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Managing Life-threatening Traumatic Hemorrhage: A New Solution for a Changing world Paradigm

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Abstract

Millions of people die from major trauma annually. 30-40% of these deaths are due to exsanguination, with nearly half dying prior to hospital arrival. When properly managed, these deaths are preventable. This paper summarizes data relating to the extent of hemorrhage as a cause of mortality in the traumatic arena. An overview of the pathophysiological steps occurring during massive bleeding and their clinical implication is presented. A variety of treatment options, both historical and current, is then discussed, including vascular occlusion methods and hemostatic dressings, along with their limitations and complications. Finally, Wound Clot, a new hemostatic gauze, is introduced, which not only requires no compression when it is applied, but allows the first responder to rapidly and effectively treat more than one casualty within seconds. Additionally, it is adaptable to a wide array of clinical applications, both traumatic and surgical, including situations where vascular occlusion methods are not practical or are contraindicated.

Key words: Exsanguination; Hemostasis; Non-compressional; Multiple casualties; All tissues; Wound Clot

Introduction and background

Five million people die from major trauma worldwide every year. It is the third most common cause of death worldwide, and the leading cause of death in the 1-44-Year-old age group [1]. Major bleeding accounts for 30-40% of these deaths, with nearly half dying prior to hospital arrival [1-2]

Exsanguination from extremity bleeding is still a frequent and important etiology of preventable trauma fatalities, civilian and military [3], ranking second behind central nervous system injuries [1]. In the UK, 80% of deaths in the operating room and 40% of all trauma deaths are due to hemorrhage [1, 2]. When properly managed, these deaths are preventable. In the US, bleeding deaths also comprise 80% of operating room mortality, and 50% of overall mortality within the first 24 hours following admission [1]. These inordinately high statistics are likely due to the patients arriving in a very unstable condition as regards the effects of hemorrhage, i.e., the result of pathophysiology stemming from the fundamental inability to initially properly contain the bleeding. Major bleeding consists of 100% blood volume loss within 24 hours, 50% loss within 4 hours, or 150 mL per minute.

Currently, the methods of dealing with major bleeding trauma primarily have been developed based on experience amassed during times of war. However, they are all limited in their usage, as all require compression via the application of sustained manual or mechanical pressure. Some studies report that exsanguination accounts for approximately one half of all battlefield deaths during conventional warfare [4-7]. A study by Kelly et al. of US fatalities during Southwest Asian conflicts found that 7.8% were due to extremity hemorrhage [8]. Analysis of Vietnam War data by the Wound Data and Munitions Effectiveness Team (WDMET) discovered that limb wound hemorrhage accounted for greater than one half of potentially preventable combat deaths [9]. Bellamy proposed that 38% of US soldier deaths from extremity bleeding in the Vietnam War may have been saved with appropriate tourniquet use [4]. But clearly then, over 60% of these casualties, the vast majority, experienced lethal extremity hemorrhage that was not conducive to tourniquet treatment.

A 2008 study of over 6000 wounded soldiers in Operation Iraqi Freedom and Operation Enduring Freedom found that extremities were the site of ballistic injury in 54%, most of who responded to tourniquet application [10, 11]. Evaluated nearly 1000 casualties from these missions and demonstrated that bleeding accounts for 85% of potentially survivable deaths, with 31% representing compressible wounds, and 69% representing non-compressible wounds. These non-compressible injuries therefore comprise over 2/3 of potentially survivable hemorrhage deaths, yet continue to have no ideal successful solution. These injuries consist of, for example, chest and abdominal hemorrhage, massive limb damage and/or amputation, and head and neck wound hemorrhage. The Wound Data and Munitions Effectiveness Team database shows that extremity wound exsanguination comprises more than one half of all potentially preventable combat fatalities [12].

Substantial vascular injury among soldiers caused by penetrating trauma was found to have a frequency of 6.6% [13] Nearly 80% of these cases, from Operation Iraqi Freedom, were in the extremities, and most were able to reach the Air Force Theater Hospital at Balad Air Base, Iraq, in under an hour. Historically, many of the personnel who died in combat died quickly, before they could be evacuated to a hospital or aid station; the majority died from exsanguination from extremity vascular damage.

Additional modern data from the Israeli Defense Force [14] as well as the US and British involvement in Iraq [15], further attest to the fundamental role of rapid external bleeding control in managing the military victims of ballistic trauma.

Unfortunately, recent years have witnessed an increasing tendency toward heretofore unseen challenges for first responders. The field of trauma first response and casualty care has unwillingly entered a new era, heralded by the sinister specter of terrorism, with militants and radicals using weapons against primarily civilian targets. This fact clarifies an unavoidable reality; it is increasingly the case that it will be the untrained lay person who is first at the

scene and required to administer life-saving initial care to victims dying of hemorrhage during the critical first minutes. Any solution must therefore be portable, easy to use, and require no previous training.

Notwithstanding the many historic causes of mass casualties, from natural disasters to war, the increasing potential and reality of evolving terrorist threats has thus profoundly affected the implications for emergency management. Nowhere is this more evident than in Israel, which will be discussed further on with our case presentation. Clearly, there are serious implications for society far beyond the scope of this paper; however, it's meaning vis a vis trauma management, particularly with respect to mass casualty bleeding management, is highly relevant.

Terror attacks involving stabbings, shootings, bombings and the like, can present mass-casualty disasters that require providing rapid attention to numerous victims, many with multiple injuries, in an often dangerous environment. Responding to these terrorist attacks can be complicated for first responders, due to a number of factors, including the previously mentioned non-compressional nature of many bleeding wounds, multiple victims with a typically very limited number of first responders and the possibility that secondary devices may be targeted at them.

Furthermore, the stage for these events has expanded beyond regions of political unrest to potentially include any city worldwide, and, in fact, virtually any publicly-accessible location, be it a bus, a store, a park or just walking down the street. Although once primarily restricted to the Middle East, targeting Israel in particular, the heinous effects of terrorist attacks have been realized in an increasing number of other Western nations around the world. Additionally, these threats and attacks are now not only originating from outside Western nations, but increasingly due to homegrown violent extremism.

It bears repeating that it is highly likely that the initial helpers in these disasters will be untrained lay people rather than professional paramedics, as bystanders will always be first at the scene. These first responders face numerous challenges; first and foremost is their ability to act effectively in a multiple casualty scenario, limited by their lack of clinical knowledge. Another significant consideration is the limited number of hands available to treat the potentially large number of victims requiring care, all amplified by the race against time to save as many bleeding people as possible. In light of these issues, the available solutions for bleeding control need to reevaluate. The reality of this worldwide shift in the bleeding trauma paradigm necessitates the seeking of an optimal hemostatic solution which is safe, effective, easy to carry, and easily and rapidly applied by a non-professional.

Pathophysiology

A person seriously hemorrhaging can die from exsanguination within five minutes. Therefore, the most elementary initial assistance to the bleeding trauma victim is to curb blood loss as soon as possible following injury. There are multiple issues and factors contributing to polytrauma patient care, but immediate management of traumatic bleeding by the first responder is a crucial factor in deciding the fate of the injured party. Many bleeding deaths in combat are due to intracavity hemorrhage, which are typically not easily accessible, and unable to be controlled by external compression methods. [9,16] Other interventions are therefore required, and some of these various options will be discussed later.

Uncontrolled bleeding can rapidly result in hypovolemia and then shock. With a 20-30% loss in blood volume, bradycardia occurs, leading to decreased arterial pressure. As the blood loss continues to over 40%, hypotension and pre-terminal tachycardia follow [2].

With superimposed trauma and pain, the hypotension may be masked, resulting in a situation where arterial pressure appears maintained even though there has been significant loss of blood volume. Through increased sympathetic nervous activity, blood is diverted from non-essential areas to maintain perfusion to vital organs. This leads to

hypoperfusion of the non-vital organs and tissues and microcirculation with inadequate oxygen transport to these areas. Continuous hypo perfusion to the microcirculation left untreated, causes an amplified inflammatory response in the vascular endothelium [2]. The hypoperfusion-induced ischemic inflammation releases cytokines and oxidants, leading to secondary organ damage preceding multiple organ failure and death [2].

It is necessary to identify patients with major bleeding as early on as possible, to prevent or reduce hypovolemia and its downward spiral of consequences. It is noteworthy that the clinical features of hypovolemia may be masked if the victim is younger and fit, due to larger physiological reserves, as well as in the elderly, who may be on medications like beta-blockers, which alter normal physiology [1].

The severe pathophysiological instability of exsanguination manifests as the "lethal triad" of hypothermia, coagulopathy and acidosis. Hemorrhaging patients with this triad of findings have a 90% mortality rate [17] and require massive transfusion.

Hypothermia

The body's inability to produce heat is a common secondary consequence of trauma. There is an alteration in overall thermoregulation, an impeded shivering response, and decrease in cellular level metabolic activity. Several factors contribute to hypothermia in the bleeding trauma patient. Patient exposure during initial examination, fluid resuscitation, i.e., administering cold intravenous fluid, and peritoneal exposure in cold operating theatres during laparotomy all can play a role. When core temperature drops to 36 degrees for more than four hours, the hypothermia becomes clinically significant.

Coagulopathy is exacerbated in hypothermia by affecting platelet function. The enzyme activation pathway of the coagulation cascade is also reduced. Factors XI and XII only work at 65% efficiency at a body temperature of 35 degrees Celsius [18]

Any victim with a core temperature of less than 35 degrees C has a poor prognosis; there is a 100% mortality rate if core temperature drops to 32 degrees C [18]. Data from the Combat Support Hospital in Iraq demonstrated that 18% of the nearly 30,000 trauma patients were hypothermic, and this correlated with their admission Glasgow Coma Score, tachycardia, hypotension, low hematocrit and acidosis, all contributing to mortality [19].

Treatment consists of passive warming, such as covering the patient and warming the operating room, in order to stop further loss of heat. Active warming involves use of heated blankets and administration of warmed IV fluids or blood, and warm body cavity lavage, with the goal to maintain core temperature at a minimum of 36 degrees.

Acidosis

Following protracted insufficient tissue perfusion, metabolic acidosis ensues. Cellular metabolism is forced to shift from aerobic to anaerobic, increasing lactate production and reducing PH. The lowering of pH negatively affects heart contractility.

With a pH drop from 7.4 to 7, there is a significant effect on the coagulation cascade. Meng et al. demonstrated a 90% reduction in activity of factor VII a on phospholipids and platelets [20].

Other studies show that acidosis reduces fibrinogen concentration, platelet counts and thrombin production, and increases prothrombin time (PT) and partial thromboplastin time (PTT) by approximately 20% [21].

Treatment for acidosis is mainly concerned with maintaining tissue perfusion through restoration of circulation via transfusion. It has been recommended (Lier at al.) that the acidosis could be neutralized while the victim is receiving a massive transfusion by buffering with sodium bicarbonate or tri hydroxy methyl aminomethane (THAM), with better results using the latter [22].

Coagulopathy

The coagulopathy following trauma, promoted by hypothermia and acidosis, has potentially lethal consequences. A retrospective study by Brohi et al [23], examined over 1000 trauma hospital admissions and evaluated

their coagulation profile, including PT, APTT and thrombin time. One quarter of these patients exhibited coagulopathy, and that group had a mortality of 46% compared with a mortality of 10.9% for the others with normal clotting.

Current treatment for acute traumatic coagulopathy requires transfusion, as early as possible, of both blood and clotting factors [24].

Massive transfusion is defined as more than 10 units of packed red cells over a 24-hour period, or 4 units within an hour. Ideally, transfusion should begin at the accident scene.

A concern here can be the potential overloading of the circulatory system with a larger volume of fluids; this dilutes the clotting factors, reduces blood viscosity and increases blood pressure. Some studies have demonstrated a lower mortality rate (intraoperative 9% vs 32% and overall 21% vs 37%) in patients receiving "hypotensive resuscitation", i.e. transfusing enough fluid/blood products to maintain a systolic blood pressure of 90, until damage control surgery can be done [25,26].

More support for the hypotensive resuscitation concept came from the Morrison et al. study in 2012. [27] Two groups of trauma patients were resuscitated with fluids; the first aiming for a mean arterial pressure of 65 mm Hg with standard fluid protocol; the second group managed by hypotensive resuscitation to a mean arterial pressure of 50. The latter group required less fluid and blood product transfusion, and demonstrated a reduced postoperative mortality and lower postoperative bleeding, as well as less severe coagulopathy, if at all.

A huge randomized control study [28], involving 274 hospitals in 40 countries and over 20,000 patients examined the effect of the antifibrinolytic, tranexamic acid, on hemorrhaging trauma patients. Results demonstrated that tranexamic acid reduced the mortality rate in trauma patients who were at risk of hemorrhage.

Of course, if hemostasis is not achieved, resuscitation efforts are wasted. Massive bleeding, while a major cause of death, is frequently reversible. Bleeding should be controlled initially by the appropriate temporary measures, and then the patient must be transferred to an intensive care facility for prevention and correction of the lethal triad and stabilization, including surgical repair of the bleeding source.

In order to deal with the lethal triad, a reestablishment of the normal physiology must take initial priority over complete surgical repair. Following hemorrhagic shock, damage control resuscitation requires that the pre-hospital and surgical caregivers work to stop the bleeding, resuscitate the microcirculation, and moderate any trauma-induced coagulopathy. This is crucial, in that studies report that up to 95% of trauma patients who succumbed to their injuries were coagulopathic [2].

Timely resuscitation, wherein whole blood is transfused into the patient in its component parts, can limit the inflammatory response that leads to coagulopathy, thereby improving outcomes.

Transfusions, however, are not without risks and complications. Sepsis, postoperative infection, even multiple organ failure and death can inadvertently occur. Significant metabolic disturbance can result from the rapid administration of a large volume of stored blood, particularly hyperkalemia and hypocalcemia. Particularly in a high stress trauma situation, it can be very difficult to guarantee a safe blood transfusion; even making certain that the right patient gets the right blood product or products [2].

The current treatment categories and options, while providing some degree of mechanical hemostasis in very specific situations and presentations, still do not address the issue of properly and optimally facilitating the coagulation cascade.

Treatment categories and options

Field treatment approaches for life-threatening bleeding wounds emphasize rapid hemorrhage management, control of coagulopathy, ensuring of sufficient tissue perfusion and reducing the inflammatory response. Of course, once the patient is able to be moved, quick evacuation to a proper medical facility is paramount [2].

An understanding of the advantages and disadvantages of each product option is required in order to choose when and where each one may be optimally applicable for a particular clinical scenario. The key is in the selection of the most appropriate option for the particular injury, while considering the environment, circumstances and training of the caregiver.

In the new world paradigm that includes terrorist attacks inflicting multiple injuries and mass casualties, the first responder faces additional challenges. With many seriously injured victims, and a limited number of, for the most part, untrained first-aid personnel, a solution is needed which facilitates a single attendant easily and effectively treating numerous bleeding patients in seconds, without the usual requirement of having to apply manual pressure to the hemostatic agent, effectively tying up the responder from the time the hemostat is applied, right through to transporting the single victim offsite to a hospital. Clearly this is inefficient, and potentially will cost lives. Additionally, the solution should be easily usable by civilians, require no compression, and ideally be biocompatible for application to all tissue and body regions. To date, no one solution has been available.

Herein, we present an overview of the available bleeding control approaches and methods available for the caregiver in light of these emerging trauma care realities.

Vascular Occlusion Methods:

Pressure Point Compression: With digital compression on proximal arterial pressure points, bleeding is controlled due to decreased pressure at the bleeding site. If done correctly, and particularly if done concurrently with direct pressure over the site of hemorrhage (assuming it can be found and isolated), this method still, at best, only temporarily and partially controls substantial arterial bleeding [29].

A major issue with this approach is that the prehospital caregivers, treating combat or civilian casualties, usually apply inadequate pressure for an insufficient period. Although part of the reason may be lack of training, the conditions and surroundings in a combat, accident or other traumatic environment make it unlikely that the caregiver can apply the required pressure for a sufficient time to even temporarily control the bleeding until the injured person can be evacuated from the scene [29].

The inaccurate and subjective application of pressure, and typical inability to maintain a uniform pressure for the requisite time, partly due to the highly stressful and even dangerous environment, make this a poor treatment option. To make matters worse, using this technique totally neutralizes the caregiver from dealing with any other facet of care, including evacuation of the injured [29].

Direct Compression Dressings: It is logical to suggest that applying external force in order to overcome vascular hydrostatic pressure is a straightforward approach to hemorrhage control. The bleeding point, if it can be identified, must be directly covered by the dressing.

Direct pressure applied on the bleeding site should allow for at least partial hemorrhage control. This is enhanced by elevating the bleeding site above heart level, which lowers the local bleeding pressure [29].

Manual external compression typically serves only as a temporary solution at best, slowing blood loss until another method is available. It is unreliable, difficult to maintain over time, and totally neutralizes the caregiver [29]. Direct compression totally ignores the aspect of enhancing the coagulation cascade to expedite hemostasis.

Disadvantages include:

1) Useless in non-compressible areas and viable only for certain cases of limb bleeding

2) Requires sufficient pressure application for sufficient time in order for dressing to work

3) Tissue maceration can result from lengthy applica-

tions

4) If insufficient (i.e. below systolic) or inappropriately placed pressure is applied, the loss of blood can actually be increased due to reduction of venous return from the constricted area

Field Bandage : From World War 1 up until today, the army field bandage has been the major dressing to control external bleeding for most armed forces. It is both surprising and regrettable that there has been no effective evolution of care in this area since that time. A thick layer of absorbent cotton is wrapped in layers of gauze. Two long straps are attached for wrapping. The bandage exerts pressure on the wound, while large volumes of blood can be absorbed; it also provides a mesh which promotes blood coagulation and platelet aggregation. Although in use for a century, it is fraught with disadvantages. Exerted pressure over most parts of the body does not approach the diastolic blood pressure of 60 mmHg. Even placing a solid, rigid object under the pad makes no difference to the negligible pressures exerted. Because it is constructed to absorb blood, assessing blood loss is virtually impossible [29].

Emergency Bandage: Also referred to as the Israeli Bandage, it consists of an elasticized bandage with a non-adhesive pad sewn in. The pad can absorb up to one half liter of blood. A pressure-bar is built in, allowing the bandage to be wound once around the body part, then the direction of the bandage is changed, wrapping in the opposite direction to create pressure on the wound. Local pressure is thus increased.

The stretched edges of the bandage are held in place via a closure clip. The sterile non-adhering pad allows bandage removal without reopening the wound. The pressure bar is placed directly over the wound to further assist is stopping the bleeding. Its ability to permit winding the bandage in different directions is especially useful for hemostasis in groin and head injuries. Notwithstanding the inability to assess blood loss or the success of the bleeding control, and, while it is still a more advanced bandage than what was used in the past, [29] it is still only applicable to certain extremity situations.

Cinch tight Dressing: This is a compression bandage which comes in very large sizes, able to cover large wound areas, particularly of the abdomen. It is secured to the wound with over five feet of strong elastic wrap which is sewn onto a large pad (up to 12" x 16"). A metal hook on the back of the pad permits the wrapping to be doubled-back and wrapped in the opposite direction, exerting pressure while at the same time preventing slippage. High pressure is difficult to obtain, as the fastening method prevents continuation of the tightening process anywhere but on a cylindrical distal limb wound [29].

Tourniquets

Tourniquet use is at least five hundred years old, [30] with similar devices tracing back to the ancient Greeks. Tourniquet use for bleeding control has been the subject of lengthy debate. Much of the early criticism of the use of tourniquets be they professional or improvised, more accurately stemmed from the delayed access to definitive care on the battlefield in many conflicts, including the Crimean and American Civil Wars. Limb salvage was rare in these circumstances, where delayed access to surgery was often of many hours' duration [3].

Military use of tourniquets in the US demonstrated a rebirth following 1993 research by the Tactical Combat Casualty Care (TCCC) program. Up until the mid-1990s, the US military was not supplying its combat medics with modern tourniquets and training in their use [30].

In 2004, Beekley studied tourniquet use at the emergency department of the coalition's combat hospital in Baghdad [31]. By the next year, several tourniquet designs were being tested for Operation Iraqi Freedom [32]. Through these efforts, the Combat Application Tourniquet (CAT) became standard issue at that time for US service personnel. [32] Another 2004 study [33] was carried out by the US Army Institute of Surgical Research (USAISR) focusing on preventable deaths in special operations units in Afghanistan and Iraq. Results found a 15% incidence of

preventable deaths, including deaths from extremity hemorrhage which could have been prevented with effective tourniquet use.

As awareness of the success of the TCCC Transition Initiative and the U.S. Central Command directive spread throughout the military, conventional units began to adopt the TCCC recommendations, including tourniquets. In 2005, US Central Command ordered that all soldiers deployed to a theater of combat be equipped with tourniquets and hemostatic dressings. Tourniquet use increased in the US military in 2005 and 2006. Dr. Colonel John Kragh, an orthopedic surgeon serving in Baghdad, documented the benefits of battlefield tourniquet use in 2006. [34,35] He studied a variety of casualties utilizing tourniquets. This research resulted in offering practical guidelines for tourniquet use. Survival rates were higher with tourniquet use (87%) *vs* without (0%), pre-hospital use (89%) *vs* hospital use (78%), and before the onset of shock (96%) vs after shock onset (4%). [35] This data demonstrates that in a war casualty situation, the proper tourniquet applied properly at the right time significantly saved lives. By 2008 tourniquets became an accepted prehospital intervention with persuasive data demonstrating their life-saving ability for limb injured casualties [36].

By 2011, a study by Eastridge demonstrated that preventable deaths from extremity bleeding had dropped from the 7.8% in the Kelly study [8] to only 2.6%, a 67% decrease. This helped establish the benefits of tourniquet use on the battlefield [37].

In 2014, it was estimated that between 1,000 and 2,000 American soldiers' lives were saved during combat trauma in Afghanistan and Iraq with tourniquet use. [30] The Israeli Defense Force (IDF) has used tourniquets extensively, and has collected some of the best data available regarding complications associated with tourniquets use on the battlefield. The IDF reported very few complications, and most were temporary in nature. [31] These studies all lend support to the proposition that tourniquets provide an effective and relatively safe method of bleeding control when quick access to decisive intervention is required.

These positive findings are no doubt in part also due to increased speed and efficiency of the evacuation of casualties, and consequent reduced time to surgery, frequently under one hour [13].

The increased survival is also partially due to improvements in body armor that reduces mortality from thoracic and abdominal trauma [13] And, fortunately, all of these factors ultimately contribute to the increased number of vascular injuries seen in the military hospitals, as the number of soldiers surviving long enough to reach hospital has also risen, from 2-3% during the Vietnam War.

No cases of serious complication following aggressive tourniquet use were reported among trauma patients presenting to the USAF Theatre Hospital at Balad, Iraq. A tourniquet, when applied properly, temporarily controls bleeding until the patient can be evacuated to a proper care facility, and also frees up the caregiver to attend to other injured troops [3].

Regardless of previous opposition to the usefulness and safety of tourniquet use, the more recent studies and technological advances have helped to dispel legitimate concerns. [29] Clearly, saving a life, even with the possible loss of a limb, must remain the top priority. Notwithstanding this consideration, every effort should be made to reduce the time the tourniquet is in place, thus reducing potential for complications [3].

Any utilization of a tourniquet must come with the awareness of its hazards and potential risks. The majority of these complications arise due to either direct pressure on underlying tissues, or the byproducts of tissue ischemia distal to the application site. Most of the complications are local; however, there can be systemic issues such as thromboembolism, most significantly pulmonary embolism, renal failure due to rhabdomyolysis, respiratory acidosis, hyperkalemia, cardiac arrhythmias and shock [38-43].

Complications of tourniquet use may be transient or permanent, and include erythema, local bullous skin lesions, paresthesia's, paralysis of the affected limb, vascular spasm, fracture of atheromatous plaque, muscle injury, gan-

grene, infection and edema [3]. Additionally, in a conscious victim, proper tourniquet application is extremely painful, which continues until the tourniquet's removal [29].

Tourniquet application with the high pressure necessary to cause complete loss of blood supply to the distal soft tissue will lead to ischemia and subsequent infarction. [29] However, ischemic damage to the limb is rare if the tourniquet is left in place less than an hour. However, tourniquets are often left in place for several hours during surgical procedures. [30] Tourniquet usage during elective surgery has resulted in cardiac arrest due to circulatory overload in patients with poor cardiac reserve; the tourniquet causes a functional increase in the blood volume which is circulating [3].

In the face of massive extremity hemorrhage, in any event, it is better to accept the small risk of ischemic damage to the limb than to lose a casualty to exsanguination [30].

New advances in tourniquet technology appear promising. The Combat Application Tourniquet (CAT) was invented by military medics, and is designed to provide US and coalition troops with a small, yet effective, tourniquet to use in the field. The CAT utilizes a durable windlass system with a free-moving internal band and a Velcro fastening system providing circumferential pressure to the extremity. When properly tightened, a hook and loop windlass retention strap is then applied, securing the windlass to maintain pressure during casualty evacuation. The CAT's effectiveness rate was the highest of the field tourniquets at 79% in stopping compressible bleeding on the battlefield. [34] The US army took the recommendation of the Committee on Tactical Combat Casualty Care and chose the CAT as the tourniquet for field training and distribution. [3] It is also used by National Health Service ambulances in the UK, and UK fire and rescue teams [29].

In summary [3]

When there is a risk of exsanguination from an extremity injury, a tourniquet should be used for hemorrhage control without hesitation or concern for potential complications.

Where rapid evacuation of the injured party is required for patient and caregiver safety, e.g. combat, risk of building collapse, fire or explosions, a tourniquet is indicated to control life-threatening bleeding.

In mass casualty situations, tourniquets may be helpful for temporary bleeding control until the entire overall situation can be stabilized. However, the need for a tourniquet to permit transport of the injured person should be reassessed as soon as possible.

A tourniquet should not be the initial treatment of choice for an amputation with hemorrhage unless the bleeding cannot be controlled by direct pressure, elevation and wound packing.

A tourniquet may be placed proximal to uncontrollable bleeding around an impaled object, but the tourniquet should never be placed over the object.

A tourniquet should never be applied over a joint or clothing, and should be applied at least 3-5 cm proximal to the edge of the wound. The treated limb should be fully exposed, the tourniquet never covered, and the patient should be marked as having a tourniquet, as well as the time it was applied.

If bleeding continues distal to the tourniquet, this means it is exerting insufficient pressure and needs to be tightened. It should never be loosened if a patient exhibits signs of shock, if used to control bleeding in an amputation, or in any situation where the wound bleeding would not be expected to be controlled by any other means.

A tourniquet that has been in place for greater than six hours should not be removed until patient arrives at a facility capable of further advanced treatment.

Currently, the Tactical Combat Casualty Care (TCCC) course of the US Army endorses tourniquet use as a "stopgap" therapy in combat, [44] keeping in mind that its use should be reassessed as soon as the situation permits.

Although there are tangible and significant risks and potential complications in tourniquet use, tourniquets have a place in the management of arterial bleeding that fails to respond to other interventions. The timely and situation-appropriate application of a tourniquet when there is life-threatening hemorrhage will continue to save lives.

Nonetheless, it is safest, when the first caregiver is only marginally trained or inexperienced with basic first aid training, to utilize simple direct pressure or some type of basic pressure dressing. This is because there is little evidence that the first care provider can properly identify the need for a tourniquet and properly apply it, particularly given the likelihood of improvising in a stressful trauma situation [46-47].

All this being said, despite the inherent benefits and life-saving data, all tourniquets remain seriously limited in their application to only a certain minority of traumatic hemorrhaging extremity scenarios.

Hemostatic Dressings

The original TCCC guidelines did not include hemostatic dressings. [30] They have emerged fairly recently, and been researched over the past 5 - 20 years. These products are categorized as either dressings or granular/powder agents. [29] These dressings have several advantages:

1) A wide range of regional application; control of hemorrhage is via promotion of clotting.

2) This treatment requires no specific training or proficiency.

The disadvantages include:

1) The caregiver must still press the hemostatic agents against the wound until hemostasis occurs, thus preventing him/her from attending to other wounded; this is not optimal or feasible during combat or when dealing with multiple patients. This also limits where the product can be applied on the body.

2) Wound must be observed, as any movement or friction can dislodge the clot and result in hemorrhage resuming even following initial full hemostasis.

3) The available options are non-absorbable; removal causes pain and re-bleeding.

4) Use may be limited by prohibitive cost.

The U.S. military began considering their use following American involvement in Afghanistan.
The first agents were the Hem Con bandage and Quick Clot granules, both commercially developed, with other products following shortly thereafter [30]. Initial studies on lethal bleeding in animals by the USAISR and the Naval Medical Research Center demonstrated improved survival with both products [36].

Quick Clot was chosen by the U.S. Marine Corps, while the Army and the USSOCOM selected the Hem Con dressing. After 2003, use of these two dressings spread quickly throughout the entire U.S. military. Positive results with these products in battlefield use were reported in 2 retrospective studies [47-48].

Although both were found to be of nearly equal efficacy, the Quick Clot granules, when contacting a liquid, including blood, produced an exothermic reaction, causing burns with substantial thermal tissue damage, causing additional pain to the injured soldier [29-30].

Later testing on Hem Con found that it produced only brief hemostasis in 71% of swine with aortic injury, and consistently failed to stop bleeding in femoral artery injury [49-50].

By 2008, newer products were becoming available. Combat Gauze, a polyester-rayon non-woven gauze impregnated with kaolin (an intrinsic pathway activating agent) and a similar product, X-Sponge, demonstrated effectiveness in swine models, with 80% survival rate, using femoral artery, carotid artery and jugular vein injuries [51-52].

The reader must bear in mind that these data resulted from highly controlled sterile lab experiments with animals; vastly different from the unpredictable severe trauma and chaotic environment of a mass human casualty scenario.

Wound Stat is comprised of smectite granules; they swell when absorbing fluid, forming a highly plastic clay-like material which sticks to tissue, sealing the site of bleeding. The product's negative electrostatic charge helps to activate the intrinsic clotting pathway, and accelerates clotting by attracting red blood cells and clotting factors.

Combat Gauze and Wound Stat were found in USAISR testing to be consistently more effective than the Hem Con and Quick Clot. Combat Gauze was soon established in the TCCC guidelines as the primary recommended battlefield option in treating life-threatening bleeding not amenable to a tourniquet. In making this decision, combat medics strongly preferred a gauze-type hemostatic dressing over a powder or granules. Wound Stat was secondarily recommended in cases where Combat Gauze was unsuccessful [30].

When further USAISR testing demonstrated that Wound Stat caused thromboembolism and vessel wall damage in animal studies, it was withdrawn from use by the U.S. military. The IDF reported a 79 percent success rate with Combat Gauze [53-54].

Continuing research is being carried out on new dressings. A review and testing of a variety of hemostatic dressings was performed by Keirabadi et al. [55] Not all products performed well.

Chitosan, a product derived from shellfish, possesses a strong muco-adhesive ability that lends itself well to hemostatic treatment. It is found in Hem Con dressing, Chito flex dressing, and Celox, which all adhere to tissue while covering the wound. Celox is a powdered form of several types of chitosan; it binds to red blood cells and adheres to the site of injured tissue [29].

The Naval Medical Research Unit in Texas demonstrated that Celox gauze and Chito gauze provided higher survival rates in animal femoral bleeding tests that Combat Gauze. [56] For a swine groin injury, Celox demonstrated equal effectiveness to Quick Clot and Hem Con in rebleeding prevention, and substantially better results than standard plain gauze treatment [57].

In another study, [58] Celox resulted in a 60% survival rate vs Hem Con and the new version of Quick Clot could only claim a 10% success rate. Although effective against severe venous (low pressure) hemorrhage or low-pressure mixed bleeding from the groin, Quick Clot has not been found to be significantly effective in controlling arterial hemorrhage [59].

Rapid Deployed Hemostatic (RDH) dressing is derived from algae. Its original version was ineffective in controlling both aortic and liver injury bleeding, [60-61] however a modified version was effective in another study [62-64] but was unsuccessful in a mixed bleeding groin injury [65].

While these various hemostatic dressings demonstrate various levels of success in their short-term application, a 2016 study on pigs by Otrocka-Domagala et al. [61] examined the effects of Quick Clot, Chito gauze PRO and Celox gauze over a longer-term application, i.e.,24 hours. This is a very important consideration for both survival and recovery in situations where the patient must be transported over a long distance in order to reach a medical treatment facility.

These hemostatic dressings demonstrated that, as they begin to break down, their residues slowly enter the circulatory system, causing circulatory distress by increasing the risk of coagulopathy via embolus formation, called Disseminated Intravascular Coagulation (DIC). Small blood clots develop throughout the bloodstream, blocking smaller blood vessels. This increased clotting depletes the platelets and clotting factors required to control bleeding, leading to increased hemorrhage as well as multiple organ damage. Damage to crucial organs, the heart, lungs, liver and kidneys, ensues. Progressing shock follows.

Thromboembolic material was observed in the pulmonary artery and lung vessels of animals treated with each of the agents. Additionally, pneumonia was observed in all lungs, and there was muscle, vessel and soft tissue damage at the site of application. Due to these harmful effects, Quick Clot, Combat Gauze, Chito gauze PRO and Celox gauze are not appropriate for long-term use.

Fibrin Sealant Dressing contains human plasma fibrinogen and thrombin. It forms an adhesive fibrin layer upon contact with blood; it conforms and tightly adheres to the wound, halting the bleeding. It has been found very effective in several animal hemorrhage studies. [67-75] It is even more effective than Combat Gauze or Wound Stat [76]. The fibrinogen-based dressings have been found to be most successful up to now, with good long-term safety.

XSTAT is a unique type of hemostat that works by injecting numerous small, quickly-expanding sponges into the wound cavity via a syringe-like applicator. On contact with blood, the sponges swell and fill the wound cavity within 20 seconds, forming a temporary barrier to the hemorrhage and offering hemostatic pressure. Each small sponge contains a marker detectable on x-ray. The product is meant only for temporary use for life-threatening, non-compressible hemorrhage in adults and adolescents, for up to four hours, at sites in the groin or axilla which cannot be treated by tourniquet. XSTAT's limitations include its non-absorbability, and it is not made for use in the thorax, pleural cavity, mediastinum, abdomen, retroperitoneal space, sacral space above the inguinal ligament, or any site cephalad to the clavicle.

Let us now examine these hemostatic options available to a first responder in the clinical reality of a mass civilian casualty scenario in order to observe their limitations. The initial factor to consider is the first responder him/herself. Prior to the hopefully rapid arrival of professional paramedics, those uninjured or less-injured lay people immediately at the scene will be thrust into the role of first responder. The severe inherent limitations are apparent. First, the vast majority of this population will be untrained in all but possibly the most basic instinctive first aid. When this is combined with the general panic, chaos and innate attempt to look for injured family/friends while seeking their own safety, this is a generally ineffective group. These people will be poorly to non-equipped, and have no ability to triage. Multiple bleeds will only be able to be handled on a single patient basis; one care-giver to one casualty. So the first limitation is on how many bleeding people can truly be helped (read: sustained to be saved) during the absolutely crucial first minutes following the disaster.

The next factor is the type of care the patient can expect. If the wound is amenable to direct pressure, the untrained person can administer some degree of direct manual pressure, perhaps with some cloth or fabric forming a makeshift bandage. The limitation becomes the length of time the person can maintain sufficient pressure to stop the bleeding. Furthermore, this pressure needs to be maintained until the victim has been transported to hospital. Certain minor head or trunk injuries may also allow for this kind of treatment. But this direct mechanical pressure method effectively eliminates this care-giver from helping another victim. The untrained lay first responder may also fashion a makeshift tourniquet to try and stop appendicular hemorrhage. As previously discussed, incorrect application may cause more harm than good. Mechanical pressure does nothing to assist the coagulation cascade, may result in tissue damage, and, if insufficient or inappropriately placed pressure is applied, the loss of blood may actually be increased because of reduced venous return from the constricted site. If the wound is large, however, or if there is bleeding from a site in the abdomen or neck that does not permit direct pressure, there is little this type of care-giver can do.

Another factor to consider is the likely possibility of one or more comorbidities in any of the casualties. As discussed earlier, a number of these comorbidities, along with some of the medications being taken to treat them, can negatively affect thrombocytes or the coagulation cascade, complicating the individual patient profile.

Moving on to the professional paramedic, the arsenal of tools is much broader. Yet, rapid deployment of any hemostatic method is vital in order to avoid shock and the lethal triad as outlined above. The first responder will likely be saddled with the unenviable task of triage, trying to decide who can be saved, in a chaotic and possibly dangerous environment. Professional application of manual or mechanical pressure to the bleeding wound has less of the risks and complications mentioned above, but virtually no additional benefits other than as an extremely temporary measure. It still removes a professional care-giver from the situation, and prevents care of more than one injured person. Tourniquet application fares poorly overall as well. While a proper tourniquet will be available and applied properly, the types of injuries it can be used for remain limited, essentially limb bleeding wherein enough of the limb remains cephalad to the hemorrhage to permit the tourniquet's application. The additional limitations and cautions regarding use of the tourniquet are listed above; as well as the pain it causes in the still-conscious patient.

The paramedic likely has access to one or more varieties of hemostatic dressings, in order to address deep wounds, trunk wounds, head and neck injuries, and any hemorrhage that does not lend itself to compressional hemostasis. These dressings, however, also possess either limitations or complicating side effects, as previously described. Most are non-bioabsorbable, with removal causing pain and re-bleeding. Hem Con demonstrated poor efficiency with major vessel (i.e., aortic or femoral artery) hemorrhage; Quick Clot exhibited exothermic reaction causing thermal tissue damage and burns; Wound Stat use causes thromboembolism and vessel damage; Combat Gauze and X-Sponge, while somewhat effective in sterile lab conditions with animal trials, are non-bioabsorbable; Chito gauze and Celox gauze cause residue deposits into the bloodstream as they break down, leading to Disseminated Intravascular Coagulation, increased hemorrhage and multiple organ damage. What's left? A need.

Wound Clot: the new alternative

It would be extremely valuable for a hemostat to facilitate a single first responder, trained or untrained, being able to treat multiple victims in seconds. Wound Clot uniquely delivers on this crucial time-saving, life-saving point, by providing rapid, effective hemorrhage control without the need for compression, i.e. pressure application, by the caregiver. Wound Clot hemostatic gauze comprises a completely new hierarchy of material engineering from its molecular level, through optimization of its physical properties, interaction with blood and maximization of its clotting promotion capabilities. Its unique biocompatibility effectively solves the major thromboembolism problem demonstrated by other major hemostatic dressings over long term use. There is no contraindication for its use in terms of tissue type, volume of bleeding, site of hemorrhage, or medications taken for comorbidities. There are no side-effects, risks or complications. It's portable and easily applied in virtually all circumstances.

Case History

The significance and benefits of Wound Clot's unique properties: its stability, bio-absorbability, self-adherence, and in particular, its application without requiring compression, are well demonstrated in this case presentation. In February, 2016, a terrorist stabbed a passerby with a knife on Hatzanhanim Street in downtown Jerusalem and then was subsequently shot and neutralized by another civilian. The first responder on the scene was a police department paramedic. He encountered two critically injured casualties, the civilian victim and the perpetrator. Immediately directing his attention to the civilian, he encountered marked bleeding from a wound in the carotid artery. He used an 8 cm x 20 cm Wound Clot trauma gauze roll, and placed it directly on the site of hemorrhage. The bleeding stream was immediately reduced, stopping completely in less than one minute. Once he was certain that the bleeding had ceased and the patient was stable by checking all vital signs, he went over to the terrorist. He was suffering from 4 gunshot exit wounds with significant bleeding. The officer took a large 8 cm x100 cm Wound Clot trauma gauze roll, cut it in four, and packed each exit wound with the gauze. He remarked surprisingly that it took him a to-

tal of less than two and one half minutes to control the 5 life-threatening bleedings the two patients.

Half an hour after the patients had been evacuated to the hospital, the officer called the vice-president of sales at Core Scientific; and this is his direct quote: "Amit, I must tell you, what I have just done could have never, and I mean never, happened with any other trauma bleeding control gauze or device; I say it with more than 25 years of trauma treatment experience, due to the need with all of the other bleeding control gauze or devices to maintain pressure for at least 3-5 minutes or for as much is required to control the bleeding. In the carotid case, normally I would have to maintain applying pressure with my fingers all the way to the hospital, meaning I would have to accompany the patient to the hospital. Needless to say that in this case I could have never helped anyone else besides the civilian with the hemorrhaging carotid artery stab wound."

Wound Clot

Wound Clot Surgical is a Class III bio-absorbable, non-compressional hemostatic dressing, made by non-oxidative chemical reaction using cellulose as a substrate to build upon advanced functional groups. Those functional molecular groups (FMGs) were specifically designed to provide special physical and performance properties. They increase the blood's affinity for the product while enhancing intermolecular forces between the polymeric chains in order to maintain product stability. These additional interactions inhibit rapid dissociation when exposed to an aqueous environment and preserve the stable gel state for an extended period of time.

A key to Wound Clot's effectiveness is its non-oxidative production method. Other hemostatic products on the market utilize an oxidative process, which accelerates their decomposition, therefore limiting the crucial initial duration of product activity.

Upon placement of Wound Clot dressing on the bleeding site, the product's unique gel utilizes the hydration forces between the soft tissue layer and itself, which results in a strong physical attraction that leads to the adherence of the product to the tissue. The stronger the bleeding pressures in the wound, the stronger the attraction.

For this to happen, the gel formed is designed to be relatively slow in forming with a vast ability to absorb bleeding without breaking down. This ability to absorb and maintain a stable membrane allows for the pooling of active coagulation factors in significant quantities to be sequestered in the membrane. Membrane flexibility on the molecular gel structure allows a hemodynamic environment in which rapid coagulation cascades are created, because of the large amount of coagulation factors present due to the product's high absorption capability.

The coagulation factors attach to the surface tissue and the membrane in the presence of a patented molecular group incorporated into the product. The coagulation process initiated is much more rapid, by enhancing the presence of platelets, multiple coagulation factors, and amino acids. This dramatically reduces the flow of blood from the wound.

In turn, this process also increases adherence of the membrane to the tissue, ensuring its stability on the wound site.

Once bleeding has stopped and the clot has formed, the capillary and hydration physical forces are reduced, allowing for the easy removal of Wound Clot, if desired, in one piece, without clot disruption.

The liquid absorption capability of Wound Clot is over 2500 times its own weight. When exposed to blood, the formed 3D matrix entraps platelets and coagulants in a hemodynamic environment. This allows for an increase in concentration of blood components at the wound site, while retaining their mobility and activity in order to form a clot. Moreover, its functional molecular groups (FMGs) are designed to have a strong impact on the natural biological clotting process.

Wound Clot initially forms a mechanical plug by adhering to the cavity, slowing down the blood flow, promoting massive absorption of platelets, and accelerating the plug formation. Once the platelets interact with Wound Clot, the FMG promotes platelet activation, initiating the intrinsic clotting pathway. Wound Clot affects the coagulation process by transforming Hageman factor (factor XII) from inactive to active (XIIa), and activating plasma thromboplastin antecedent (factor XI) for a longer duration when

compared to other common hemostats.

Wound Clot provides a variety of relevant clinical considerations, including orthopedics, cardiovascular, endoscopic, obstetric/gynecologic, bariatric/gastrointestinal surgery, trauma resulting in many types of bleeding, as well as a valuable adjunct for dialysis patients.

Wound Clot provides numerous and significant advantages to both doctor and patient. It is versatile, adjustable and flexible. Wound Clot is therefore extremely user friendly; it can be cut to custom size or rolled for optimal wound insertion; it does not stick to gloves or instruments. Importantly, it uniquely involves a non-pressure application, allowing for effective use in situations where maintained pressure is contraindicated. Although bioabsorbable, it also possesses ease of removal. There are no active ingredients, and the product even lends itself to use by coagulopathic patients.

As a simple to use, versatile, non-compressional hemostat, Wound Clot finally provides a new and improved solution to the clinical problem of uncontrolled hemorrhage for virtually all pre-hospital civilian and military hemorrhaging trauma, as well as in the operating room and post-surgical applications.

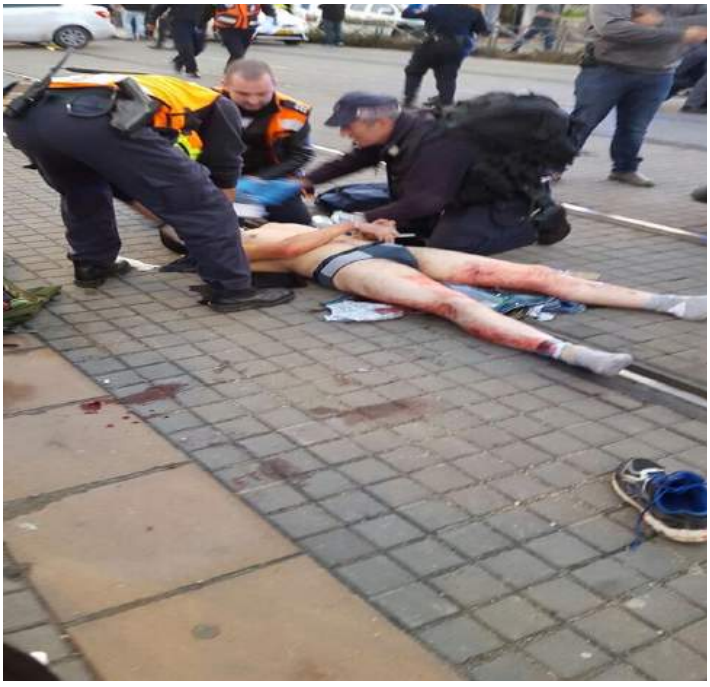

Figure 1: Handcuffed terrorist being attended to by police and paramedics

Figure 2: Handcuffed terrorist being attended to by police and paramedics

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