keratinocytes in treated patients, and no therapy-related adverse events were observed.[12] A second clinical trial examining the safety and efficacy of StrataGraft skin tissue as an alternative to autografting for the treatment of deep partial-thickness burns recently completed patient enrollment. Importantly, in this trial, allogeneic DNA was not detectable at 3 months post-treatment (data not published) suggesting that NIKS-based skin does not persist in the wound site.

Clinical experience with fractional photothermolysis[13] has demonstrated that full-thickness columns of skin tissue up to ~300 μm in diameter can be removed without concomitant scarring.[14] Consequently, a strategy was devised to harvest full-thickness microscopic tissue columns (MTCs) from healthy skin with negligible donor site morbidity. A device has been created to harvest full-thickness MTCs from uninjured skin in lieu of a traditional autograft harvested as a sheet from a donor site. Numerous MTCs assembled in the correct position and orientation in a recipient material create a graftable construct, essentially a "copy" of autologous skin tissue containing both epidermal and dermal elements, that can be applied to wounds instead of full- or partial-thickness skin grafts. Unlike commercially available allogeneic bioengineered skin tissues, MTCs contain complex skin structures including whole or partial hair follicles, sweat glands, dermal and epithelial stem cells, epidermal pigmentation, and vessels. Preliminary studies suggest that, when applied to deep wounds in a large animal model, MTCs provide healing that may be able to approach that of a split-thickness skin graft (data not published). The tissue-copying device enables transfer of autologous cells, including cutaneous appendages, to a wound bed without creating a donor site; however, the micrografts do not provide complete epithelial coverage, are prone to desiccation, and require establishment of vasculature within the wound bed to ensure graft take *in vivo*. Embedding MTCs within NIKS-based skin tissues to generate chimeric autologous/allogeneic constructs harnesses the benefits of both bioengineered skin substitutes and autologous MTCs to promote wound healing and reconstitution of skin's complex appendages.

The use of relatively few autologous cells interspersed within a larger population of allogeneic cells has been proposed as a means to address the challenging clinical problem of severe skin loss.[15–17] A chimeric autologous/allogeneic construct that combines the advantages of a next-generation bioengineered skin substitute with the benefits of autologous tissue copying may offer a comprehensive approach to tissue repair and regeneration. Restoration of the epidermal permeability barrier by the allogeneic component prevents desiccation of autologous MTCs and simultaneously provides exogenous growth factors to enhance the probability of survival and subsequent engraftment of autologous tissue. We hypothesize that this novel therapeutic approach would enhance healing in complex skin defects by establishing immediate wound coverage while simultaneously delivering autologous tissue for skin regeneration, providing for full functional and cosmetic skin restoration (Fig. 1). Here, we describe the proof-of-concept studies examining the ability to successfully combine bioengineered skin substitutes with the tissue-copying technology while retaining key aspects of biological activity. Our results demonstrated the feasibility of generating chimeric autologous/allogeneic constructs that preserved the viability, proliferative capacity, and structure of autologous pigmented skin.

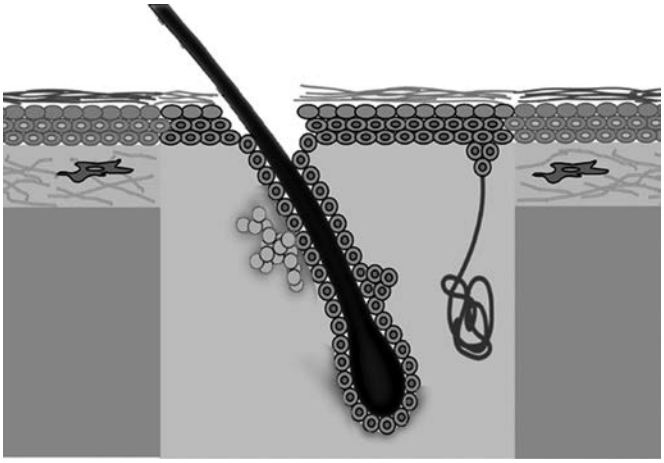

FIGURE 1. Generation of chimeric constructs. This schematic portrays the insertion site of a MTC containing adnexal skin structures (darker shaded cells) within a skin substitute tissue composed of stratified NIKS keratinocytes (lighter shaded cells) cultivated on a dermal matrix of fibroblast-populated collagen.

MATERIALS AND METHODS

Generation and Maintenance of Chimeric Constructs

To facilitate identification of the NIKS population within chimeric autologous/allogeneic constructs, human NIKS cells genetically engineered to express green fluorescent protein (GFP) were utilized.[17] Allogeneic skin tissues (44 cm^2), composed of $NIKS^{GFP}$ keratinocytes cultivated on a dermal matrix of human fibroblast-populated type I collagen, were produced at Stratatech Corporation (Madison, Wisconsin) using organotypic culturing methods as previously described.[17] Mature $NIKS^{GFP}$ skin tissues were transported to Dr. Anderson's laboratory and stored at 4°C. $NIKS^{GFP}$ skin tissues were reintroduced into air-medium interface culture for at least 16 hours before MTC insertion. Human skin tissue, discarded from abdominoplasties, was obtained through the Department of Plastic and Reconstructive Surgery, Massachusetts General

Hospital (MGH), with approval by the MGH Institutional Review Board. Full-thickness microscopic columns of human skin tissue approximately 700 μm in diameter and 750 μm in depth, which model the autologous component of chimeric constructs, were collected by a specialized harvesting needle and inserted into NIKS^{GFP} skin tissue. As controls, NIKS^{GFP} skin tissue lacking MTCs, as well as MTCs directly inserted into a gelled matrix composed of fibrin and collagen, were included in all experiments. A total of three independent experiments were completed. Chimeric constructs and controls were maintained *in vitro* at the air-medium interface for up to 8 weeks postinsertion. Biopsy samples (8 mm) were periodically taken for various endpoint analyses. Samples were fixed in 10% buffered formalin, equilibrated in 20% sucrose in PBS overnight at 4°C, frozen in Tissue-Tek O.C.T. Compound (Sakura, Tokyo, Japan), and stored at −80°C until sectioned. Using standard histological techniques, tissue sections (5 μm) were stained with hemotoxylin and eosin to visualize tissue architecture. Digital images were captured using an Olympus IX-71 microscope equipped with fluorescein, Texas Red, and Hoechst band pass filters and an Olympus DP70 digital camera with DP Controller software (Olympus, Center Valley, Pennsylvania).

Viability Assessment

At 2, 4, 6, and 8 weeks post-MTC insertion, biopsy samples (8 mm) were evaluated for viability as previously described.[18] For each of three experimental replicates, triplicate biopsy samples per condition were incubated with 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyl tetrazolium bromide (MTT reagent, Sigma, St. Louis, Missouri) at 1 mg/mL in serum-free medium for 90 min at 37°C. Viable cells metabolize MTT into an insoluble purple formazan derivative, which was extracted with 2-propanol. The extent of MTT reduction was quantified by measuring absorbance of the samples at 570 nm. To assess the change in viability over time, the mean absorbance values for a given condition or control were analyzed by one-way ANOVA.

Proliferation Index Determination

The proliferation index (PI) is calculated by determining the fraction of Ki67-positive basal keratinocytes within a defined area. For each experimental replicate, the PI for chimeric constructs or controls at 2, 4, 6, and 8 weeks post-MTC insertion was determined as previously described.[19] Briefly, indirect immunofluorescence was used to detect Ki67 (rabbit anti-Ki67, Neomarkers, Fremont, California) in cryopreserved tissue sections (5 μm). Sections were counterstained with Hoechst 33258 (5 μg/mL in PBS) to facilitate nuclei localization. Identification of NIKS^{GFP} cells was determined by localization of GFP. For each sample, digital images of unique NIKS^{GFP}- or MTC-containing regions were captured using the imaging system previously described and tricolor images were created by overlaying single color images of the same field. Basal keratinocytes were visually identified and nuclei were scored as positive or negative for Ki67. The PI was calculated by determining the percent of Ki67-positive basal keratinocytes in each image. PI for NIKS^{GFP} or MTCs was independently assessed and mean PI values were analyzed by one-way ANOVA.

Assessment of Tissue Morphology

Tissue architecture evaluation employed indirect immunofluorescence for protein localization. Cryopreserved sections (5 μm) were fixed in cold acetone, washed, and blocked with 3% goat or donkey serum in PBS. Samples were incubated for 1 hour at 37°C with mouse or goat monoclonal antibodies against E-cadherin (BD Biosciences, San Jose, California), keratin 2 (Progen, Heidelberg, Germany), keratinocyte-specific type I transglutaminase (Biomedical Technologies, Stoughton, Massachusetts), melan-A, keratin 7, or keratin 77 (Santa Cruz Biotechnology, Dallas, Texas) diluted in appropriate blocking agent. Samples were incubated for 30 minutes at room temperature with goat anti-mouse or donkey anti-goat IgG Alexa 594 secondary antibody (Invitrogen, Carlsbad, California) and counterstained with Hoechst 33258. As nonspecific staining controls, sections were incubated with species-specific blocking solution. Digital images of individual fluorescence signals were captured using the imaging system previously described. Identical image manipulations were performed for each set and tricolor images were created by overlay of single color captures of the same field.

RESULTS

Chimeric Constructs Display the Morphology of Stratified Squamous Epithelia

Histological evaluation of chimeric constructs confirmed the presence of basal, spinous, granular, and cornified layers in the epidermal compartments of both biological components throughout the initial stages of *in vitro* cultivation (Fig. 2). Within MTCs, distinct epidermal layers persisted throughout the observation period (data not shown). As anticipated, over

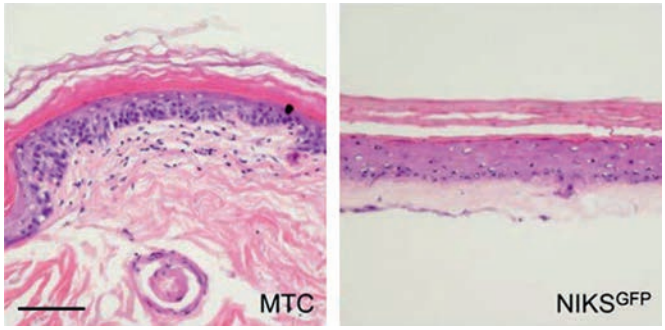

FIGURE 2. Tissue architecture of chimeric construct components. The tissue integrity of both inserted MTCs and NIKS^{GFP} skin substitute tissue was retained throughout this culture period. These representative images were obtained from a sample collected 2 weeks after MTC insertion. Small vacuole-like structures visible throughout the tissues are artifacts of sample freezing. Bar = 100 μm.

time the epidermal compartment of NIKS^{GFP} skin tissues showed morphological changes consistent with extended culture *in vitro*, such as loss of a well-defined basal layer resulting from ongoing keratinocyte differentiation (data not shown). A thickening of the cornified layer was seen in both MTC and NIKS^{GFP} components over time. As anticipated, over time the inserted MTCs retained the structure of intact skin, whereas skin substitute tissues became progressively populated with enucleated squames. Accumulation of squames over time is typically observed *in vitro* due to the lack of desquamation resulting from friction or other physical dislodging. Although infrequently observed, adnexal skin structures were detected within the dermal tissue of MTCs. Most importantly, no evidence of gross necrosis or aberrant growth was seen during extended cultivation. These results demonstrated the feasibility of successfully combining the technologies.

Chimeric Constructs Retain Viability and Proliferative Capacity up to 8 Weeks After Combination of Allogeneic and Autologous Components

The MTT cell viability assay was used to evaluate the extent of tissue viability exhibited by chimeric constructs after extended periods of *in vitro* cultivation. Tissue viability remained fairly consistent throughout the 8-week cultivation period (Fig. 3). A loss in viability (38%) was noted for the NIKS^{GFP}-only control over this same period ($p < 0.05$). An initial increase in viability was noted at week 4 for the MTC-only control, which corresponded to epithelialization of the fibrin/collagen surface with keratinocytes originating from the inserted MTC. However, by week 8, the mean viability returned to the level initially seen at week 2.

To evaluate the proliferative capacity of keratinocytes within MTCs and NIKS^{GFP} tissue throughout cultivation, the PI of each chimeric construct component was calculated. The presence of proliferating cells within human skin is readily identified by immunodetection of Ki67. A significant decrease in PI from about 16% to 1%, first detected at 4 weeks post-MTC insertion, was observed for NIKS^{GFP} cells within chimeric constructs ($p = 0.0033$) (Fig. 2). In contrast, the PI for NIKS^{GFP} tissue controls remained constant for 6 weeks at about 7% before decreasing to <1%. The PI for MTCs, whether in a chimeric construct or inserted into a gelled extracellular matrix, remained consistent at approximately 20%. These studies confirmed that chimeric constructs retained tissue viability and that MTCs within chimeric constructs maintained proliferative capacity after extended *in vitro* cultivation.

Proteins Associated With Cell–Cell Adhesion and Keratinocyte Terminal Differentiation Are Expressed Within Chimeric Constructs

To further evaluate the morphology of chimeric constructs, indirect immunofluorescence was used to visualize markers characteristic of the interfollicular epidermis. Samples taken

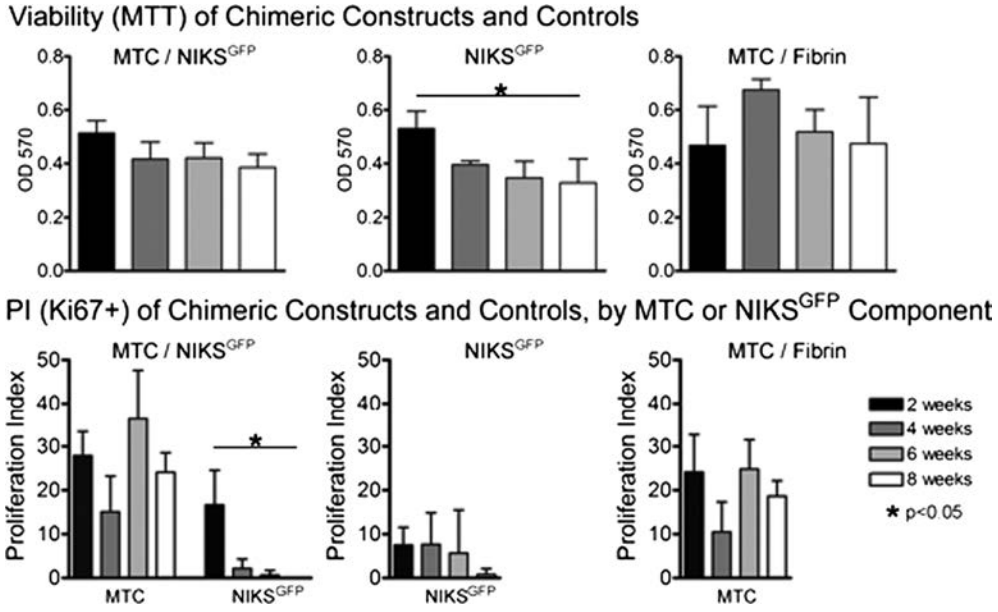

FIGURE 3. Viability and PI comparison of chimeric constructs and controls during extended *in vitro* cultivation. The upper panel depicts viability values (OD570) for chimeric constructs, NIKS^{GFP} skin tissue alone, or MTCs inserted into a fibrin/collagen gel. Data are from experimental replicates (2, 6, and 8 weeks, $n = 3$; 4 weeks, $n = 2$) and represent the mean ± standard deviation. When mean OD570 values were compared, only the viability for the NIKS^{GFP} skin tissue control was found to vary significantly over time ($p < 0.05$) The lower panel shows the PI as calculated for each cellular component of chimeric constructs and controls throughout extended cultivation. Data represent the mean ± standard deviation from three experiments, with replicate images evaluated for each construct or control. The PI over time for each contributing cell type was compared. The difference in mean PI values at 2, 4, 6, and 8 weeks post-MTC insertion for NIKS^{GFP} cells in chimeric constructs were significantly different ($p = 0.0033$); however, no other groups were found to be significantly different ($p > 0.05$).

periodically throughout extended cultivation of chimeric constructs and experimental controls were examined for expression and localization of E-cadherin, keratin-2, and transglutaminase-1. Discrimination between MTC-derived keratinocytes and NIKS^{GFP} cells was facilitated by localization of GFP, particularly to the terminally differentiated layers. Figure 4 depicts protein expression patterns at an MTC insertion site with each component contributing tissue to form a contiguous interfollicular epidermis. As expected, some tissue disorganization was observed at the MTC/NIKS^{GFP} tissue junction and was likely the result of tissue disruption during MTC insertion. The images presented are representative of all timepoints examined for chimeric MTC/NIKS^{GFP} constructs. The cell–cell adhesion protein E-cadherin was routinely found to be appropriately localized to the membrane of epithelial cells in both MTCs and NIKS^{GFP} skin tissue. E-cadherin expression also clearly revealed a continuous layer of basal keratinocytes bridging the MTC/NIKS^{GFP} tissue junction. For MTC-only controls, epithelialization of the fibrin/collagen surface by the third week post-MTC insertion was confirmed by E-cadherin staining of keratinocytes originating from the MTC (data not shown). Keratin 2 expression was consistently observed in the cytoplasm of both differentiated NIKS^{GFP} and MTC keratinocytes throughout the 8-week period of *in vitro* cultivation. By the third week, the level of keratin 2 in NIKS^{GFP}-only controls became less pronounced as squames accumulated. As is typical for squamous stratified epithelia, transglutaminase-1 was discretely expressed at the cell membrane in the spinous and granular layers. Strong expression was observed in all terminally differentiating keratinocytes out to 8 weeks post-MTC insertion including differentiating keratinocytes in areas of outgrowth in MTC-only controls (data not shown). Taken together, these proof-of-concept studies demonstrate successful integration of MTCs in NIKS^{GFP} tissue to form chimeric constructs with tissue morphology characteristic of the interfollicular epidermis.

Chimeric Constructs Possess Melanocytes and Complex Dermal Structures

Immunofluorescence was also used to detect proteins indicative of pigmentation and complex skin structure. Staining for melan-A revealed the presence of melanocytes resident to the basal layer of the interfollicular epidermis of MTCs (Fig. 5). Since NIKS^{GFP} skin tissue did not contain melanocytes, detection of melan-A was not anticipated and correspondingly was not observed. Melanocyte migration was only observed in MTC/fibrin controls, and the extent of migration from the inserted tissue was limited (data not shown). The dermal compartments of inserted MTCs were then examined for evidence of adnexal skin structures. NIKS^{GFP} skin tissues recapitulate the tissue of interfollicular epidermis but do not generate the structures of the cutaneous appendages. As depicted in Figure 5, both keratin 7, a protein expressed in the lumen of sebaceous glands, and keratin 77, associated with eccrine glands, were detected within the dermis of inserted MTCs. The frequency of detection was extremely low, but this was not unanticipated given the random nature of MTC harvest and the dermal depth achieved in these feasibility studies. Nonetheless, the presence of melanocytes and complex skin structures supports the concept that chimeric constructs, after *in vivo* engraftment, may promote restoration of a fully functional, pigmented skin tissue possessing hair follicles, sweat glands, and sebaceous glands.

DISCUSSION

The standard of care for the treatment of complex skin defects typically requires autograft placement for definitive wound closure. Autologous skin grafting is costly, labor intensive and creates another wound at the donor site. Although replete with pigmentation and cutaneous appendages, autografts often fail to yield skin tissue that is aesthetically pleasing, possessing functional adnexal structures and appropriate pigmentation. Also, donor site wounds are

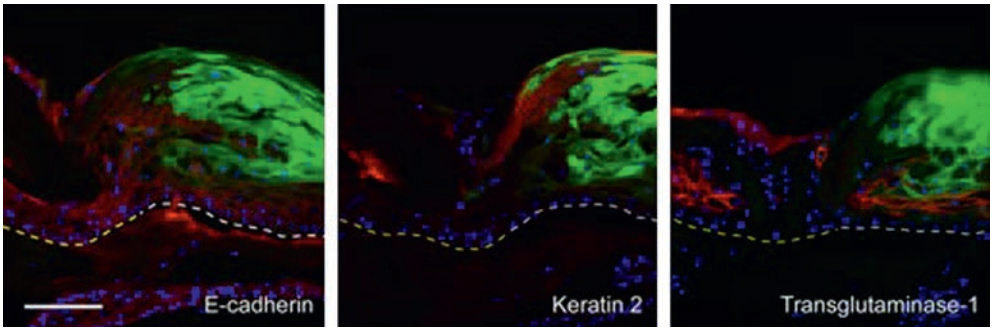

FIGURE 4. Expression and localization of proteins associated with cell adhesion and keratinocyte terminal differentiation within chimeric constructs. Images depict localization of the stated proteins (red) at the site of MTC insertion into NIKS^{GFP} skin tissue (green). Sections were counterstained with Hoechst 33258 to facilitate nuclei localization (blue). The dashed yellow line denotes the dermal–epidermal junction of the inserted MTC, whereas the dashed white line denotes the dermal–epidermal junction of the NIKS^{GFP} skin tissue. These representative images were obtained from a sample collected 1 week after MTC insertion. These localization patterns were found in chimeric constructs, as well as NIKS^{GFP} and MTC controls, over the entire *in vitro* cultivation period. Bar = 100 μm.

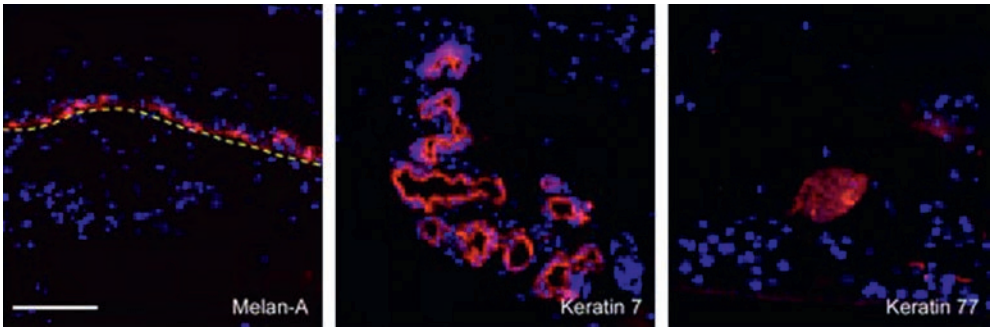

FIGURE 5. Detection of melan-A and proteins associated with complex skin structures. Representative images depict the localization of melan-A (red) expressed by melanocytes residing in the basal layer of MTCs within chimeric constructs. Sections were counterstained with Hoechst 33258 to facilitate nuclei localization (blue). The dashed line denotes the dermal–epidermal junction within the MTC. Although this representative image was obtained from a sample collected 8 weeks post-MTC insertion, melanocytes were detected in MTCs of chimeric constructs and MTC controls over the entire *in vitro* cultivation period. Proteins expressed by the appendages of skin, specifically keratin 7 which is expressed in the sebaceous gland and keratin 77 which is expressed in eccrine gland tissue (red), were also detected in the dermal compartment of MTCs at all timepoints examined. Bar = 100 μm.

painful and may suffer reduced cosmesis upon healing. Perhaps the most challenging aspect of this treatment regime is that for patients suffering from extensive burns where potential donor sites are limited, autograft harvesting is simply not feasible. Although biological therapies, such as bioengineered skin substitutes, have proven useful for the treatment of some chronic nonhealing wounds,[20] significant challenges remain with the use of cell-based therapies for complex skin defects such as burns. Currently, skin substitutes that are autologous in nature, such as Epicel (Genzyme Corporation, Cambridge, Massachusetts), require weeks of *in vitro* cultivation to permit sufficient time for cell expansion and ultimately yield a thin, fragile material that exhibits aberrant stratification and lacks cutaneous barrier function. Although the incorporation of melanocytes within skin substitutes has been examined,[21] the use of autologous melanocytes would require the harvest, isolation, and expansion of this cell population before or during skin substitute production. As with other autologous-sourced cells, the time required to generate sufficient cell numbers becomes a barrier to prompt treatment and the costs associated with a custom biomanufacturing process become prohibitive. Use of allogeneic melanocytes would address these concerns; however, retention of the cell type needed for pigmentation, and thus restoration of skin coloration, poses a new challenge. Re-establishing adnexal skin structures presents an even greater obstacle. Due to the complexity of the pilosebaceous unit, successful generation of cutaneous appendages *in vitro* has been elusive. As recently reviewed by Mahjour et al,[22] although animal experiments have demonstrated the capacity for hair morphogenesis when the appropriate cell types are provided external environmental cues, folliculogenesis requires complex mesenchymal–epidermal interactions that have yet to be replicated *in vitro*. Nonetheless, substantial development work is required for these approaches to become readily available for the treatment of damaged skin.

Currently, no therapeutic approach addresses both the need for immediate wound coverage and restoration of fully functional skin. Although a chimeric mixture of autologous and allogeneic cells has been proposed for use in the treatment of severe cutaneous trauma,[15–17] the lengthy time-to-treatment and the increased costs resulting from production of patient-specific, fully stratified skin substitutes make this approach unattractive. A chimeric autologous/allogeneic construct that utilizes both fully stratified bioengineered and autologous skin tissue addresses these concerns and offers a novel approach to cutaneous repair and regeneration. Although this study utilized *in vitro* endpoints to evaluate the feasibility of combining these two components, during clinical use, the harvest and insertion of autologous MTCs into allogeneic skin tissue is anticipated to occur immediately before patient application. NIKS-based skin substitutes would be uniformly produced at commercial scale in compliance with all applicable regulations and would provide immediate wound closure, whereas incorporation of MTCs at the point of procedure would virtually eliminate the need to cultivate patient cells *in vitro*.

The experiments in this study were designed to investigate whether these two approaches, combining immediate wound closure with allogeneic human skin and point-of-care autologous cell delivery, were complimentary. Although ultimately *in vivo* assessment will be required to evaluate performance and efficacy, evaluations of tissue integrity, viability, and proliferative capacity were performed after extended *in vitro* cultivation as a proof-of-concept for the chimeric approach. In this study, NIKS cells genetically engineered to express GFP and MTCs harvested from human skin tissue were used to model the allogeneic and autologous components of chimeric constructs. Chimeric constructs and control NIKS^{GFP} tissue maintained complete coverage of the culture surface with fully stratified skin tissue throughout the 8-week *in vitro* cultivation period, whereas MTCs implanted into a gelled matrix composed of fibrin and collagen required several weeks to achieve epithelialization of the wound site with additional time needed to achieve full stratification. Inserted MTCs retained viable progenitor cells, whereas skin substitute tissues became progressively populated with enucleated

squames resulting from terminal differentiation of the $NIKS^{GFP}$ keratinocyte population. Ultimately, during clinical application of chimeric constructs, we envision that the allogeneic cells would be depleted through terminal differentiation and be replaced by autologous cells contributed by the MTCs.

An examination of tissue viability and proliferative capacity demonstrated that MTCs within chimeric constructs retained both of these key biological activities throughout extended *in vitro* cultivation. MTCs, which retain the three-dimensional structure of progenitor cell niches resident to the cutaneous appendages, may serve as a source of highly proliferative autologous progenitors. A decrease in $NIKS^{GFP}$ cell proliferation was observed in both chimeric constructs and controls, which corresponded to the loss of a well-organized basal layer as *in vitro* cultivation proceeded. Interestingly, the loss of proliferative $NIKS^{GFP}$ within chimeric constructs occurred at a more rapid rate than $NIKS^{GFP}$ tissue alone, suggesting that the presence of MTCs in some way reduced the proliferative capacity of $NIKS^{GFP}$ cells; however, the mechanism for this remains unclear. Further studies examining the tissue morphology confirmed normal tissue architecture for chimeric constructs demonstrating accurate expression of proteins essential for the structure and function of stratified squamous epithelial tissue. The cell–cell adhesion protein E-cadherin, as well as keratin 2 and transglutaminase-1, both biomarkers associated with keratinocyte terminal differentiation, were found to be appropriately expressed in patterns typical of the interfollicular epidermis. Standard histological and immunological-based protein detection analysis revealed no indications of aberrant growth and confirmed successful integration of MTCs in $NIKS^{GFP}$ tissue. The presence of melanocytes within MTCs was also confirmed throughout extended cultivation. Migration of melanocytes out of MTCs into the surrounding tissue was only observed in MTC controls and was limited in nature. The lack of extensive melanocyte migration could result from the *in vitro* culture conditions, which utilized medium optimized for keratinocyte differentiation and maintenance. The presence of cutaneous appendages was also evaluated by immunodetection of keratins 7 and 77, found in sebaceous and eccrine glands, respectively. Both proteins were found to be expressed and appropriately localized in structures residing in the dermal compartment of MTCs. Because of the relatively low number of MTCs used during chimeric construct generation in these feasibility studies, the frequency of detection for these structures was limited. Subsequent *in vivo* studies will enable a more thorough analysis of adnexal skin structures within chimeric constructs. Nonetheless, the presence of melanocytes and complex skin structures establishes the ability of chimeric constructs to restore a fully functional, pigmented skin tissue once engrafted *in vivo*.

This study has demonstrated the feasibility of generating chimeric autologous/allogeneic constructs that retain tissue integrity, viability, and proliferative capacity of autologous pigmented skin tissue possessing cutaneous appendages. Chimeric constructs combining the advantages of a next generation bioengineered skin substitute with the benefits of autologous tissue copying present an innovative approach to comprehensive tissue repair and regeneration. The allogeneic component restores the epidermal permeability barrier, providing immediate wound coverage and preventing desiccation of the autologous tissue, and provides a source of exogenous growth factors to improve the wound bed, enhancing the probability of construct survival and subsequent engraftment. Furthermore, NIKS-based allogeneic skin substitutes are highly amenable to genetic manipulation using nonviral vectors,[23] which allows for the targeted, transient delivery of growth factors to promote engraftment and/or regeneration of autologous structures within the healing wound. In particular, NIKS cells engineered to exogenously express elevated levels of the angiogenic factor VEGF would stimulate revascularization of the wound bed and potentially enhance inosculation of the existing vessels within embedded MTCs. The therapeutic use of chimeric constructs represents a transformational approach to the treatment of severe cutaneous trauma, facilitating tissue repair and regeneration for the restoration of fully functional skin tissue.

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