ABSTRACT

Military medicine is a field of medicine that pertains to the needs and treatment of soldiers and military personnel. Although there is a great deal of overlap between civilian medicine and military medicine, military personnel are likely to experience more nuanced forms of injury than their civilian counterparts and thus require novel treatment methods that are unique to the combat environment. Within battlefield environments, there are an increasing number of traumatic injuries that result from explosive devices, high-caliber projectile weapons, and an array of devastating chemical weapons. Many of the injuries are widespread and affect multiple organ systems. Current treatment methods incorporate alleviation of pain and symptoms, life-saving surgeries to prevent further damage and repair present ones, as well as a variety of prosthetic devices and other assistive equipment. Although there is currently no treatment method that can serve to restore and regenerate damaged tissue resulting from the traumatic injuries currently, new avenues of medicine are being worked on. Potential applications of stem cells within military medicine will be reviewed as well as an exploration of the current state of stem cell research on regenerative medicine. Specifically, tissue regenerative technologies of various organ systems and the storage of these tissues will be explored. Commentary will also be provided specifically to field medicine within a combat environment in which novel new protocols may be implemented with a stem cell application.

Keywords

Stem cells, Military, Combat injuries.

Introduction

Bodily trauma resulting from combat during active military service reflects a tremendous challenge for defense medicine, particularly in nations that prioritize defense spending. One such nation is the United States which spends over 700 billion USD on national defense [1]. Despite the plethora of nations that spend tremendous amounts of money on defense medicine, current medical treatment for traumatic injury is still confined to treatments such as medication, surgery, transplantation, and the use of prosthetics [2]. Many of today’s defense medical treatments focus on reducing damage already created rather than restorative medicine [3]. It is for this reason that restorative treatment options are highly sought after by military and government organizations across the globe. Stem cells are a possible tool needed within medicine that may be able to answer the question of restorative treatments for traumatic injury. Stem cells, independently, serve a vital role in the proliferation and restoration of body tissue that may be lost due to injury. In addition to stem cells’ proliferative properties, they may produce cytokines and chemokines to aid in recovery and stimulate proliferation in existing body tissue [4]. Furthermore, Stem Cells can display various amounts of cytoskeletal anchors and junctions that may allow restoration of the physical interactions of damaged tissue with neighboring tissue. These technologies are currently being developed and researched in all aspects of restorative medicine, from scaffolding and stem cell tissue grafts of the integument to deep tissue organogenesis.

Despite the progress made surrounding regenerative medicine, there are shortcomings in being able to research and then apply the
Stem Cells

Stem cells are a unique type of cell that can differentiate into various other types of cells within the body. Their ability to differentiate and proliferate is particularly important in the research, development, and application of regenerative medicine.

Stem cells can be divided into various categories based on their ability to differentiate, known as their potency. Totipotent stem cells can differentiate into any cell type within the human body. Pluripotent stem cells have a wide range of differentiative capabilities but are slightly more limited than totipotent stem cells. Multipotent stem cells can differentiate into various cell types within a given cell lineage. The level of potency within a stem cell can determine what applications they can be utilized in. Totipotent and pluripotent stem cells are the most desirable for the purposes of regenerative medicine, however, realistic acquisition on a large scale may prove more challenging than that of a multipotent stem cell.

The sources of stem cells may also influence the potency of the cell. The primary types of stem cells are embryonic stem cells (ESC), induced pluripotent stem cells (iPSC), and adult stem cells (ASC). As seen in Figure 1, ESCs are a type of pluripotent stem cell and are typically obtained from the blastocyst of an embryo during early human development. ESCs, although contain a high degree of potency, are highly controversial and may be difficult to obtain on a large scale. iPSCs are another form of pluripotent stem cells that have instead been reprogrammed from adult somatic cells that function similarly to ESC. ASCs are stem cells that are found within the adult human body but are typically more restricted in their ability to differentiate into other cell types, usually restricted to a specific lineage or lineages. ASCs such as hematopoietic stem cells and mesenchymal stem cells have been highly researched and, unlike that of ESC or iPSC, have a lower chance of inducing an immune response from the host due to their nativity to the host.

The ever-changing nature of stem cell research and its application is likely to cause military and private researchers to continue to explore the applications of all the forms and sources of stem cells.

Military vs Civilian Perspective

Although there is a great deal of overlap between civilian medicine and military medicine there are some notable differences between them that one would have to consider when considering specific stem cell applications within a combat or wartime environment. Injuries such as those resulting from high-energy blasts and high-caliber bullet wounds are disproportionately seen within battlefield environments when compared to civilian environments and require novel treatment methods [7]. Oftentimes, injuries from weapons of war affect multiple organ systems and require highly complicated treatment and recovery methods. Specifically, high-energy blast injuries highlight the desire for military medicine to develop regenerative tissue options for soldiers. Highly destructive weapons such as improvised explosive devices (IED) (as seen in Figure 2) and pipe bombs (as seen in Figure 3) have seen an increase in use in modern warfare and are capable of being constructed quickly and easily. Other aspects that are unique to military medicine in a battlefield setting are the immediate treatment of the injury as well as the recovery of the soldier from the battlefield. Unlike their civilian counterparts, military medicine often requires health care to be administered in hazardous conditions, often at times during combat. This limits the treatment options available within battlefield environments as there may not be accessible to the conveniences of hospitals and clinics. Another critical difference between battlefield medicine and civilians is the potential lack of resources available immediately to healthcare providers. These differences between military medicine and civilian medicine highlight how medicine
is approached where the most technologically advanced treatment option may not be as desirable as a more user-friendly and rugged treatment option when considering battlefield environments.

Figure 2: Example of the basic components required to construct an improvised explosive device [8].

Figure 3: Example of the basic components required to construct a pipe bomb [9].

**Trauma**

Increased prevalence of high explosive weapons used in the battlefield accounts for an increase in traumatic injuries that involve multiple organ systems. However, organ systems such as the integumentary system, muscular system, skeletal system, nervous system, and respiratory system are more commonly affected by high explosive injuries. For this reason, it is in the best interest of military researchers to be able to repair and regenerate tissues damaged from these weapons.

The most common types of military injuries include musculoskeletal injuries such as fractures, sprains, and strains, as well as traumatic brain injuries (TBIs), post-traumatic stress disorder (PTSD), and hearing loss. Musculoskeletal injuries can result from physical training, combat-related activities, and carrying heavy equipment. TBIs can occur from exposure to blasts or other head injuries, while PTSD can result from exposure to traumatic events. Hearing loss is often caused by exposure to loud noises and explosions. Other common types of injuries in the military include respiratory and nervous system injuries, as well as burns and wounds.

**Integumentary System**

The integumentary system is comprised of the largest organ in the human body and serves to protect and maintain the body. It functions as a primary barrier between the outside world and the inside of our bodies. The integumentary system encompasses a wide array of parts such as the three layers known as the epidermis, dermis, and hypodermis respectively (superficial to deep). Furthermore, the Integumentary system consists of accessory structures such as various glands, hair, and nail. In almost all forms of battlefield injury, the integumentary system is heavily involved and is subsequently damaged as the integument is typically the initial point of access for any weapon to enter the body.

Unique to only a few organ systems including the integument, the skin has an impressive ability to self-renew and regenerate damaged tissue. The skin can regenerate itself through a bizarre process of wound healing that incorporates various stem cells and associated tissue. However, the extent of this repair is often highly dependent on the type, scale, and location of injury.

Both civilian and combat environments pose a threat to the integumentary system. However, combat environments are exposed to a much higher risk of integumentary damage due to the various lethal weapons used against soldiers. The types of integumentary damage range from minor to severe, with the most severe resulting in injuries such as third- and fourth-degree burns, large area chemical exposure, severe sunburns, and large lacerations causing separation in the integument. In study that analyzed a total of 701 casualties 70% of the injuries were due to explosions, which were often accompanied with severe damage to the integumentary system in addition to various other organ systems [7].

Current treatment for integumentary damage often depends on the size, extent, and type of damage done to the integument. Many injuries that only pertain to the integumentary system such as 1

\[\text{st}\] and 2

\[\text{nd}\] degree burns can often be treated on the battlefield with medicated ointment and proper use of antiseptics to prevent infection or debridement [10]. When observing injuries that result from high explosives or high caliber weaponry, integumentary repair is often the last to be dealt with as musculoskeletal structure beneath the integument is often surgically attended to. Following surgery, the integument is often kept as sterile as possible to prevent secondary infections or debridement in patients.

One experimental method that utilizes stem cells for the purposes of restoring the integument is using MSC and Stromal cell derived exosomes for the purposes of immunomodulation and regeneration of the skin. Exosomes are extracellular vesicles that are released by cells via a form of budding. Exosomes derived from MSC are packed with a variety of important organic molecules and compounds that aid in the regeneration of the skin and displayed various clinical benefits such as anti-inflammatory properties, anti-aging benefits, as well as wound healing [11].

**Musculoskeletal System**

Another organ system that often faces a high degree of potential damage resulting from combat injuries is the muscular and skeletal
Within the muscular system exists three distinct types of muscle tissue: Skeletal muscle, cardiac muscle, and smooth muscle. Within the skeletal muscle are muscle tissues that attach to bones via tendons and can produce force to provide movement and stability [12].

Within the army, accidents as well as explosive injuries account for 14% of the injuries sustained to the musculoskeletal system. However, 70% of the musculoskeletal injuries come in the form of a variety of stress-induced fractures, bursitis, tendinitis, and various other overuse and training related injuries [13].

The current treatment of musculoskeletal injuries in the military typically follows a multi-disciplinary approach that includes medical management, rehabilitation, and, in some cases, surgical intervention. The specific treatment approach depends on the type and severity of the injury. Initially, medical management may include rest, ice, compression, and elevation (RICE) to manage pain and inflammation [14]. Pain medication and nonsteroidal anti-inflammatory drugs (NSAIDs) may also be prescribed. Rehabilitation plays a critical role in the recovery process and may include physical therapy, occupational therapy, and other modalities such as ultrasound, electrical stimulation, and massage. In cases where surgical intervention is necessary, procedures such as arthroscopy or joint replacement surgery may be performed [15].

Stem cells hold potential for treating musculoskeletal injuries, as they can differentiate into multiple cell types including those found in bone, cartilage, and muscle tissue. One approach to using stem cells for musculoskeletal repair involves the use of mesenchymal stem cells (MSCs), which can be obtained from various sources such as bone marrow, adipose tissue, and umbilical cord tissue.

In preclinical studies, MSCs have been shown to promote tissue repair and regeneration in a variety of musculoskeletal conditions, including fractures, osteoarthritis, and muscle injuries. They are thought to work by differentiating into cells that can form bone or cartilage, as well as by releasing anti-inflammatory and growth-promoting factors [16].

Clinical trials are currently underway to investigate the use of MSCs for musculoskeletal injuries. In some cases, MSCs are combined with scaffolds or other materials to enhance their ability to repair damaged tissue. However, more research is needed to determine the optimal dosing and delivery methods for stem cell therapy, as well as to assess long-term safety and efficacy [17].

Respiratory System

Combat environments can have a significant impact on the respiratory system of military personnel. Exposure to toxic chemicals, smoke, and dust from explosions can lead to lung damage, respiratory distress, and chronic respiratory conditions such as asthma, chronic bronchitis, and chronic obstructive pulmonary disease (COPD) [18]. In addition, exposure to high altitude and extreme temperatures can also affect respiratory function and lead to conditions such as high-altitude pulmonary edema (HAPE) and heat stroke. These respiratory system damages can have long-lasting effects on the health and well-being of military personnel and can significantly impact their ability to perform their duties and maintain physical readiness. As such, it is critical for military medicine to find ways to alleviate or solve the issues surrounding damage to the respiratory system.

The most common respiratory damage experienced by military personnel in combat environments is likely to be associated with exposure to airborne particles and irritants. These can include dust, smoke, and other pollutants generated by explosions, fires, and vehicular exhaust. Exposure to these irritants can cause inflammation and irritation of the airways, leading to symptoms such as coughing, wheezing, and shortness of breath. Over time, repeated exposure to these irritants can cause chronic respiratory conditions such as chronic bronchitis and COPD. In addition, exposure to toxic chemicals such as nerve agents, mustard gas, and other chemical agents can also cause respiratory damage, leading to lung injury and respiratory distress [19].

The percentage of military injuries that are specifically respiratory damage is difficult to estimate as it can vary widely depending on the conflict, location, and type of military operation. However, respiratory conditions have been identified as a significant health concern for military personnel in many conflicts. For example, a study conducted by the Department of Defense found that respiratory conditions, including asthma and COPD, were the most common medical diagnoses among US military personnel deployed to Iraq and Afghanistan between 2004 and 2007. Another study found that during the Gulf War, respiratory illnesses were the second most common cause of hospitalization for US Army personnel. While there is no specific percentage for respiratory injuries in the military, these findings highlight the significant impact that respiratory conditions can have on military personnel deployed in combat environments [20].

The treatment of COPD in the military is similar to the treatment provided to civilians. The primary goals of COPD treatment are to manage symptoms, prevent exacerbations, and improve quality of life. Treatment options for COPD include medications such as bronchodilators and inhaled corticosteroids, pulmonary rehabilitation programs, supplemental oxygen therapy, and surgery in some cases. In addition, smoking cessation is a critical component of COPD management as smoking is a significant risk factor for the development and progression of the disease. Military personnel with COPD may also receive additional support and resources such as disability compensation and counseling services. Ultimately, the specific treatment approach for COPD will depend on the severity of the disease, the individual’s symptoms and preferences, and the availability of medical resources in the military setting [21].
Stem cells have the potential to regenerate and repair damaged lung tissue, making them a promising therapeutic option for treating lung damage. One approach involves the use of mesenchymal stem cells (MSCs). MSCs can differentiate into multiple cell types, including those found in lung tissue, and can also release anti-inflammatory and growth-promoting factors that support tissue repair.

Studies have shown that administration of MSCs can lead to improved lung function and reduced inflammation in animal models of lung injury and disease. Additionally, clinical trials have been conducted to evaluate the safety and efficacy of MSCs in treating lung conditions such as chronic obstructive pulmonary disease (COPD) and idiopathic pulmonary fibrosis (IPF). While the results of these studies have been mixed, they suggest that stem cell therapy may hold promise as a potential treatment for lung damage in the future [22].

**Nervous System**

Traumatic brain injury (TBI) is one of the most common types of nervous system damage seen in military personnel who have been deployed to combat environments. TBI occurs when a sudden jolt or blow to the head causes damage to the brain. This can result in a range of symptoms, from mild (such as headache and dizziness) to severe (such as loss of consciousness and cognitive impairment) [23]. TBI can occur in a variety of ways in combat environments, including from blasts or explosions, falls, and direct blows to the head. The risk of TBI is highest for individuals serving in combat roles, such as infantry soldiers and special operations forces.

In addition to TBI, other types of nervous system damage that can occur in combat environments include spinal cord injuries, nerve injuries, and peripheral neuropathy. These injuries can result from a variety of causes, such as falls, motor vehicle accidents, and exposure to environmental toxins. The severity of these injuries can vary widely, ranging from mild to severe and permanent.

The percentage of military injuries resulting in nervous tissue damage is difficult to estimate due to the wide range of injuries that can occur in combat environments. However, it is known that traumatic brain injury (TBI) is one of the most common types of nervous tissue damage seen in military personnel, particularly those who have been deployed to combat zones. According to a report by the Department of Defense, over 408,000 cases of TBI were diagnosed in military service members between 2000 and 2020. Additionally, a study published in JAMA Neurology in 2020 found that nearly 20% of military personnel who were deployed to Iraq and Afghanistan between 2001 and 2014 reported symptoms of TBI [24]. Other types of nervous tissue damage that can occur in military personnel include spinal cord injuries, nerve injuries, and peripheral neuropathy. The prevalence of these injuries varies depending on the nature of the combat environment and the types of operations being conducted. Current Treatment stem cells hold promise for the treatment of traumatic brain injury (TBI) due to their ability to regenerate damaged tissue and promote healing in the brain. Several types of stem cells have been studied for their potential use in TBI treatment, including neural stem cells, mesenchymal stem cells (MSCs), and induced pluripotent stem cells (iPSCs) [25].

One approach being studied involves the use of MSCs, which can be derived from a variety of sources, such as bone marrow or adipose tissue. These cells have been shown to have anti-inflammatory and neuroprotective effects, which may help to reduce the damage caused by TBI. In animal studies, MSCs have been shown to improve cognitive function and reduce inflammation in the brain following TBI [26].

Another approach involves the use of neural stem cells, which can differentiate into various types of neurons and glial cells. These cells have the potential to replace damaged brain tissue and promote functional recovery following TBI. In animal studies, neural stem cells have been shown to promote the growth of new neurons and improve cognitive function following TBI [27]. While the use of stem cells for TBI treatment is still in the early stages of development, these therapies hold promise for improving outcomes for individuals with TBI. Further research is needed to determine the safety and efficacy of stem cell therapies for TBI, as well as to identify the optimal types of stem cells and delivery methods for this condition.

**Biopharming**

Blood is a critical aspect in many lifesaving procedures that involve traumatic injury. Blood is vital to effective treatment and regenerative medicine as it is involved in almost every organ system in the human body and serves various functions such as transportation of nutrients and waste, immunological response, regulation bodily functions, and as a way in which hormones are carried throughout the human body. Furthermore, due to the specificity of blood with different blood types, acquiring, and maintaining a plentiful supply of Type O blood, a universal blood type, is a massive priority for any organization that deals with traumatic injury on a consistent basis [28]. Particularly within military medicine, blood is a bottleneck for patients in being able to receive adequate medical care as front-line locations often experience blood shortages and suffer from a lack of efficient transfer of blood.

"Blood pharming" refers to the process of producing blood products, such as red blood cells, platelets, and plasma, outside of the human body. It is a technology that is being developed to enable in vitro production of blood that is readily available, safe, and effective that can be used in life saving medical care. While the technology for producing blood products through biopharming exists, it is still in the experimental stage and has not yet been approved for use in clinical settings [29].

One of the challenges of blood pharming is reproducing the complex processes that occur in the human body to produce blood products. For example, the production of red blood cells requires the differentiation of stem cells into erythroblasts, which then undergo a series of maturation steps to become mature red blood cells.
Blood cells. Recreating this process outside of the human body is a complex and challenging task [30].

Being able to generate Type O blood alongside various other cell types using stem cells is only one part of the issue associated with stem cell technology. Another issue, and perhaps more pertinent to all forms of stem cell regenerative therapy, is the issue of storage. Bio-banking allows specific stem cell types to be made and stored for later use if a soldier needed it. Currently, biobanking is utilized for storage of various things such as infant tissue, sperm, eggs, and various other forms of repository for cell therapy [31]. However, current research is being done to make biobanking less costly restrictive, more energy efficient, and be able to be utilized on a much larger scale so that a repository for stem cells may be akin to blood storage.

Soldiers may receive blood on the battlefield through a process known as “blood transfusion in austere environments” (BTAE). In BTAE, pre-packaged blood products, such as freeze-dried plasma and red blood cells, are used to provide life-saving transfusions to injured soldiers in remote or challenging environments where traditional blood products may not be available [32]. The pre-packaged blood products used in BTAE are typically stored in compact, lightweight containers that can be easily transported and stored in field hospitals or other medical facilities. These blood products are designed to be compatible with a wide range of blood types, reducing the need for extensive blood typing and cross-matching [32].

To administer a BTAE transfusion, medical personnel will typically first assess the injured soldier's blood type and other medical needs. They will then prepare the appropriate blood product and administer it using a special transfusion device. In some cases, soldiers may also receive whole blood transfusions, which involve transfusing whole blood directly from a donor to the injured soldier [32]. BTAE transfusions can be critical in situations where soldiers have suffered significant blood loss due to injuries sustained in combat. By providing life-saving blood products quickly and efficiently, BTAE can help to save the lives of soldiers on the battlefield [32].

One potential application of stem cell biopharming for combat injuries is the production of growth factors, which can promote the growth and regeneration of damaged tissues. For example, stem cells could be genetically modified to produce insulin-like growth factor 1 (IGF-1), which has been shown to promote bone growth and healing in animal studies. This approach could potentially be used to accelerate the healing of bone fractures and other musculoskeletal injuries commonly seen in combat environments [33].

Another potential application of stem cell biopharming for combat injuries is the production of neurotrophic factors, which promote the growth and survival of neurons. These factors could potentially be used to promote the regeneration of damaged neurons following traumatic brain injury (TBI) or other types of nervous system damage. Stem cell biopharming could also be used to produce anti-inflammatory cytokines, which could help to reduce inflammation and promote healing in tissues damaged by combat injuries. While stem cell biopharming is still in the early stages of development, this approach holds promise for the development of new and innovative therapies for combat injuries that could potentially improve outcomes for military personnel.

Discussion

After reviewing the state of stem cell research as it stands as well as the level of implementation present today, it is not unrealistic to depict what sort of applications may be present in the future. Perhaps when clinical trials have been proven positive and successful, complete tissue regeneration may be able to be used to heal the traumatic injuries of soldiers. Specifically, being able to reconstruct all four tissue types (muscular, epithelial, connective, and neural) in both structure and function, allows doctors and healthcare providers to shift away from alleviation and mitigation of injury, but complete rehabilitation. It is also not unreasonable to depict that in the future, on-field medicine can be developed to be used for battlefield traumas that utilize stem cells. Field sprays that contain stem cells and various cytokines may be available for immediate use by combat medics in case of traumatic injury. Field sprays may also potentially be supplemented by field bandages, highly specialized plasters that contain stem cells and are anti-pathogenic, rendering them invaluable at protecting a lacerated or damaged area while promoting the process of regeneration. Biobanking and biopharming may also play a critical role in the future of military medicine in which blood can be made readily available on bases that do not require lengthy shipments of blood, while also being able to store various stem cells of soldiers in the immediate combat zone.

Future Applications

In the future, stem cells could be used on the battlefield to treat a wide range of injuries and conditions. For example, stem cells could be used to help regenerate damaged tissues and organs, including muscles, bones, and nerves. This could help to speed up the healing process and reduce the long-term impact of combat injuries. In addition, stem cells could be used to produce blood products for transfusions, reducing the need for blood donations and making it easier to provide life-saving treatments in remote or challenging environments. This could include using iPSCs or gene-edited hematopoietic stem cells to produce different types of blood products, including red blood cells, white blood cells, and platelets.

Stem cells could also be used to help develop new treatments for combat-related injuries and conditions. For example, researchers could use stem cells to develop new drugs or therapies that help to repair damaged tissues or protect the body from the effects of radiation exposure. Overall, stem cells offer a promising avenue for the development of new treatments and therapies for combat-related injuries and conditions. While much research is still needed to fully develop and optimize these techniques, the potential benefits could be significant for soldiers on the battlefield and beyond.
Stem cell application has gained tremendous ground in terms of clinical research and potential applications; however, implementation of stem cell treatment methods and tissue regeneration is far from being able to be utilized in wartime environments. Due to the nature of traumatic injuries typically seen within battlefield medicine, it is not a surprise that the frontier of stem cells and their auxiliary applications are highly researched by militaries around the world. Throughout history, various combat-related injuries have been overcome with novel treatment methods demonstrating the possibility of stem cell medicine becoming widespread and successful. However, even if stem cell treatment methods are capable of being utilized within a hospital environment, it is only field testing in wartime conditions that will determine if stem cell medicine is viable for the purposes of military medicine.

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References
6. Pin Harry, XN. Illustration of the potential sources for stem cells. from left to right, the potential site of acquisition for adult stem cells, induced pluripotent stem cells, as well as embryonic stem cells. 2023.
8. Pin Harry, XN. Example of the basic components required to construct an improvised explosive device. 2023.


