OMNI-STAT®

CLINICAL AND SCIENTIFIC MONOGRAPH

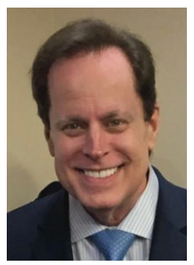
Contents

Foreword

Whether by accident or intent, the body suffers from an injury that damages the integument, unless this is a minor abrasion, the likelihood is that bleeding will occur. Fairly minor bleeds from small injuries are generally quickly dealt with by the body as a result of the clotting cascade that "kicks in" to coagulate the blood at the site of the injury and "plug" the damaged tissue and stop egress of blood. However larger injuries in which blood loss is great may overcome this coagulation mechanism and the resulting severe bleeding can lead to exsanguination and death. Excessive or disruptive blood loss from patients undergoing hospital procedures are at risk particularly if those patients are on anticoagulants (e.g. heparin, warfarin, and more recently developed direct oral anticoagulants (DOACs)). Major trauma injuries and general surgical procedures both pose a risk of excessive bleeding events. Hemostasis and its control is a fundamental requirement in any surgical procedure as any bleeding must be stopped before a wound can heal.

Attaining hemostasis is of primary importance to clinicians faced with significant bleeding. With tissue bleeding and severe blood loss being common in surgical procedures, adjunctive hemostatic agents (including mechanical hemostats, active hemostats, flowable hemostats and fibrin sealants) have been developed that aid in preventing blood loss. More recently, new options such as hemostatic dressings have been developed that act quickly and efficiently in providing hemostasis. Chitosan derived hemostatic topical agents/dressings are a promising adjunctive and proven treatment for preventing blood loss.

This Clinical and Scientific Monograph examines the evidence relating to OMNI-STAT®[1], a chitosan derived topical temporary external hemostat that meets the criteria for the ideal hemostat and provides rapid and effective hemostasis. Showing great success in the battlefield providing effective hemostasis in cases of traumatic bleeding, positive results and technological advances led to an increase in the momentum for the use of OMNI-STAT and its adoption by a growing number of hospitals in, for example, wound care clinics, emergency rooms, operating rooms and catheterization laboratories.



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1. OMNI-STAT is the brand name of the chitosan derived hemostat marketed for hospital application by MPL. The equivalent base material and granules is marketed for military applications under the Celox™ brand name and also marketed by MPL. For the purpose of this discussion OMNI-STAT is used as a general term for this group of MPL hemostats containing chitosan and its derivatives.

Executive Summary

- The primary objective of this document is to review the scientific and clinical evidence in support of the chitosan derived hemostatic agent, OMNI-STAT
- Scientific evidence: laboratory studies provide evidence for the effectiveness of OMNI-STAT as a hemostatic agent
- Scientific evidence: animal model studies provide evidence for the effectiveness of OMNI-STAT as a topical temporary external hemostatic agent for traumatic bleeding and bleeding in presence of some anticoagulant drugs
- Clinical evidence: OMNI-STAT provides effective hemostasis in patients with chronic wounds where sharp debridement is used as part of the treatment regime to remove devitalized tissue. OMNI-STAT offers the opportunity for rapid debridement of necrotic tissue to patients receiving antithrombotic therapies to prevent further deterioration of necrotic wound tissue. This allows for safe and effective debridement in an ambulatory (outpatient) setting or for inpatients at the bedside and avoiding the operating room
- Clinical evidence: OMNI-STAT promotes rapid hemostasis in several examples of traumatic hemorrhage and in patients who exhibit compromised coagulation. This could help prevent further serious deterioration of the patient condition.
- OMNI-STAT as a granular chitosan derived topical temporary external hemostatic agent meets several of the characteristics of an "ideal hemostatic agent". It is an effective hemostat and should be removed once hemostasis is achieved and not left inside the body
- OMNI-STAT is cleared under several 510Ks as a topical temporary external hemostat. Under the supervision of a healthcare professional
    - OMNI-STAT is indicated for use as a temporary topical dressing for bleeding control associated with minor wounds, including control of minor external bleeding and exudate from sutures and/or surgical procedure
    - OMNI-STAT is indicated for temporary external treatment for controlling moderate to severe bleeding

1. Abstract

Wound healing progresses via a series of co-ordinated phases and hemostasis is the first step of this healing response. Initiated at the time of injury, the role of hemostasis is to halt blood loss arising from damage to blood vessels during injury. Tissue bleeding is a common risk during surgical procedures (e.g. sharp wound debridement) and with any bleeding event, if uncontrolled can have significant implications for patient outcomes leading to increased morbidity and mortality. Additionally blood loss is a particular problem in patients where normal coagulation pathways are compromised such as those that are undergoing anticoagulant therapy or have coagulation dis-orders.

In the first instance the use of compression with gauze is a prevalent practice for most injuries (traumatic or surgical), however, this method of hemostasis is suitable only for the treatment of low blood flow loss and utilizes valuable healthcare resources. If greater blood loss occurs as a result of high blood flow/pressure then the application of compression is not suitable to enable hemostasis. In order to overcome this problem a wide range of hemostatic agents have been developed that can prevent or reduce high flow/volume blood loss by use of single-application materials with rapid action. These topical hemostatic agents have been developed with varying modes of action including passive (physical blocking of blood loss) and active (agents that contain coagulation pathway components) hemostats, flowable (combinations of physical blockage and active components) and adhesive (synthetic) hemostats. More recently, external topical temporary hemostats have shown great success in the hospital setting (e.g. emergency rooms, wound clinics, operating rooms) with chitosan derived hemostats showing particular efficacy.

OMNI-STAT is a chitosan derived topical temporary external hemostat that is fast, safe and effective for controlling minor, moderate and severe bleeding. The mechanism of action of OMNI-STAT is independent of the normal coagulation pathway and is effective in patients receiving anticoagulation therapy. It is easy to use and shows many of the characteristics of an ideal hemostat, including cost-effectiveness. This Clinical and Scientific Monograph summarizes the scientific and clinical evidence supporting the use of OMNI-STAT as an effective and fast-acting hemostat. OMNI-STAT is effective in a variety of clinical situations including as an adjunct for treatment during sharp wound debridement, as well as for uncontrolled hemorrhage and bleeding in presence of some anticoagulant drugs.

Keywords: OMNI-STAT; hemorrhage; anticoagulant; emergency room; vascular closure; chitosan, heparin; wound care; wound healing; clinical effectiveness; health economics; debridement

2. Introduction

Section key points

- Hemostasis is a critical early step after wounding
- Bleeding is a significant risk during surgery
- Hemostatic agents offer an effective tool to stop excessive bleeding
- Hemostatic agents that work independent of clotting cascade may offer benefits to patients with impaired coagulation

The injuring of the body initiates a series of events in order to repair the injured tissues. These series of events are a complex cascade of overlapping and interconnected processes and can be grouped into four main phases: hemostasis, inflammatory phase, proliferative phase and maturation.

Hemostasis, the first phase of the wound healing response, is initiated at the time of injury and the role of this phase is to stop any bleeding resulting from wounding. Under normal circumstances, hemostasis is an emergency response to injury, attempting to limit the loss of blood via the wound and to initiate the subsequent phases of healing (Figure 1). There is an initial constriction of blood vessels (vasoconstriction) in order to reduce the level of blood flow to the region of the wounding. Activation of the blood clotting cascade via platelet activation leads to a number of subsequent processes such as platelet activation/ aggregation and fibrin clot formation that leads to blood coagulation and the formation of a physical "plug" that fills the wound defect. Coagulopathies – bleeding disorders that affect the way blood clots – affect the body's ability to provide an effective hemostatic response. For example, patients with the rare condition hemophilia suffer from deficiencies in the factors necessary for blood clotting and this manifests itself as extended bleeding times after injury. However, larger injuries may result in a large loss of blood which may overcome the normal coagulation mechanisms leading to excessive blood loss and the possibility of death due to exsanguination. It has been estimated that injuries to the major arteries with significant hemorrhage accounts for 50% and 31% of the total deaths in war and civilian settings, respectively (Zhang et al, 2015).

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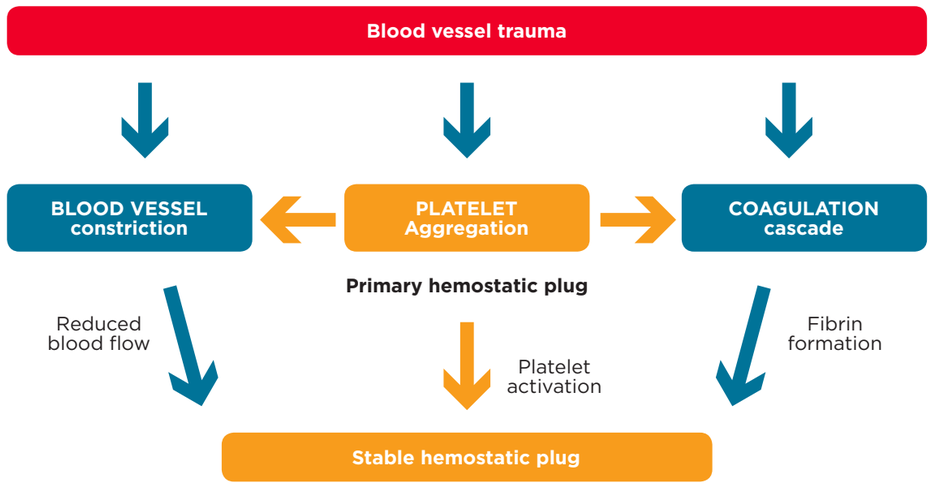
Figure 1: Overview of hemostasis (modified from Seyednejad et al, 2008)



Tissue bleeding is a common risk for surgical procedures. For example, cardiac surgery has one of the highest risks of bleeding, with upwards of 50% of patients experiencing some type of bleeding related complication during surgical procedure (Shander, 2007). Other common surgical procedures have bleeding rates ranging from <10% to 35% (Shander, 2007). In the emergency room setting, exsanguination (i.e., death from uncontrolled hemorrhage) has accounted for over one-third of all deaths (Evans et al, 2010), and is a number that has been consistently at this level of a number of years (Behrens et al, 2014). Uncontrolled bleeding has been linked to increases in morbidity and mortality (Marietta et al, 2006), and significantly increased costs (Stokes et al, 2011; Corral et al, 2015). Excessive blood loss during surgical procedures is a particular problem in patients on significant antithrombotic therapies (e.g. warfarin, DOACs) where normal coagulation pathways are compromised (Kuar et al, 2013) or those with bleeding disorders (e.g. coagulopathies such as hemophilia). It is important for patients to continue taking anticoagulants prescribed to them as discontinuation of their use may put them at increased risk of thrombotic episodes (e.g. stroke, deep vein thrombosis, etc.) (Kovich and Otley, 2003).

The use of compression with gauze is a prevalent practice for most injuries and for the majority of common surgical procedures this is still the main way to achieve hemostasis, and this method has remained relatively unchanged (Behrens et al, 2014). The control of blood loss by the application of pressure are not suitable in non-compressible regions. Alternate solutions may be found in the use of hemostatic dressings which act rapidly in a single application.

The development of hemostatic dressings composed of hemostatic agents or where these agents are combined with a supportive matrix have allowed for effective hemostasis in wounds at sites where compression is not suitable. Recently, the number and forms of hemostatic dressings have increased significantly as dressing and material technology has advanced (Behrens et al, 2014). The myriad of hemostatic dressings now presents the opportunity to aid in the treatment of large traumatic wounds where excessive blood loss interrupts normal coagulation processes and offers an alternate mechanism for stemming blood loss in cases where normal coagulation processes are hindered by patient coagulopathies or anticoagulant therapies.

Wound debridement is the first step to enabling the quick and successful closure of some wounds. However, radical sharp or surgical debridement can increase the risk of bleeding which would require effective hemostasis, ideally in the form of a topical medical device (e.g. dressing). "Wound bed preparation" is a key concept for transforming problematic wounds into wounds better able to respond to wound care interventions and debridement is key (Suzuki and Cowan, 2009). Sharp surgical debridement is an important tool for clinicians to cleanse difficult-to-heal wounds such as chronic ulcers (e.g. leg ulcers, pressure ulcers, diabetic foot ulcers). These chronic wounds frequently contain devitalized necrotic tissue and slough (including biofilm) on their surface that prevents significant healing of these wounds. As well as promoting healing, sharp debridement also reduces the risk of wound infection which, in turn, can lead to reduced hospital stays and improvements in a patient's quality of life. Many of these patients are on anticoagulant therapies meaning that radical sharp debridement – which results in removal of all devitalized tissue and tissue bleeding of viable tissue – is risky, particularly when the procedure is carried out in an ambulatory setting (i.e., outside of the operating room).

There are a number of different hemostatic methods available to minimize blood loss. Clinicians face an increasing challenge in choosing the most appropriate route to achieve hemostasis, a challenge that is made more difficult because of the increased drive to limit costs (Camp, 2014). The various methods of hemostasis can be classified into two general categories: traditional hemostatic methods and topical hemostatic agents. Within each of these two broad groups there are several sub-groups (Camp, 2014; Schreiber and Neveleff, 2011).

2.1 TRADITIONAL HEMOSTATIC METHODS

There are three main types of traditional hemostatic methods: mechanical, thermal and chemical (Camp, 2014). Mechanical methods of achieving hemostasis are the most common and include the application of direct pressure on the site of blood loss, ligature and the application of a tourniquet. These methods may be easy to apply but may be labour intensive and the application of pressure or

tourniquet may be difficult due to the location of the blood loss. In addition, the application of pressure may not be effective if the patient is on anticoagulation therapy or suffers from a present coagulopathy. Thermal-based energy methods such as electrocauterization or laser cauterisation are quick methods of hemostasis. However, this method involves the generation of devitalized tissue (including necrosis) which may lead to subsequent localized infection of devitalized tissue, damage to wound margins and an overall delay in downstream wound healing. The use of chemical agents such as epinephrine, vitamin K and protamine are a third method to halt bleeding but can have detrimental effects on normal clotting cascade mechanisms.

2.2 TOPICAL HEMOSTATIC AGENTS

An alternative to the traditional methods of hemostasis is the use of topical hemostatic agents. A large number of topical hemostats have been developed and are being used today. As with traditional hemostatic methods, topical hemostatic agents can be grouped into two major classes (Table 1) with each group having unique properties.

2.2.1 ABSORBABLE INTERNAL HEMOSTATS

This group of hemostatic agents currently account for the majority of topical hemostatic agents and can be subdivided depending upon their properties (Camp, 2014; Schreiber and Neveleff, 2011).

- Passive (mechanical) agents (e.g. porcine gelatin, oxidised regenerated cellulose, beeswax): these agents block blood flow and provide a matrix at the wound site for clot formation (Spotnitz and Burks, 2008) and activate the patient's own clotting cascade (Davie and Kulman, 2006)
- Active agents (e.g. thrombin): active agents are based on the use of thrombin (pooled human, bovine or recombinant) to promote the rapid production of a fibrin clot (Davie and Kulman, 2006). These agents provide concentrated thrombin at the site of bleeding to promote rapid clot formation. These agents can be used in patients with impaired coagulation systems (e.g. heparinization, mild coagulopathy) (Spotnitz and Burks, 2008), although the action of thrombin can be affected by some coagulopathies (Camp, 2014). Safety is a major consideration with thrombin products depending upon which form of thrombin is used (Camp, 2014; Schreiber and Neveleff, 2011)
- Flowables (e.g. bovine gelatin particles with or without thrombin): flowable hemostats are composite hemostatic agents in that they provide both a passive (mechanical) and an active hemostat component in one application. These agents physically block the flow of blood from the site of blood loss and promote the formation of a fibrin clot

- Fibrin sealants (human plasma-derived fibrin, patient's own plasma): fibrin sealants are absorbable materials and result in hemostasis by providing concentrated levels of fibrinogen and thrombin and promoting clot formation (Spotnitz and Burks, 2010). These agents can be used in patients who do not have sufficient fibrinogen to form a clot (Schreiber and Neveleff, 2011)
- Adhesives (e.g. synthetic tissue sealants, glutaraldehyde, and polyethylene glycol): adhesive hemostats is an umbrella term for a number of chemicals and materials with different mechanisms of hemostasis that leads to cessation of blood loss or tissue sealing (Camp, 2014). For example, cyanoacrylate adhesives are synthetic tissue adhesives used to stop bleeding and consist of a blend of two monomer cyanoacrylates that, when brought together, the monomers polymerize to form a flexible sealing film which is adherent to both the polymer and human tissue and is independent of the patient's clotting processes (Barnard and Millner, 2009). Polyethylene glycol (PEG) polymers promote rapid crosslinking with tissue components (e.g. collagen) at the site of application and forms a cohesive matrix that adheres strongly to the applied tissue (Barnard and Millner, 2009)

A common feature of these internal absorbable hemostats is that, once applied, they can be left in situ at the site of application.

2.2.2 TEMPORARY EXTERNAL HEMOSTATS

A relatively recent option for hemostasis is the development of temporary external hemostats or "hemostatic dressings" (Schreiber and Neveleff, 2011) (Table 1). These hemostats are designed to be applied topically and to be removed once hemostasis has been achieved. Originally developed for combat situations, they are being increasingly used in the hospital setting (Schreiber and Neveleff, 2011). Although this group of hemostatic agents is relatively small they can be grouped according to their composition.

- Chitosan-based: hemostatic dressings composed of or containing chitosan derived materials. The hemostatic properties of these chitosan derived materials vary greatly depending upon the material's chemical properties. Chitosan is a natural polysaccharide derived from shrimp shells which, when modified, possess excellent hemostatic properties. Chitosan derived materials have been shown to promote hemostatus independently of the natural clotting cascade (Yang et al, 2008). Proposed modes of action are described later.
- Kaolin-based: kaolin is an inorganic mineral that has the property of being able to promote the body's own clotting cascade (Trabattoni et al, 2011; Lamb et al, 2012).

A significant body of evidence exists on the use of topical hemostatic agents (internal absorbable and topical temporary (external)) in numerous applications (Schreiber and Neveleff, 2011; Seyednejad et al, 2008). However, it is noted that there is a lack of good, rigorous studies comparing these agents (Seyednejad et al, 2008).

The challenge associated with providing effective hemostasis in patients with impaired coagulation, including patients receiving anticoagulant therapy, is particularly acute in patients with necrotic chronic wounds requiring significant wound debridement (Snyder and Sigal, 2013). There are few high-quality randomized controlled trials (RCTs) in this area and no definitive guidelines for chronic wound patients on anticoagulant therapy (Douketis, 2011). In the absence of a significant body of RCTs being available, considerations such as suitability of a specific hemostat for the presenting wound or situation, ease of use, a clean safety profile and cost effectiveness will all play a role in deciding the most appropriate hemostat (Table 2). Chitosan derived hemostatic agents provides a safe and effective method in controlling bleeding in a number of different situations and exhibits many of the properties required of an ideal hemostatic agent.

3. Chitosan derived hemostatic dressings

Section key points

- Chitin and its derivative, chitosan, is a natural polysaccharide with a good safety profile
- Chitosan derivatives are novel hemostatic agents
- Chitosan derivatives initiates hemostasis independent of platelets and coagulation factors
- Chitosan derivatives are effective hemostats in coagulation-compromised patients
- Chitosan derived hemostatic dressings can be used in a number of different areas

Section 3 of the monograph details a broad range of references and data describing Chitin, Chitosan and Chitosan derivatives and their proposed modes of action. The information within this section is to give a general overview of data readily available and does not relate directly to OMNI-STAT. Information relating to OMNI-STAT is specifically described in section 4 with supporting evidence detailed in section 5.

Chitosan is a novel hemostatic agent (Recinos et al, 2008). Chitosan derived hemostats have been used for a range of clinical situations in hospital settings (Seyednejad et al, 2008) and have a very good safety profile (Baldrick, 2010; Waibel et al, 2011). Chitosan derived material's ability to bind red blood cells (RBCs) promotes the immobilisation of RBCs and the formation of an adherent gel clot (Bennett et al, 2014). This property suggests chitosan derived materials as potential materials as hemostats and leading to their use in bandages and other hemostatic devices (Kozen et al, 2008; Millner et al, 2009).

3.1 WHAT IS CHITIN/CHITOSAN?

Chitin is a natural polysaccharide (Singla and Chawla, 2001), a homo-polymer composed of the glucose derivative N-acetylglucosamine (GlcNAc). It is the structural element in the exoskeleton of crustaceans (e.g. crabs, shrimp) and the cell walls of fungi. Partial deacetylation of chitin result in the production of chitosan (Figure 2), a polysaccharide comprising copolymers of the amino sugar glucosamine and N-acetylglucosamine. Chitosan is an 'umbrella term' used to describe a number of chitosan polymers with different molecular weights (ranging from 50 to 2000 kDa), different levels of viscosity and degrees of deacetylation (i.e., the ratio of GlcNAc to glucosamine). The degree of deacetylation in commercial chitosans ranges from 60-100%. Chitosan is a natural molecule and is biocompatible, biodegradable and non-toxic (Stępniewski et al, 2017). Chitosan is naturally broken down by the body into glucosamine and N-acetylglucosamine (Aiba, 1992), and these breakdown products are further metabolized and then undergo rapid clearance via the kidney and liver and are finally excreted in the urine (Levin et al, 1961). Residual chitosan in the plug is broken down and digested in the body by the enzymatic action of lysozyme, an enzyme commonly found in human body tissues and fluids including serum and wound fluid (Frohm et al, 1996). **OMNI-STAT is a topical temporary external hemostat and should not be left inside the body**

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Chitosan is a water-insoluble polymeric material at alkaline and neutral pH values (Cheung et al, 2015). This low solubility hinders the applicability of chitosan but it can form water-soluble salts by treatment with certain acids (Suzuki et al, 2000) and this allows for these chitosan derived salts to be soluble in blood. The chemical structure of chitosan (Figure 2) provides the opportunity for chemical modification – both covalent and ionic – that allows for there to be many changes of the mechanical and biological properties of the chitosan molecule (Mercy et al, 2012).

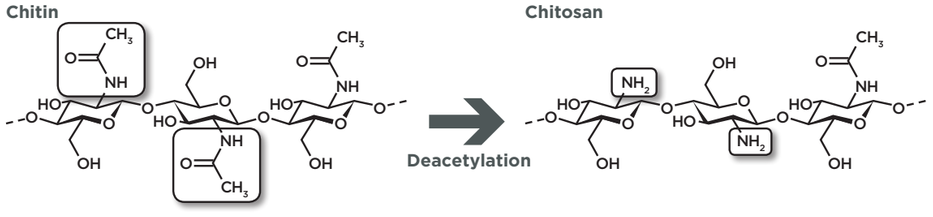
It is important to note that not all of chitosan's potential biological activities are to be found in one kind of chitosan, and each chitosan's profile of chemical and biological activities has been designed by specific chemical modification and enzyme hydrolysis processes (Xia, 2003).

The biological properties of chitosan derived materials have meant that these materials have been used in numerous biomedical and industrial applications including hemostasis, antimicrobial applications, wound healing, tissue engineering and a myriad of biotechnology, agricultural and environmental protection applications (Gerente et al, 2007; Bernkop-Schnurch and Dunnhaupt, 2012; Dragostin et al, 2016).

The response of tissues to chitosan can vary due to a number of factors. These may include the degree of (de)acetylation (Howling et al, 2001), the molecular weight and structure of the polymer (Howling et al, 2001; Iyer et al, 2012), the various combinations with other materials than may be found in composite forms (e.g. dressings) (Kratz et al, 1997).

With such a range of possible forms of chitosan derivatives, each type of which is likely to have different chemical and biological activities, the use of the term "chitosan" can be confusing and misleading and the scientific and medical literature inaccurately uses the terms "chitosan", "chitosan derived" and "modified chitosan" interchangeably.

Figure 2: Deacetylation of chitin to chitosan



3.2 CHITOSAN AS A HEMOSTATIC AGENT

Materials derived from chitosan are effective as hemostatic agents (Mercy et al, 2012). However, studies have indicated that chitosan is hemostatically inactive, i.e., chitosan do not exhibit hemostatic activity (Lootsik et al, 2015). The hemostatic properties of chitosan are enhanced by chemical modifications and the resulting chemical properties of the modified chitosan (e.g. molecular weight, extent of ionization and degree of deacetylation) (Malette et al, 1983; Whang et al, 2005). Studies have shown that chitosan forms with no previous hemostatic activity, when chemically modified by acid treatment, become active hemostats (Lootsik et al, 2015). Studied have also shown that, in addition to chemical modification leading to hemostatic activity, the molecular weight of chitosan derived molecules can affect hemostatic activity: high molecular weight chitosan derived molecules are more effective as hemostatic agents compared with low molecular weight types (Lootsik et al, Lee, 1974).

The mechanism of action of chitosan derivatives as a hemostat is not clearly understood (Hu et al, 2018) but a number of proposed mechanisms for the mode of action of chitosan specifically as a hemostat.

Chitosan has been shown not to swell in water, nor is it water soluble (Lootsik et al, 2015). However, these studies showed that chitosan derivatives do exhibit both water swelling and solubility. Pogorielov and Sikora (2015) note that chitosan (presumably chitosan derived materials) can absorb from 50-300% liquid and absorbs a significant amount of fluid when it comes into contact with blood. As a result, these chitosan derivatives swell, gel and forms a gel-like clot. In addition, gel formation leads also to a concentration of red blood cells and platelets as they are trapped within the chitosan derived gel.

Chitosan derived material has been shown to initiate hemostasis independent of platelets and coagulation factors (Yang et al, 2008), and alters red blood cell morphology and increases the affinity between red blood cells (Klokkevold et al, 1999). This interaction with red blood cells may promote their agglutination further promoting the formation of a hemostatic plug (Chung et al, 2016). Chitosan has also been shown to increase platelet aggregation (Chou et al, 2003).

Pogorielov and Sikora have proposed that the absorption of blood plasma by chitosan (chitosan derivatives) may also lead to concentration of blood cells and promoting hemostasis via the formation of a hemostatic plug, red blood cell coagulation and platelet aggregation/activation (Pogorielov and Sikora, 2015).

Recently, chitosan-coated gauze dressings have been shown to promote red blood cell binding to the dressing surface (Pogorielov et al, 2015). Chitosan has also been shown to encourage platelet adhesion and activation via protein adsorption and orientation (Chou et al, 2003; Lord et al, 2011). This dual

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mechanism forms a cross-linked ‘pseudo-thrombus’ that adheres to the surrounding tissue and plugs the bleeding site (Rao and Sharma, 1997).

It has also been proposed that the direct electrostatic interaction between positively-charged chitosan polymers and negatively-charged cell membranes of the red blood cells may account for the hemostatic activity of chitosan (Mirzadehl et al, 2002; Millner et al, 2010). This may be particularly true for chitosan derivatives where further modifications of native chitosan may increase the ionic nature of the polymer molecule and increasing the electrostatic interactions between these forms of chitosan and red blood cells. **This particular mode of action is not one claimed for OMNI-STAT. The mode of action for OMNI-STAT is covered in section 4.**

As previously mentioned, the hemostatic mechanism of chitosan-based materials is independent of natural clotting mechanisms (Yang et al, 2008). As a result of this independence, chitosan derived hemostats can act in the presence of anticoagulants (Croisier and Jérôme, 2013; Klokkevold et al, 1999).

3.3 CHITOSAN DERIVATIVES AND COAGULOPATHIC BLEEDING

Hemostasis and the clotting cascade is a complex process that results in blood clotting after injury (Figure 3). Any deficiencies in this process leads to impaired clotting (coagulopathy) and that may lead to dangerous excessive bleeding. Impaired blood clotting can arise as a result of a number of causes. Patients with bleeding disorders have impaired clotting because their clotting factors or blood platelets do not function properly, or there is a deficiency in sufficient levels of these factors to provide an optimal clotting function. Examples of bleeding disorders (the majority being inherited) include hemophilia, blood factor deficiencies and Von Willebrand’s disease. Significant physical trauma can also lead to coagulopathy. Significant blood loss as a result of severe trauma induces the so-called “trauma triad” of hypothermia, acidosis and coagulopathy in patients (Mitra et al, 2012) and a number of hypotheses have been presented to account for the effects of trauma on blood coagulation (Martini, 2016). The coagulation component of the triad makes it harder to stop bleeding and to prevent re-bleeding and trauma-associated coagulopathy is associated with a higher risk of death (Mitra et al, 2012). Coagulopathy is vital to consider in treating severe traumatic bleeding, and could also impair the healing process (Jin and Gopinath, 2016).

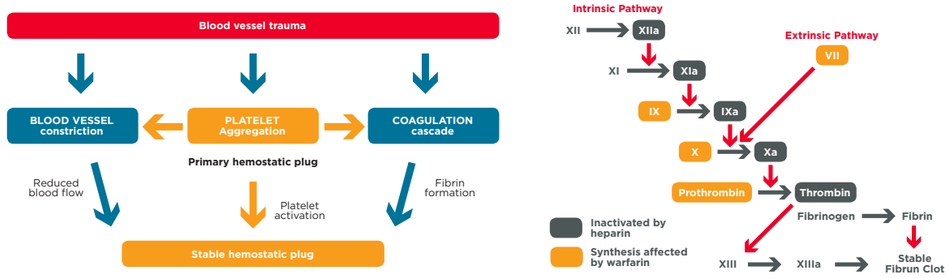
Individuals receiving anticoagulant therapies are a significant population where impaired blood clotting is found. Heparin is used as a blood thinner to treat and prevent blood clotting (deep vein thrombosis, pulmonary embolism and arterial thromboembolism), and is used in the treatment of heart attacks and unstable angina. It is also used before surgical procedures to reduce the risk of blood clot formation. Heparin is given by injection and the mechanism of action appears to be by the prevention of certain

clotting cofactors from working correctly (Figure 3) (Mulloy et al, 2016). Warfarin, a vitamin K antagonist, is an oral anticoagulant that has been used for many years in reducing the risk of stroke in patients and treating and preventing venous thromboembolism. As with heparin, a serious side effect of warfarin is the risk of severe bleeding. Recently, direct oral anticoagulants (DOACs) have been developed as an alternative to warfarin (https://natfonline.org/2018/01/anticoagulant-comparison-chart-2018/). These DOACs target and inhibit a number of the blood clotting factors (Joppa et al, 2018). However, despite being shown as being more effective than warfarin, safety issues for these newer DOACs have been highlighted (Monaco et al, 2017; Burn and Pirmohamed, 2018).

Even a minor wound could present significant challenges for patients who use anticoagulants. As discussed earlier, chitosan derived materials acts as a hemostat independently of the clotting cascade (Yang et al, 2008) and have been shown to be an effective hemostat in patients with coagulopathy (Misgav et al, 2017) and in a number of animal models (Klokkevold et al, 1999).

Previous pre-clinical studies have shown that chitosans are effective to clot heparinised blood: chitosan is able to be effective at stopping lingual bleeding in heparinised rabbits (Klokkevold et al, 1999), and is able to stop bleeding after carotid punctures in both heparinised and non-heparinised sheep (Mirzadehl et al, 2002).

Figure 3: Hemostasis and the clotting cascade – influence of common anticoag-ulants



Anticoagulant agents heparin and warfarin affect blood clotting via influencing the clotting cascade. The primary anticoagulant effect of heparin results in the inactivation of several clotting factors crucial for normal blood clotting (Lee and Arepally, 2012). Warfarin interferes in a pathway vital for the formation of a number of clotting factors (Ageno et al, 2012).

Bochicchio et al, using a porcine liver injury model in which coagulopathy was induced via hypothermia, found that post-treatment blood loss was significantly less and resuscitation mean arterial pressure were significantly greater in the chitosan dressing group compared with the control group (Bochicchio et al, 2009). Hemostasis was achieved approximately 5 minutes after chitosan application whereas the

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standard packing showed no hemostasis. By one hour post-treatment, all animals in the chitosan-based dressing group survived compared with only 50% of controls. The authors concluded that chitosan-based dressings may provide a simple, rapid treatment of life-threatening liver injuries.

Excessive bleeding is also a complication in wounds that do not involve major blood vessels. Routine wound debridement in patients receiving anticoagulation treatment is also a problem. Sharp debridement removes necrotic tissue down to the level of well-vascularised tissue (Fife et al, 2012) and there is a high probability that many chronic wound patients presenting for sharp debridement may be taking anticoagulants and discontinuation of anticoagulation therapy is often required for debridement of large or multiple wounds (Snyder and Sigal, 2013). It has been suggested that anticoagulation therapy may not need to be halted for debridement of smaller wounds (Douketis, 2011). However, it is likely that sharp debridement in these clotting-compromised patients could lead to excessive blood loss since even a small bleeding wound would result in significant blood loss over time without adequate hemostasis. The use of chitosan based wound dressings to promote hemostasis in excisional wounds has been reported. Stricker-Krongrad et al documents the hemostatic efficacy of a chitosan based wound dressing in heparinised rats with excisional wounds (Stricker-Krongrad et al, 2018). This study found that chitosan based dressings application to wounds resulted in quick and effective hemostasis in an animal model utilising heparin anticoagulation.

3.4 CHITOSAN AND WOUND HEALING

Chitosan and its derivatives have the potential to be beneficial at several points in the wound healing response (Dai et al, 2011). Studies have shown that the this group of materials is able to promote healing (Li et al, 1992; Khor and Lim, 2003; Foda et al, 2007; Lee et al, 2009) with minimal scarring (McCarty, 1996). Chitosan promotes the immune response (Lee et al, 2009), may help control the inflammatory mediators required for healing (Stępniewski et al, 2017) and chitosan fibres and hydrogels have been shown to promote inflammatory cell migration to the site of a wound (Ueno et al, 1999; Boucard et al, 2007). Degradation products of both chitin and chitosan have been shown to promote fibroblast proliferation (Mohandas et al, 2018) and promotion of revascularisation (Ashkani-Esfahani et al, 2012).

Chitosan and its derivatives can also be easily formed into films, hydrogels and scaffolds without the use of toxic chemicals during the manufacturing process (Stępniewski et al, 2017), and this material shows a number of biological and physical properties that make it a potential wound dressing material. The material has been shown to have antimicrobial properties due to its positive charge binding to the cytoplasmic membrane of bacteria (Felt et al, 2000; Liu et al, 2001; Tashiro, 2001; Ong et al, 2008). Chitosan and its derivatives have have antifungal properties (Seyfarth et al, 2008). It is non-toxic to the wound bed (Khor and Lim, 2003; Foda et al, 2007; Jayakumar et al, 2011), is biocompatible and

biodegradable (Li et al, 1992; Khor and Lim, 2003; Niekraszewicz, 2005; Foda et al, 2007; Jayakumar et al, 2011) and has been shown to manage exudate (Li et al, 1992; Khor and Lim, 2003; Foda et al, 2007).

Recently an absorbent gelling fibre wound dressing composed of chitosan has been developed (Stephen-Haynes et al, 2014). Designed for moderately-to-heavily exuding chronic and acute wounds, this dressing has been suggested to aid autolytic debridement and can be used to control minor bleeding in superficial wounds. A recent report describes positive results in two patients (Stephen-Haynes et al, 2014). Topical chitosan mats have been used for hemostasis (Charernsriwilaiwat et al, 2012; Wang et al, 2012) and for stimulating wound healing, particularly in the treatment of burn wounds (Dai et al, 2011; Alsarra, 2009).

Chitosan has also been blended with other materials (e.g. collagen, hyaluronan, fibrin) and loaded with bioactive molecules (e.g. growth factors) in order to improve a number of material properties, including cell-material interaction between tissue cells and chitosan fibres and increasing the efficacy of tissue regeneration activities of chitosan (Yang, 2011).

Recently, the hemostatic properties of chitosan derivatives have shown benefit in the treatment of difficult-to-heal wounds where wound debridement – the physical removal of devitalized tissue from the wound bed – is required and where excessive bleeding should be avoided (Snyder and Sigal, 2013; Schierle and Krol, 2009). Hemostasis had been achieved after sharp wound debridement and the hemostatic properties of chitosan had allowed wound debridement in these patients who might otherwise not been suitable for sharp debridement (patients had received anticoagulants (Snyder and Sigal, 2013)).

The information provided above in section 3 was a general overview and proposed modes of actions of chitin, chitosan and chitosan derived hemostatic dressings. OMNI-STAT a chitosan derived hemostatic agent is discussed specially in sections 4 & 5 below.

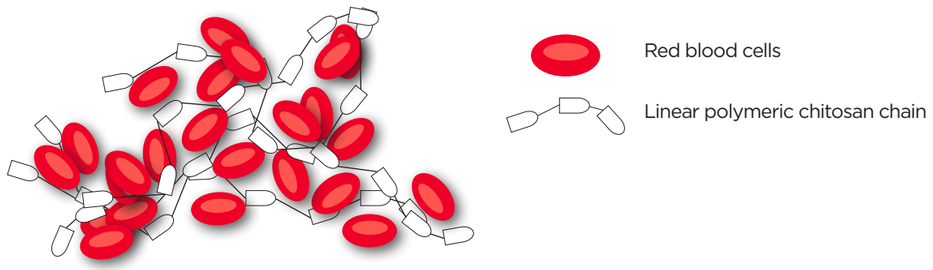
4. OMNI-STAT Hemostatic Agents

Section key points

- OMNI-STAT is a chitosan derived hemostat
- OMNI-STAT is safe and effective and is cleared under several 510Ks
- OMNI-STAT granules are very high surface area flakes. When they come in contact with blood, OMNI-STAT swells, gels, and sticks together to make a gel like clot. It works independently of the body's normal clotting mechanism, works in hypothermic conditions and clots blood containing the blood-thinning drug heparin
- OMNI-STAT is a topical temporary external hemostat

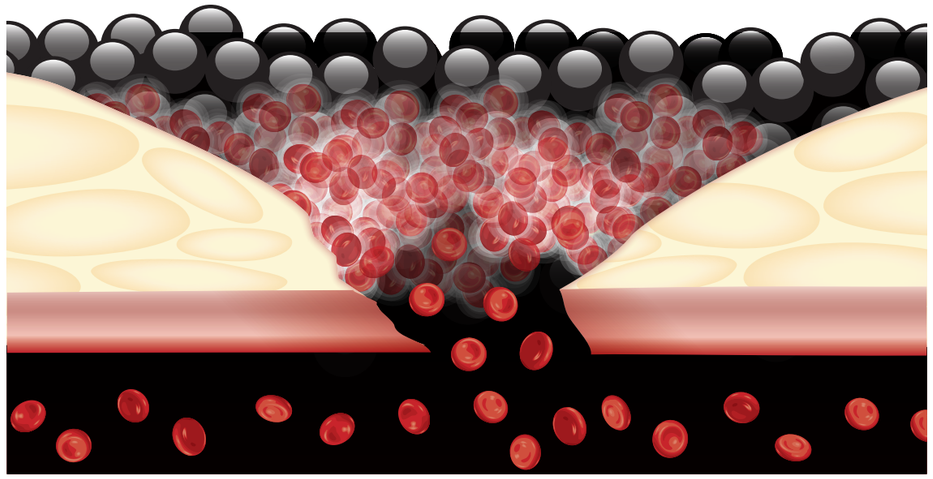
OMNI-STAT is an ideal and effective topical temporary external hemostatic agent and is a fast, safe and effective method for controlling minor, moderate and severe bleeding. It is made of a proprietary composition which contains chitosan in the form of macroscopic high surface area granular flakes designed for maximum effectiveness in controlling bleeding. OMNI-STAT hemostats are available in a number of forms (Table 3). OMNI-STAT is non-toxic and there have been no known or suspected allergic reactions as a result of using OMNI-STAT. The mechanism of action for OMNI-STAT is through the absorption of fluid in the blood, swelling and gelling and sticking together. Gelling of the OMNI-STAT and trapping of red blood cells creates a robust mechanical gel-like clot (Figure 4) that plugs the bleeding source and seals the wound (Figure 5) (Millner et al, 2011). This mechanism works independently of classical coagulation pathways (i.e., does not initiate a thrombogenic response) (Millner et al, 2010). In laboratory tests looking at the wetting of chitosan and chitosan derived materials in water, it was shown that chitosan forms that showed a lack of swelling (and solubility) exhibited no hemostatic activity (Lootsik et al, 2015). This was in contrast to OMNI-STAT which showed good hemostatic activity and active swelling.

Figure 4: schematic interaction between chitosan derived materials and red blood cells to form hemostatic plug (modified from Chan et al, 2016)



OMNI-STAT is easily removed from wounds after bleeding has stopped. Any residual material can be irrigated away with water or saline. Kheirabadi et al found OMNI-STAT granules to be easy to remove when tested in an extreme arterial hemorrhage porcine model (Kheirabadi et al, 2009) and Kozen et al found that OMNI-STAT was easily removed when used in a complex groin injury model and that residual material was easily washed from the wound with simple saline lavage (Kozen et al, 2008). **OMNI-STAT is a topical temporary external hemostat not intended for internal use and should not be used in the eyes or mouth.**

Figure 5: Hemostatic plug at wound site formed by OMNI-STAT and red blood cells



5. Scientific and Clinical Evidence

Section key points

- Significant level of evidence supporting OMNI-STAT as an effective hemostat
- Laboratory studies show rapid clot formation in normal and coagulation-deficient blood, and in hypothermic blood
- OMNI-STAT is an effective hemostat in a number of pre-clinical models of uncontrolled bleeding and bleeding in presence of some anticoagulant drugs
- Clinically, OMNI-STAT has been shown to be an effective hemostat in wound debridement, traumatic and bleeding in presence of some anticoagulant drugs
- OMNI-STAT could provide cost-saving benefits

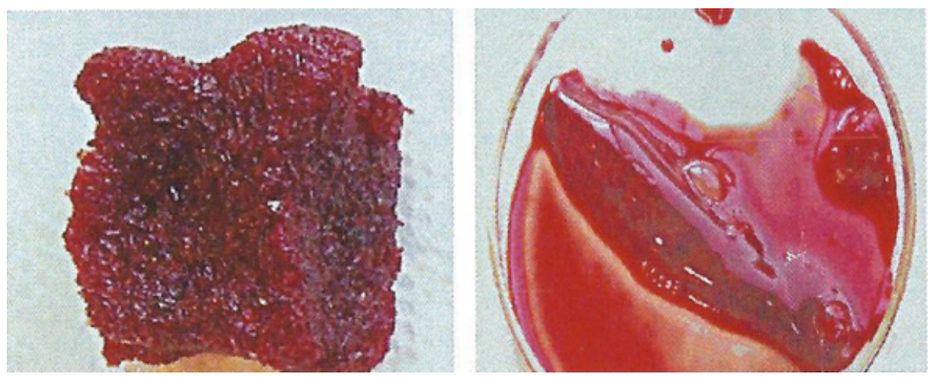
5.1 LITERATURE SEARCH METHODOLOGY

Search of internet reference databases (e.g. MEDLINE) were undertaken to identify published articles related to the scientific and clinical evidence for the use of OMNI-STAT as a hemostatic dressing. The search included articles published between January 1970 and June 2018. In addition, manual searches of peer-reviewed journals and conference proceedings of relevance to wound management and not catalogued in reference databases were also performed.

5.2 PRE-CLINICAL STUDIES (INCLUDING IN VITRO DATA)

5.2.1 IN VITRO STUDIES

Figure 6: Blood clots after 20 minutes (Johnson et al, 2008)

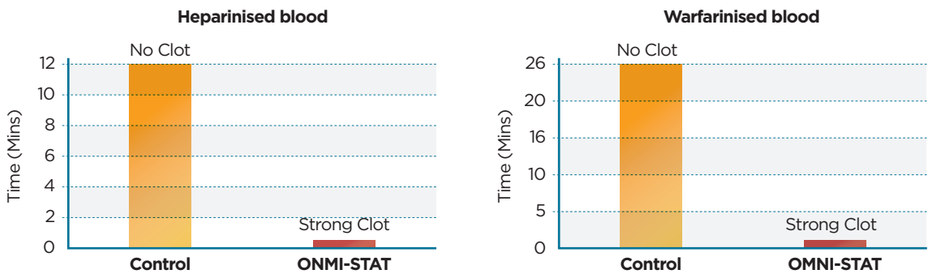


OMNI-STAT | Control

Standardized laboratory studies have been used to show the effectiveness of OMNI-STAT as a hemostatic dressing. The blood clotting time was tested with freshly drawn rabbit blood (Figure 6). Twenty minutes after the addition of OMNI-STAT to the rabbit blood a good clot had formed. When the time at which the blood had clotted was assessed, OMNI-STAT significantly reduced the clotting time compared with the control tests (30.5 seconds vs. 816.5 seconds, respectively) (Table 4) (Johnson et al, 2008).

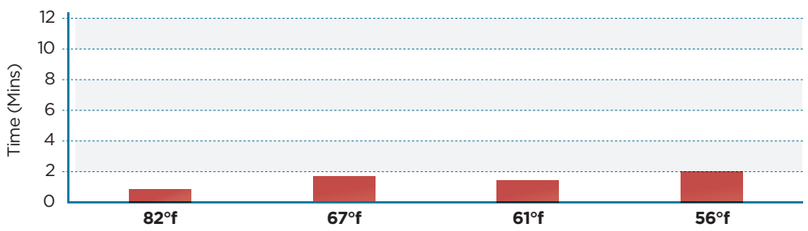
Studies examining the hemostatic effect of the chitosan derived dressing on coagulation of anticoagulant treated blood showed that hemostasis is largely unaffected by the presence of anticoagulants (Figure 7). Whereas anticoagulant treated blood showed significant delays in coagulation in the standard laboratory tests, the presence of chitosan derived material led to coagulation times similar to those seen in the non anticoagulant treated blood (Johnson et al, 2008).

Figure 7: Anticoagulant treated blood clotting times (Johnson et al, 2008)



OMNI-STAT was able to clot freshly drawn rabbit heparinized blood that has been cooled to a temperature of 56°F (Figure 8). The mean clotting time for the OMNI-STAT treated blood was 20 seconds, whereas control blood failed to clot within the 10 minute test period (data on file).

Figure 8: Performance of OMNI-STAT in hypothermic blood



5.2.2 UNCONTROLLED HEMORRHAGE

A number of pre-clinical animal model studies show the effectiveness of OMNI-STAT at controlling significant bleeding. In a study comparing a number of hemostatic gauzes using a porcine model of groin arterial hemorrhage, OMNI-STAT Gauze achieved 90% survival compared with 50-70% in other dressings (Rall et al, 2013). By the conclusion of the study, OMNI-STAT Gauze had achieved the lowest level of blood loss and the highest percentage of instances of intact hemostasis. OMNI-STAT Gauze was also found to achieve hemostasis in a significant number of cases (6/8) of uncontrolled hemorrhage in pigs that has received a femoral artery injury where no compression was applied (Watters et al, 2011). Although there was no difference in performance between the hemostatic gauze dressing and plain gauze (probably due to the user experience with plain gauze), Total blood loss and time to clot after 30 minutes parameters were better in pigs treated with OMNI-STAT Gauze compared to other hemostatic dressings (Combat gauze) and plain gauze. No inflammation, necrosis or deposition of dressing particles in vessel walls was observed.

The effectiveness of OMNI-STAT as a hemostatic agent was assessed in a comparison study of 10 hemostatic dressings in a porcine femoral transection model. OMNI-STAT was found to be one of a group of products with the highest animal survival ($p<0.01$) (Arnaud et al, 2009a). The OMNI-STAT group (Including Woundstat, Xsponge and ACS+) were also found to be superior for limiting blood loss ($p<0.05$) and instances of re-bleeding ($p<0.005$). In an accompanying article from the same group that examined the effect on hemostatic agents in a porcine groin puncture model (Arnaud et al, 2009b), OMNI-STAT was in the group of dressings (Including Woundstat, Xsponge and ACS+) that again significantly outperformed ($p<0.01$). The group containing OMNI-STAT were superior for post-treatment blood loss ($p<0.001$). The conclusions were that hemostats in the OMNI-STAT group were superior in improving survival, hemostasis and maintenance of mean arterial pressure in an actively bleeding wound. In an additional study in a porcine model where the femoral artery and vein were transected and OMNI-STAT was applied as a hemostat, the systolic blood pressure (SBP) and mean arterial pressure (MAP) at which re-bleeding occurs was assessed on clots formed by the applied hemostatic agent (Burgert et al, 2010). OMNI-STAT stopped bleeding and maintained control as blood pressure increased to >160 mmHg systolic, and this dressing was superior compared to standard dressing application in preventing re-bleeding ($p=0.008$ for mean arterial pressure).

Gegel et al conducted a study to compare the effectiveness of OMNI-STAT and a biopolymeric, microporous particle hemostatic agent in a porcine model of hemorrhage (Gegel et al, 2010). After transection of the femoral artery and vein followed by one minute of free bleeding, the dressings were

poured into the wound followed by standard wound packaging. The main outcome measure for this study was blood loss after 35 minutes. Results found a significant reduction in blood loss ($p<0.01$) compared with a standard pressure dressing. Although there was no significant difference between OMNI-STAT and the biopolymeric dressing in terms of blood loss, the authors concluded that OMNI-STAT was "clinically superior".

Hemostatic dressings (including OMNI-STAT) were applied to wounds applied to the femoral artery in a porcine model to assess the efficacy of the dressings (Conley et al, 2015). After the femoral artery injury had been given the wound was allowed to bleed freely for 40 seconds. A stack of 5 pieces of plain gauze was applied to the wound and pressure was applied. The plain gauze was then removed and replaced with a previously randomized hemostatic gauze. The hemostatic gauze was held in place for 3 minutes using manual pressure. After this time the dressing was removed and the wounds observed for hemostasis and rebleeding over the following 150 minutes. All products were similar in initial hemostasis, levels of blood loss and rebleeding and required only minimal training.

In a porcine model of peripheral vascular injury, hemostatic dressings (including OMNI-STAT) were found to reduce the tourniquet times (MacIntyre et al, 2011). A tourniquet was placed proximally in 50 forelimb-injured pigs after 30 seconds of induced hemorrhage with cessation of bleeding in all cases. Hemostatic dressings were placed over the wounds for 3 minutes and then the tourniquet was removed to assess blood loss. Successful hemostatic action by the dressings was assessed as no blood loss after removal of the tourniquet. Standard gauze resulted in 100% failure with active bleeding. OMNI-STAT was successful in maintaining hemostasis in 60% (6/10) of subjects. The authors suggested that the use of hemostatic dressings in conjunction with a tourniquet may allow for reduced tourniquet times with improved outcomes in peripheral vascular injury.

In a goat arterial injuries model, 126 injuries were made in 45 animals and several chitosan derived dressings (including OMNI-STAT) were tested for hemostasis (Satterly et al, 2013). All chitosan-containing hemorrhagic dressings performed equally well in promoting hemostasis at 2 and 4 minutes and, although many of the study variables (e.g. location and degree of wounding) were uncontrolled, the findings of this study added to the evidence for chitosan derived gauze dressings as effective hemostatic agents (Bennett et al, 2014).

5.2.3 COAGULOPATHIC BLEEDING

Millner et al examined the effectiveness of two chitosan derived hemostatic agents (OMNI-STAT granules and OMNI-STAT Gauze) in a porcine model of major hepatic injury in the presence of impaired clotting (Millner et al, 2010). OMNI-STAT Gauze and OMNI-STAT granules achieved hemostasis in 100% cases

(n=18 and n=6, respectively), supporting the hypothesis that chitosan derived products act independently of classical clotting pathways. OMNI-STAT was assessed on normal and warfarinized blood in a femoral artery bleeding rat model and compared to gauze and compression (Köksal et al, 2011). OMNI-STAT achieved hemostasis in 100% (8/8) cases, 75% on first compression and the remaining on second compression. The control treatment was successful in only 25% (2/8) and only on the third attempt at compressing the injury.

The effectiveness of OMNI-STAT as a hemostatic agent in situations of clotting dysfunction was assessed in a porcine femoral artery model where the animals had been previously been given heparin to disrupt the normal blood clotting mechanism (Millner et al, 2011). After a 6mm vascular punch wound to the femoral artery was applied and 45 seconds of uncontrolled hemorrhage followed, OMNI-STAT was applied directly to the wound and manual pressure was applied for 5 minutes. Hemostasis was successfully achieved in all subjects (12/12) compared with no hemostasis on the control group and there was no incidence of re-bleeding in 92% (11/12) of test subjects. The authors concluded that OMNI-STAT was effective at initiating hemostasis in subjects with clotting dysfunction and that the hemostatic dressing should be effective in patients with disturbed blood clotting function.

Laboratory tests have been used to help assess the quality of clots formed during blood clotting. For example, rotational thromboelastometry (ROTEM) has been used to assess speed of clot formation and clot firmness, both important for the quality of formed clots. Lechner et al (2016) found that OMNI-STAT-initiated clots were firmer and better stabilized compared with normal blood clots. A small (n=8) evaluation by Bar et al (2017) investigated the blood coagulation in patients presenting to the emergency department who were receiving the anticoagulant rivaroxaban. ROTEM studies showed OMNI-STAT improved the coagulation of anticoagulated blood. Of blood samples treated with OMNI-STAT, six (75%) showed reductions in clotting time, three (37.5%) showed reductions in clot formation time and five (62.5%) showed increases in maximum clot firmness. The authors concluded that chitosan derived hemostatic agents may be effective at improving coagulation in patients receiving anticoagulants. Other studies using ROTEM have also suggested that the hemostatic function of OMNI-STAT is mediated predominantly via tissue adhesiveness (Kheirabadi, 2011; Kheirabadi et al, 2010).

5.3 CLINICAL EVALUATIONS

Effective hemostasis is required for excessive and disruptive bleeding and is a significant risk in surgical procedures. Individuals with genetic coagulopathies and the use of anticoagulants as a prophylactic agents in patients contributes to the risk of excessive bleeding. Trauma resulting in significant blood loss can also lead to blood coagulation problems. Significant bleeding from surgical wounds in vulnerable patients with and without associated anticoagulant therapies and traumatic wounds must be controlled

in order for wounds to heal, patient recovery and for limiting overall treatment costs.

5.3.1 WOUND DEBRIDEMENT

The presence of devitalized tissue in wounds may impair the healing process and removal of this tissue promotes wound healing (Saap and Falanga, 2002). The removal of devitalized tissue can be achieved by debridement and sharp debridement removes this necrotic tissue down to the level of well-vascularized tissue (Fife et al, 2012). Sharp debridement can increase the risk of bleeding and this risk is exacerbated by the use of anticoagulants in the aging population where chronic wounds are particularly prevalent. Clinical evaluations have been reported demonstrating positive outcomes of using OMNI-STAT in providing effective hemostasis after sharp debridement, including patients receiving anticoagulants (Appendix, Table 5).

Open-label, controlled evaluation (n=40) evaluating chronic wounds of varying etiology with or without concomitant use of anticoagulants

Figure 9: Debridement of ulcer by chitosan derived dressing (Snyder and Sigal, 2013)

Left: leg ulcer post debridement; middle: leg ulcer with chitosan-based gauze applied; right: ulcer 7 days post-treatment

Snyder and Sigal (2013) reported on the results of an open-label, controlled clinical investigation designed to evaluate the hemostatic properties of the chitosan-impregnated gauze, OMNI-STAT, in patients with open wounds of various aetiologies (including diabetic foot ulcer and venous leg ulcer) post-debridement. Forty patients were recruited into the study (n=20, OMNI-STAT; n=20, standard of care). Both groups included a large proportion of patients on anticoagulant therapy (15/20 OMNI-STAT, 16/20 control). After debridement, excess blood was wiped away and the wound was then treated with the OMNI-STAT or the control gauze followed by pressure for 2 minutes. The dressings were left in place for 7 days and then removed at a follow-up visit after being saturated with saline for five minutes (Figure 9). The primary endpoint in the study was the time required to achieve hemostasis with secondary endpoints being an assessment of the patient's pain levels at the start and end of the treatment and an assessment of the wound bed. The mean time hemostasis in the OMNI-STAT-treated group was 1 minute

19 seconds compared with 5 minutes and 19 seconds for the control group (p<0.0001) (Figure 10). The quality of the granulation tissue of the wound after 1 week was significantly improved in the OMNI-STAT-treated group (OMNI-STAT group: 18/20 improved, none deteriorated; control group: none improved, 4/20 deteriorated; p<0.05) (Figure 11). Pain scores in the OMNI-STAT group were consistently lower compared with the control group upon application, during application and on dressing removal after one week. The authors conclude that, as well as promoting hemostasis leading to reduced treatment time, the OMNI-STAT provided a moist wound environment and improved the quality of the wound granulation tissue. The establishment of a moist environment may be due to the absorbent nature of the chitosan granules component of OMNI-STAT. The authors suggest that the use of chitosan-impregnated hemostatic dressings may lead to an alteration in clinical practice, allowing for the rapid control of bleeding after wound debridement in patients with chronic wounds despite the prevalence of anticoagulants.

Figure 10: Time to hemostasis (minutes) (Snyder and Sigal, 2013)

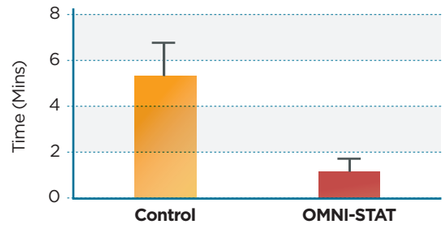
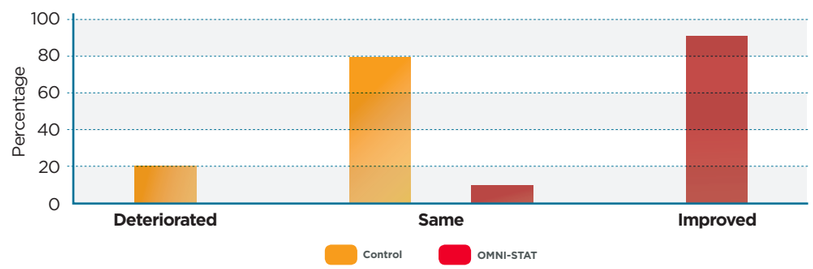


Figure 11: Tissue quality after 1 week (Snyder and Sigal, 2013)



5.3.2 TRAUMATIC BLEEDING

Traumatic wounds can result in significant tissue damage accompanied by serious vascular damage. The associated disruptive bleeding is a particularly difficult challenge for hemostatic agents. A number of clinical evaluations have been reported to evaluate the use of OMNI-STAT in the treatment of wounds with disruptive bleeding (Appendix, Tables 6 and 7).

Clinical evaluation in patients with penetrating trauma

In a randomized clinical evaluation set in an urban emergency department, 160 patients with penetrating (stab) limb trauma and where bleeding was a concern were treated with OMNI-STAT gauze. Time to achieve hemostasis and the volume of blood lost through the wound after application of the dressing were the main outcome measures (Hatamabadi et al, 2015). Control wounds were treated with a gauze pressure bandage. Hemostasis was achieved within five minutes in 51.3% of OMNI-STAT-treated wounds compared with 32.5% of the control group. Using the OMNI-STAT gauze significantly reduced the time to hemostasis ($p=0.01$) and blood loss was also lower compared to the control group ($p<0.05$). It was concluded that hemostasis can be achieved sooner and with less blood loss using the OMNI-STAT gauze compared with the control treatment suggesting that fewer wounds would require more advanced and invasive intervention to achieve hemostasis and physicians would be able to focus on other possible life-threatening conditions sooner.

Case report: hemostasis in a major head/neck hemorrhage

OMNI-STAT granules have been used in control of hemorrhage in a 48-year old patient known to have a malignant peripheral nerve sheath sarcoma originating from the left parapharyngeal space and who presented at hospital with a life-threatening head and neck bleed (Crunkhorn et al, 2013). Bleeding was successfully controlled with the application of OMNI-STAT granules.

Clinical evaluation in 21 patients with gunshot wounds

The use of OMNI-STAT in the control of massive traumatic bleeding was assessed in 21 patients with gunshot wounds in a number of locations (e.g. lower limb, shoulder). Eighteen patients achieved successful hemostasis within one minute upon the first application of OMNI-STAT, with the 3 remaining patients achieving hemostasis after further applications (Pozza and Millner, 2011). Tourniquets had been used in 15/17 limb wounds but had not stopped the bleeding and in 15/21 cases bleeding was assessed to have been life-threatening. There was no reported pain and there were no changes to the tissue surrounding the injuries.

Case series (n=7) evaluating OMNI-STAT Gauze in hemostasis

Tan and Bleeker reported their experience in seven cases of traumatic bleeding, examining the effectiveness of chitosan derived hemostatic agents as a hemostat. Injury sites included the lower limb/groin area, pelvic girdle and the neck. Use of OMNI-STAT Gauze successfully stopped bleeding where pressure dressings failed. No re-bleeding was noted and there was no leakage or complications reported over the course of the subsequent observation period (up to 5 days) (Tan and Bleeker, 2011). For example,

a 25-year old patient received a gunshot to the buttock which resulted in significant blood loss from muscle. This persistent bleeding was not controlled by plain gauze with pressure. Upon packing with OMNI-STAT gauze the bleeding was stopped and when removed after 24 hours there was no further bleeding. In a second case, a 20-year old female cyclist received a high energy trauma to the side of the neck as a result of a collision with a motor vehicle. Significant venous bleeding from the neck was not stopped by the application of a pressure dressing did not provide hemostasis. However, the application of OMNI-STAT gauze stopped the bleeding allowing the patient to be transported to hospital without further leakage.

5.3.3 COAGULOPATHIC BLEEDING

Acute coagulopathy has been found in a significant number of individuals both in severely injured military casualties and civilian trauma patients (38% and 25%, respectively) (Niles et al, 2008; Brohi et al, 2003).

6. Cost-effectiveness of Chitosan derived Hemostatic Dressings

Uncontrolled bleeding in the surgical and trauma settings results in a significant clinical and economic impact and achieving hemostasis is a crucial focus for clinicians (Schreiber and Neveleff, 2011).

6.1 THE COST OF BLEEDING FOLLOWING SURGICAL PROCEDURES

Bleeding is a common complication in surgical procedures and ranges in extent from mild/moderate to severe/traumatic/disruptive and may occur intra- or post-operatively (Ghadimi et al, 2016). Bleeding complications in surgical patients represent a significant proportion of the total number of surgical procedures and a recent large retrospective analysis identified almost 30% of bleeding-related complications (Stokes et al, 2011). Other data suggests bleeding rates ranging from <10% to 35% (Marietta et al, 2006). Cardiac procedures have some of the highest risks of bleeding, with almost 50% of patients experiencing some bleeding-related complication (Shander, 2007). Uncontrolled bleeding is associated with increased risk of death blood transfusions, and increased costs due to increased health care resource utilization (Stokes et al, 2011).

The management of complications arising from disruptive bleeding may require a number of additional clinical procedures:

1. Extending the duration of the original surgical procedure
2. The requirement for transfusion with whole blood, plasma and/or plasma substitutes
3. The use of hemostats
4. Re-operative surgery
5. The need for an extension to hospital stay

As well as the health consequences associated with bleeding (e.g. increased morbidity and mortality) there will also be increase in costs as a result of the additional use of hospital resources highlighted above (Zimmerman, 2007; Boucher and Traub, 2009). A recent US retrospective study of the Premier Perspectives Database[2] demonstrates this. In this study, discharges from 2012 were used to identify patients treated with hemostats during eight surgery types. Patients were stratified by procedure and presence or absence of major bleeding (uncontrolled) despite hemostat use. Outcomes were as follows: (a) all cause hospitalization costs; (b) hemostat costs; (c) length of stay; (d) reoperation and surgery-related complications (e.g. mortality). The results showed that among 25,048 procedures, major bleeding events occurred in 14,251 cases and major bleeding occurred in 32%–68% of cases. All cause costs were

2. The Premier Perspectives Database includes monthly feeds from hospitals across the United States, ranging from major health systems to community hospitals. Overall, the database includes information from more than 535 million encounters, which represent more than 25% of all hospital discharges in the United States. The Premier data includes the complete "charge master" for each admission, which reflects a comprehensive list of items and services billed to an individual patient or insurer, and in addition to detailed information about prescription drugs, also includes information regarding disease codes, supplies used, laboratory tests ordered and results, complications, devices used, procedures and CPT codes, length of stay, charged costs and reimbursed costs, complications, payor and outcomes including readmissions and mortality.

significantly higher in patients with uncontrolled bleeding use versus controlled bleeding (US$24,203–$61,323 [uncontrolled], US$14,420–$45,593 [controlled], P=0.001). The overall conclusion from this study was that uncontrolled intraoperative bleeding is prevalent and associated with significantly higher hospital costs and worse clinical outcomes across several surgical procedures compared to controlled bleeding (Corral et al, 2015). A recent study found that severely bleeding major trauma patients are a high cost subgroup of all major trauma patients (Campbell et al, 2015). Data from this study also estimated that over 40% of major trauma patients presenting with severe bleeding are likely to be aged 65 and over. With this age category projected to increase by almost 22% from 2014 to 2030, the authors concluded that significant additional costs are likely in the future.

A retrospective analysis of over 1.5 million surgical procedures by Stokes and co-workers (2011) found that major bleeding was associated with an increase in length of hospital stay of up to 9 days and increased costs of up to more than $17,000. Cost analysis studies have shown that the use of adjunct hemostats such as oxidized regenerated celluloses (ORCs) can lead to a reduction in costs and the use of healthcare resources when used to assist with the control of intraoperative bleeding (Martyn et al, 2015a). However, a retrospective analysis of the use of hemostats in a variety of surgical procedures found that, despite the use of hemostats, major bleeding occurred in 32%-68% of all cases (Corral et al, 2015). Suggesting that current hemostats were lacking in their hemostatic benefit, the authors identified a number of limitations with these hemostatic agents (e.g. insufficient adhesion strength, inability to withstand the forces of a significantly major bleed, etc.) and suggest that better selection process for choosing the appropriate hemostat for any given situation together with the development of new hemostats. Newer topical hemostats have been developed that exhibit improved hemostatic properties over previous forms that have shown better hemostatic properties in patients undergoing a variety of procedures which translates to reductions in length of hospital stay and reduced costs (Martyn et al, 2015b).

Specific detailed cost effectiveness studies have at this stage not been conducted for OMNI-STAT. OMNI-STAT is a topical temporary external hemostat not intended for internal use and should not be used in the eyes or mouth.

6.2 HEMOSTATS IN SURGICAL WOUND DEBRIDEMENT – COST IMPLICATIONS

There is an increased risk of bleeding associated with surgical (sharp) debridement and this risk is exacerbated by the use of anticoagulants in the aging population where chronic wounds are particularly prevalent (Snyder and Sigal, 2013). If during surgical debridement, the application of pressure fails to control bleeding there are a number of alternate procedures open to the surgeon in the operating room (Madhok et al, 2013):

1. Ligation of the bleeding vessel(s)
2. Cauterize wound with silver nitrate
3. Electrocautery
4. Topical application of hemostatic agents (e.g. thrombin, oxidized regenerated cellulose (ORC)

As discussed above, the use of hemostats in surgical procedures is prevalent, particularly in their use in preventing blood loss during or after surgical debridement (Schierle and Krol, 2009; Snyder and Sigal, 2013). These authors state that the use of chitosan derived hemostatic bandages (dressings) are beneficial for a number of reasons including healing outcomes and cost effectiveness.

6.3 ANTICOAGULATED PATIENTS – RISK AND ASSOCIATED COSTS

With significant bleeding being a common complication in surgical procedures (Ghadimi et al, 2016), patients receiving anticoagulant therapy (e.g. heparin, warfarin) further complicates and increases the risk associated with the surgical procedure because of the increased likelihood of excessive or uncontrolled bleeding resultant from the anticoagulant treatment. Because of the known risks, clinicians with anticoagulant patients undergoing surgery have several options to minimize risk of complications:

1. If the surgical procedure is of low risk, then anticoagulant therapy can be continued. However, a major bleeding episode has a case-fatality rate of 8-10% (Linkins et al, 2003; Douketis et al, 2007; Carrier et al, 2010)
2. Temporarily halting anticoagulant therapy. However, this increases the risk of thromboembolic episodes (thrombosis is fatal in 15% of patients, embolic stroke results in death or major disability in 70% of patients, while vascular thromboembolism has a case-fatality rate of approximately 5%-9%) (Spyropoulos and Douketis, 2012)
3. Bridging anticoagulation therapy. This involves the administration of a short-acting anticoagulant (e.g. intravenous heparin) during the interruption of a longer-acting anticoagulant. This method can be costly and time-consuming due to peri-procedural hospitalization for anticoagulant administration and laboratory monitoring is essential (Won et al, 2014)
4. Use alternative direct oral anticoagulants (DOACs) such as dabigatran, rivaroxaban, and apixaban. Their relatively short half-life, rapid onset of action, and predictable pharmacokinetics should simplify peri-procedural use (Stacy and Richter, 2017)

All these clinical options have a significant clinical and economic perspective to them. Any hemostat that works independent of the coagulation system, and is thus effective in patients with ongoing anticoagulant therapy would be a significant benefit from both a clinical and economic standpoint since none of options 2-4 would be required, and there would be no potentially serious adverse event consequences.

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7. Conclusion

OMNI-STAT provides a safe, rapid and effective solution to hemorrhage and evidence indicates that it provides hemostasis in a range of conditions where significant bleeding occurs, including chronic wounds where sharp debridement is required, emergency room traumatic wounds and vascular access/ closure sites.

Furthermore, OMNI-STAT acts independently of classical clotting pathways and is effective in patients with clotting dysfunction, e.g. patients receiving anticoagulant therapy (Warfarin and Heperin). As well as offering effective treatment in cases of disruptive bleeding (e.g. traumatic wounds), OMNI-STAT provides hemostasis in patients where bleeding may be moderate (e.g. sharp debridement of difficult-to-heal wounds) but where significant bleeding is a risk due to concomitant anticoagulant therapy.

This document summaries the current pre-clinical and clinical evidence for OMNI-STAT as an effective topical temporary hemostatic agent.

8. References

Ageno W, Gallus AS, Wittkowsky A, Crowther M, Hylek EM, Palareti G. Oral anticoagulant therapy: antithrombotic therapy and prevention of thrombosis, 9th ed: American College of Chest Physicians evidence-based clinical practice guidelines. Chest 2012; 141(2 Suppl):e44S-e88S

Aiba S. Studies on chitosan: 4. Lysosymic hydrolysis of partially N-acetylated chitosans. Int J Biol Macromol 1992; 14(4):225-228

Alsarra IA. Chitosan topical gel formulation in the management of burn wounds. Int J Biol Macromol 2009; 45(1):16-21

Arnaud F, Parreño-Sadalan D, Tomori T, Delima MG, Teranishi K, Carr W, NcNamee G, McKeague A, Govindaraj K, Beadling C, Lutz C, Sharp T, Mog S, Burris D, MvCarron R. Comparison of 10 hemostatic dressings in a groin transection model in swine. J Trauma 2009a; 67(4):848-855

Arnaud F, Teranishi K, Tomori T, Carr W, McCarron R. Comparison of 10 hemostatic dressings in a groin puncture model in swine. J Vasc Surg 2009b; 50(3):632-639

Ashkani-Esfahani S, Emami Y, Esmaeilzadeh E, Bagheri F, Namazi MR. Glucosamine enhances tissue regeneration in the process of wound healing in rats as animal model: a stereological study. J Cytol Histol 2012; 3:1000150

Baldrick P. The safety of chitosan as a pharmaceutical excipient. Regul Toxicol Pharmacol 2010; 56(3):290-299

Bar J, David A, Khader T, Mulcare M, Tedeschi C. Assessing coagulation by rotational thromboelastometry (ROTEM) in rivaroxaban-anticoagulated blood using hemostatic agents. Prehosp Disaster Med 2017; 32(3):580-587

Barnard J, Millner R. A review of topical hemostatic agents for use in cardiac surgery. Ann Thorac Surg 2009; 88(4):1377-1383

Behrens AM, Sikorski MJ, Kofinas P. Hemostatic strategies for traumatic and surgical bleeding. J Biomed Mater Res A 2014; 102(11):4182-4194

Bennett BL, Littlejohn LF, Kheirabadi BS, Butler FK, Kotwal RS, Dubick MA, Bailey JA. Management of external hemorrhage in tactical combat casualty care: chitosan-based hemostatic gauze dressings – TCCC Guidelines – change 13-05. J Spec Oper Med 2014; 14(3):40-57

Bernkop-Schnurch A, Dunnhaupt S. Chitosan-based drug delivery systems. Eur J Pharm Biopharm 2012; 81(3):463-469

Bochicchio G, Kilbourne M, Kuehn R, Keledjian K, Hess J, Scalea T. Use of a modified chitosan dressing in a hypothermic coagulopathic grade V liver injury model. Am J Surg 2009; 198(5):617-622

Boucard N, Viton C, Agay D, Mari E, Roger T, Chancerelle Y, Domard A. The use of physical hydrogels of chitosan for skin regeneration following third-degree burns. Biomaterials 2007; 28(24):3478-3488

Boucher BA, Traub O. Achieving hemostasis in the surgical field. Pharmacotherapy 2009; 29(7 Pt 2):2S-7S

Brohi K, Singh J, Heron M, Coats T. Acute traumatic coagulopathy. J Trauma 2003; 54(6):1127-1130

Burgert JM, Gegel BT, Austin R 3rd, Davila A, Deeds J, Hodges L, Hover A, Lockhart C, Roy J, Simpson G, Weaver S, Wolfe W, Johnson D. Effects of arterial blood pressure on rebleeding using Celox and TraumaDEX in a porcine model of lethal femoral injury. AANA J 2010; 78(3):230-236

Burn J, Pirmohamed M. Direct oral anticoagulants versus warfarin: is new always better than the old? Open Heart 2018; 5(1):e000712

Camp MA. Hemostatic agents: a guide to safe practice for perioperative nurses. AORN J 2014; 100(2):131-147

Campbell HE, Stokes EA, Bargo DN, Curry N, Lecky FE, Edwards A, Woodford M, Seeney F, Eaglestone S, Brohi K, Gray AM, Stanworth SJ. Quantifying the healthcare costs of treating severely bleeding major trauma patients: a national study for England. Crit Care 2015; 19:276

Carrier M, Le Gal G, Wells PS, Rodger MA. Systematic review: case-fatality rates of recurrent venous thromboembolism and major bleeding events among patients treated for venous thromboembolism. Ann Intern Med 2010; 152(9):578-589

Chan LW, Kim CH, Wang X, Pun SH, White NJ, Kim TH. PolySTAT-modified chitosan gauzes for improved hemostasis in external hemorrhage. Acta Biomater 2016; 31:178-185

Charernsriwilaiwat N, Opanasopit P, Rojanarata T, Ngawhirunpat T. Lysozyme-loaded, electrospun chitosan-based nanofiber mats for wound healing. Int J Pharm 2012; 427(2):379-384

Cheung RCF, Ng, TB, Wong JH, Chan WY. Chitosan: an update on potential biomedical and pharmaceutical applications. Mar Drugs 2015; 13:5156-5186Chou TC, Fu E, Wu CJ, Yeh JH. Chitosan enhances platelet adhesion and aggregation. Biochem Biophys Res Commun 2003; 302(3):480-483

Chung YJ, An SY, Yeon JY, Shim WS, Mo JH. Effect of a chitosan gel on hemostasis and prevention of adhesion after endoscopic sinus surgery. Clin Exp Otorhinolaryngol 2016; 9(2):143-149

Conley SP, Littlejohn LF, Henao J, DeVito SS, Zarow GJ. Control of junctional hemorrhage in a consensus swine model with hemostatic gauze products following minimal training. Mil Med 2015; 180(11):1189-1195

Corral M, Ferko N, Hollmann S, Broder MS, Chang E. Health and economic outcomes associated with uncontrolled surgical bleeding: a retrospective analysis of the Premier Perspectives Database. ClinicoEcon Outcomes Res 2015; 7:409-421

Croisier F, Jérôme C. Chitosan-based biomaterials for tissue engineering. Eur Polym J 2013; 49:780-792

Crunkhorn R, Burnham R, Walton G. Successful use of a military-grade haemostatic agent for a major head and neck bleed. J Laryngol Otol 2013; 127(10):1031-1033

Dai TH, Tanaka M, Huang YY, Hamblin MR. Chitosan preparations for wounds and burns: antimicrobial and wound-healing effects. Expert Rev Anti-Infect Ther 2011; 9(7):857-879

Davie EW, Kulman JD. An overview of the structure and function of thrombin. Semin Thromb Hemost 2006; 32(Suppl 1):3-15

Douketis JD, Gu CS, Schulman S, Ghirarduzzi A, Pengo V, Prandoni P. The risk of fatal pulmonary embolism after discontinuing anticoagulant therapy for venous thromboembolism. Ann Intern Med 2007; 147(11):766-774

Douketis JD. Perioperative management of patients who are receiving warfarin therapy: an evidence-based and practical approach. Blood 2011; 117(19):5044-5049

Dragostin OM, Samal SK, Dash M, Lupascu F, Panzariu A, Tuchilus C, Ghetu N, Danciu M, Dubruel P, Pieptu D, Vasile C, Tatia R, Profre L. New antimicrobial chitosan derivatives for wound dressing applications. Carbohydr Polym 2016; 141:28-40

Evans JA, van Wessem KJ, McDougall D, Lee KA, Lyons T, Balogh ZJ. Epidemiology of traumatic deaths: comprehensive population-based assessment. World J Surg 2010; 34(1):158-163

Felt O, Carrel A, Baehni P, Buri P, Gurny R. Chitosan as tear substitute: a wetting agent endowed with antimicrobial efficacy. J Ocul Pharmacol 2000; 16(3):261-270

Fife CE, Carter MJ, Walker D, Thomson B. Wound care outcomes and associated cost among patients treated in US outpatient wound centers: data from the US Wound Registry. Wounds 2012; 24(1):10-17

Foda NH, El-laithy HM, Tadros MI. Implantable biodegradable sponges: effect of interpolymer complex formation of chitosan with gelatin on release behavior of tramadol hydrochloride. Drug Dev Ind Pharm 33(1):7-17

Frohm M, Gunne H, Bergman AC, Agerberth B, Bergman T, Boman A, Lidén S, Jörnvall H, Boman HG. Biochemical and antibacterial analysis of human wound and blister fluid. Eur J Biochem 1996; 237(1):86-92

Gegel BT, Burgert J, Cooley B, MacGregor J, Myers J, Calder S, Luellen R, Loughren M, Johnson D. The effects of BleedArrest, Celox, and TraumaDex on hemorrhage control in a porcine model. J Surg Res 2010; 164(1):e125-e129

Gerente C, Lee VKC, Le Cloirec P, McKay G. Application of chitosan for the removal of metals from wastewaters by adsorption - Mechanisms and models review. Crit Rev Environ Sci Technol 2007; 37:41-127

Ghadimi K, Levy JH, Welsby IJ. Perioperative management of the bleeding patient. Br J Anaesth 2016; 117(Suppl 3):iii18-iii30

Hatamabadi HR, Asayesh Zarchi F, Kariman H, Arhami Dolatabadi A, Tabatabaey A, Amini A. Celox-coated gauze for the treatment of civilian penetrating trauma: a randomized clinical trial. Trauma Mon 2015; 20(1):e23862

Howling GI, Dettmar PW, Goddard PA, Hampson FC, Dornish M, Wood EJ. The effect of chitin and chitosan on the proliferation of human skin fibroblasts and keratinocytes in vitro. Biomaterials 2001; 22(22):2959-2966

Hu Z, Zhang DY, Lu ST, Li PW, Li SD. Chitosan-based composite materials for prospective hemostatic applications. Mar Drugs 2018; 16(8):273

Iyer P, Walker KJ, Madihally SV. Increased matrix synthesis by fibroblasts with decreased proliferation on synthetic chitosan-gelatin porous structures. Biotechnol Bioeng 2012; 109(5):1314-1325

Jayakumar R, Prabaharan M, Sudheesh Kumar PT, Nair SV, Tamura H. Biomaterials based on chitin and chitosan in wound dressing applications. Biotechnol Adv 29(3):322-337

Jin NZ, Gopinath SCB. Potential blood clotting factors and anticoagulants. Biomed Pharmacother 2016; 84:356-365

Johnson L, Luksch P, Ranfield J, Hardy C. The laboratory assessment of a new hemostat able to clot blood containing anticoagulants. Presented at the 21st Annual Symposium on Advanced Wound Care and the Wound Healing Society, San Diego, 2008

Joppa SA, Salciccioli J, Adamski J, Patel S, Wysokinski W, McBane R, Al-Saffar F, Esser H, Shamoun F. A practical review of the emerging direct anticoagulants, laboratory monitoring, and reversal agents. J Clin Med 2018; 7(2):pii:E29

Kheirabadi B. Evaluation of topical hemostatic agents for combat wound treatment. US Army Med Dep J 2011; Apr-Jun 25-37

Kheirabadi BS, Edens JW, Terrazas IB, Estep JS, Klemcke HG, Dubick MA, Holcomb JB. Comparison of new hemostatic granules/powders with currently deployed hemostatic products in a lethal model of extremity arterial hemorrhage in swine. J Trauma 2009; 66(2):316-326

Kheirabadi BS, Mace JE, Terrazas IB, Fedyk CG, Valdez KK, MacPhee MJ, Beall D, Estep JS, Dubick MA, Blackbourne LH. Clot-inducing minerals versus plasma protein dressing for topical treatment of external bleeding in the presence of coagulopathy. J Trauma 2010; 69(5):1062-1072

Khor E, Lim LY. Implantable applications of chitin and chitosan. Biomaterials 2003; 24(13):2339-2349

Klokkevold PR, Fukayama H, Sung EC, Bertolami CN. The effect of chitosan (poly-N-acetyl glucosamine) on lingual hemostasis in heparinized rabbits. J Oral Maxillofac Surg 1999; 57(1):49-52

Köksal Ö, Özdemir F, Çam Etöz B, İşbil Büyükcoşkun N, Siğirli D. Hemostatic effect of a chitosan linear polymer (Celox) in a severe femoral artery bleeding rat model under hypothermia or warfarin therapy. Turk J Trauma Emerg Surg 2011; 17(3):199-204

Kovich O, Otley CC. Thrombotic complications related to discontinuation of warfarin and aspirin therapy perioperatively for cutaneous operation. J Am Acad Dermatol 2003; 48(2):233-237

Kozen BG, Kircher SJ, Henao J, Godinez FS, Johnson AS. An alternate hemostatic dressing: comparison of CELOX, HemCon, and QuikClot. Acad Emerg Med 2008; 15(1):74-81

Kratz G, Arnander C, Swedenborg J, Back M, Falk C, Gouda I, Larm O. Heparin-chitosan complexes stimulate wound healing in human skin. Scand J Plast Reconstr Surg Hand Surg 1997; 31(2):119-123

Kuar RR, Glick JB, Siegel D. Achieving hemostasis in dermatology – Part 1: preoperative, intraoperative, and postoperative management. Indian Dermatol Online J 2013; 4(2):71-81

Lamb KM, Pitcher HT, Cavarocchi NC, Hirose H. Vascular site hemostasis in percutaneous extracorporeal membrane oxygenation therapy. Open Cardiovasc Thorac Surg J. 2012; 5:8-10

Lechner R, Helm M, Mueller M, Wille T, Friemert B. Efficacy of hemostatic agents in humans with rotational thromboelastometry: an in-vitro study. Mil Med 2016; 181(8):907-912

Lee DW, Lim H, Chong HN, Shim WS. Advances in chitosan material and its hybrid derivatives. Open Biomater 2009; 1(1):10-20

Lee G, Arepally GM. Anticoagulation techniques in apheresis: from heparin to citrate and beyond. J Clin Apher 2012; 27(3):117-125

Lee VF. Solution and shear properties of chitin and chitosan. Ph.D. Dissertation, University of Washington, University Microfilms, Ann Arbor, USA. 1974

Levin RM, Krieger NN, Winzler RJ. Glucosamine and acetylglucosamine tolerance in man. J Lab Clin Med 1961; 58:927-932

Li Q, Dunn ET, Grandmaison EW, Goosen MFA. Applications and properties of chitosan. J Bioact Compat Polym 1992; 7:370-397

Linkins LA, Choi PT, Douketis JD. Clinical impact of bleeding in patients taking oral anticoagulant therapy for venous thromboembolism: a meta-analysis. Ann Intern Med 2003; 139(11):893-900

Liu X, Guan Y, Yang D, Li Z, Yao K. Antibacterial action of chitosan and carboxymethylated chitosan. J Appl Polym Sci 2001; 79:1324-1335

Lootsik MD, Bilyy RO, Lutsyk MM, Stoika RS. Preparation of chitosan with high grade blood clotting activity and its hemostatic potential assessment. Biotechnol Acta 2015; 8(6):32-40

Lord MS, Cheng B, McCarthy SJ, Jung M, Whitelock JM. The modulation of platelet adhesion and activation by chitosan through plasma and extracellular matrix proteins. Biomaterials 2011; 32(28):6655-6662

MacIntyre AD, Quick JA, Barnes SL. Hemostatic dressings reduce tourniquet time while maintaining hemorrhage control. Am Surg 2011; 77(2):162-165

Madhok BM, Vowden K, Vowden P. New techniques for wound debridement. Int Wound J 2013; 10(3):247-251

Malette WG, Quigley HJ, Gaines RD, Johnson ND, Rainer WG. Chitosan: a new hemostatic. Ann Thorac Surg 1983; 36(1):55-58

Marietta M, Facchini L, Pedrazzi P, Busani S, Torelli G. Pathophysiology of bleeding in surgery. Transplant Proc 2006; 38(3):812-814

Martini WZ. Coagulation complications following trauma. Mil Med Res 2016; 3:35

Martyn D, Meckley LM, Miyasato G, Lim S, Riebman JB, Kocharian R, Scaife JG, Rao Y, Corral M. Variation in hospital resource use and cost among surgical procedures using topical absorbable hemostats. ClinicoEcon Outcomes Res 2015a; 7:567-574

Martyn D, Kocharian R, Lim S, Meckley LM, Miyasato G, Prifti K, Rao Y, Riebman JB, Scaife JG, Soneji Y, Corral M. Reduction in hospital costs and resource consumption associated with the use of advanced topical hemostats during inpatient procedures. J Med Econ 2015b; 18(6):474-481

McCarty MF. Glucosamine for wound healing. Med Hypotheses 1996; 47(4):273-275

Mercy HP, Halim AS, Hussein AR. Chitosan-derivatives as hemostatic agents: their role in tissue regeneration. Regen Res 1(1):38-46

Millner R, Lockhart AS, Marr R. Chitosan arrests bleeding in major hepatic injuries with clotting dysfunction: an in vivo experimental study in a model of hepatic injury in the presence of moderate systemic heparinisation. Ann R Coll Surg Engl 2010; 92(7):559-561

Millner RW, Lockhart AS, Bird H, Alexiou C. A new hemostatic agent: initial life-saving experience with Celox (chitosan) in cardiothoracic surgery. Ann Thorac Surg 2009; 87(2):e13-e14

Millner RWJ, Lockhart AS, Marr R, Jones K. Omni-Stat (chitosan) arrests bleeding in heparinised subjects in vivo: an experimental study in a model of major peripheral vascular injury. Eur J Cardiothorac Surg 2011; 39(6):952-954

Mirzadehl H, Yaghobi N, Amanpour S, Ahmadi H, Ali Mohagheghi M, Hormozi F. Preparation of chitosan derived from shrimp's shell of Persian Gulf as a blood hemostasis agent. Iranian Polym J 2002; 11(1):63-68

Misgav M, Lubetszki A, Brutman-Barazani T, Martinowitz U, Kenet G. The hemostatic efficacy of chitosan-pads in hemodialysis patients with significant bleeding. J Vasc Access 2017; 18(3):220-224

Mitra B, Tullio F, Cameron PA, Fitzgerald M. Trauma patients with the 'triad of death'. Emerg Med J 2012; 29(8):622-625

Mohandas A, Deepthi S, Biswas R, Jayakumar R. Chitosan based metallic nanocomposite scaffolds as antimicrobial wound dressings. Bioact Mater 2018; 3(3):267-277

Monaco L, Biagi C, Conti V, Melis M, Donati M, Venegoni M, Vaccheri A, Motola D. Safety profile of the direct oral anticoagulants: an analysis of the WHO database of adverse drug reactions. Br J Clin Pharmacol 2017; 83(7):1532-1543

Mulloy B, Hogwood J, Gray E, Lever R, Page CP. Pharmacology of heparin and related drugs. Pharmacol Rev 2016; 68(1):76-141

Niekraszewicz A. Chitosan medical dressings. Fibres and Textiles in Eastern Europe vol. 13 2005; 6(54):16-18

Niles SE, McLaughlin DF, Perkins JG, Wade CE, Li Y, Spinella PC, Holcomb JB. Increased mortality associated with the early coagulopathy of trauma in combat casualties. J Trauma 2008; 64(6):1459-1463

Ong SY, Wu J, Moochhala SM, Tan MH, Lu J. Development of a chitosan-based wound dressing with improved hemostatic and antimicrobial properties. Biomaterials 2008; 29(32):4323-4332

Peng T. Biomaterials for haemorrhage control. Trends Biomater Artif Organs 2010; 24(1):27-68

Pogorielov M, Kalinkevich O, Deineka V, Garbuzova V, Solodovnik A, Kalinkevich A, Kalinichenko T, Gapchenko A, Sklyar A, Danilchenko S. Haemostatic chitosan coated gauze: in vitro interaction with human blood and in-vivo effectiveness. Biomater Res 2015; 19:22

Pogorielov MV, Siroka VZ. Chitosan as a hemostatic agent: current state. Eur J Med B 2015; 2(1):24-33

Pozza M, Millner RWJ. Celox (chitosan) for haemostasis in massive traumatic bleeding: experience in Afghanistan. Eur J Emerg Med 2011; 18(1):31-33

Rall JM, Cox JM, Songer A, Comeaux JA, Estep JS, Cestero RF, Ross JD. Comparison of novel hemostatic dressings with QuikClot combat gauze in a standardized swine model of uncontrolled haemorrhage. J Trauma Acute Care Surg 2013; 75(2 Suppl 2):S150-S156

Rao SB, Sharma CP. Use of chitosan as a biomaterial: studies on its safety and hemostatic potential. J Biomed Mater Res 1997; 34(1):21-28

Recinos G, Inaba K, Dubose J, Demetriades D, Rhee P. Local and systemic hemostatics in trauma: a review. Turk J Trauma Emerg Surg 2008; 14(3):175-181

Saap LJ, Falanga V. Debridement performance index and its correlation with complete closure of diabetic foot ulcers. Wound Repair Regen 2002; 10(6):354-359

Schierle C, Krol J. Can new hemostatic dressings facilitate sharp debridement in high-risk patients? Podiatry Today 2009; 22(7):20-22

Schreiber MA, Neveleff DJ. Achieving hemostasis with topical hemostats: making clinically and economically appropriate decisions in the surgical and trauma settings. AORN J 2011; 94(5):S1-S20

Seyednejad H, Imani M, Jamieson T, Seifalian AM. Topical haemostatic agents. Br J Surg 2008; 95(10):1197-1225

Seyfarth F, Schliemann S, Elsner P, Hipler UC. Antifungal effect of high- and low-molecular-weight chitosan hydrochloride, carboxymethyl chitosan, chitosan oligosaccharide and N-acetyl-D-glucosamine against Candida albicans, Candida krusei and Candida glabrata. Int J Pharm 2008; 353(1-2):139-148

Shander A. Financial and clinical outcomes associated with surgical bleeding complications. Surgery 2007; 142(4 Suppl):S20-S25

Singla AK, Chawla M. Chitosan: some pharmaceutical and biological aspects – an update. J Pharm Pharmacol 2001; 53(8):1047-1067

Snyder RJ, Sigal BD. Evaluation of hemostatic gauze versus standard of care for the treatment of chronic wounds in the presence of anticoagulants. Presented as a poster at SAWC 2013

Snyder RJ, Sigal BD. The importance of hemostasis in chronic wound care: an open-label controlled clinical study of OMNI-STAT (chitosan) versus standard of care in post-debridement treatment of patients with chronic wounds with or without concomitant use of anticoagulants. Wound Care Hyperb Oxygen 2013; 4(2):9-16

Spotnitz WD, Burks S. Hemostats, sealants, and adhesives: components of the surgical toolbox. Transfusion 2008; 48(7):1502-1516

Spotnitz WD, Burks S. State-of-the-art review: hemostats, sealants, and adhesives II: update as well as how and when to use the components of the surgical toolbox. Clin Appl Thromb Hemost 2010; 16(5):497-514

Spyropoulos AC, Douketis JD. How I treat anticoagulated patients undergoing an elective procedure or surgery. Blood 2012; 120(15):2954-2962

Stacy Z, Richter S. Practical considerations for the use of direct oral anticoagulants in patients with atrial fibrillation. Clin Appl Thromb Hemost 2017; 23(1):5-19

Stephen-Haynes J, Gibson E, Greenwood M. Chitosan: a natural solution for wound healing. J Community Nurs 2014; 28(1):48-53

Stępniewski M, Martynkiewicz J, Gosk J. Chitosan and its composites: properties for use in bone substitution. Polim Med 2017; 47(1):49-53

Stokes ME, Ye X, Shah M, Mercaldi K, Reynolds MW, Rupnow MF, Hammond J. Impact of bleeding-related complications and/or blood product transfusions on hospital costs in inpatient surgical patients. BMC Health Serv Res 2011; 11:135

Stricker-Krongrad, AH, Alikhassy Z, Matsangos N, Sebastian R, Marti G, Lay F, Harmon JW. Efficacy of chitosan-based dressing for control of bleeding in excisional wounds. Eplasty 2018; 18:122-130

Suzuki K, Cowan L. Current concepts in wound debridement. Podiatry Today 2009; 22(7):40-48

Suzuki Y, Okamoto Y, Morimoto M, Sashiwa H, Saimoto H, Tanioka SI, Shigemasa Y, Minami S. Influence of physico-chemical properties of chitin and chitosan on complement activation. Carbohydr Polym 2000; 42(3):307-310

Tan ECTH, Bleeker CP. Field experience with a chitosan-based haemostatic dressing. MCI Forum 2011; 3(4):11-15

Tashiro T. Antibacterial and bacterium absorbing macromolecules. Macromol Mater Eng 2001; 286:63-87

Trabattoni D, Montorsi P, Fabbiocchi F, Lualdi A, Gatto P, Bartorelli A. A new kaolin-based haemostatic

bandage compared with manual compression for bleeding control after percutaneous coronary procedures. Eur Radiol 2011; 21(8):1687-1691

Ueno H, Yamada H, Tanaka I, Kaba N, Matsuura M, Okumura M, Kadosawa T, Fujinaga T. Accelerating effects of chitosan for healing at early phase of experimental open wounds in dogs. Biomaterials 1999; 20(15):1407-1414

Waibel KH, Haney B, Moore M, Whisman B, Gomez R. Safety of chitosan bandages in shellfish allergic patients. Mil Med 2011; 176(10):1153-1156

Wang T, Zhu XK, Xue XT, Wu DY. Hydrogel sheets of chitosan, honey and gelatin as burn wound dressings. Carbohydr Polym 2012; 88(1):75-83

Watters JM, Van PY, Hamilton GJ, Sambasivan C, Differding JA, Schreiber MA. Advanced hemostatic dressings are not superior to gauze for care under fire scenarios. J Trauma 2011; 70(6):1413-1419

Whang HS, Kirsch W, Zhu YH, Yang CZ, Hudson SM. Hemostatic agents derived from chitin and chitosan. J Macromolec Sci, Part C 2005; 45(4):309-323

Won KB, Lee SH, Chang HJ, Shim CY, Hong GR, Ha JW, Chung N. Safety and cost-effectiveness of bridge therapies for invasive dental procedures in patients with mechanical heart valves. Yonsei Med J 2014; 55(4):937-943

Xia WS. Physiological activities of chitosan and its application in functional foods. J Chinese Inst Food Sci Tech 2003; 3:77-81

Yang J, Tian F, Wang Z, Wang Q, Zeng YJ, Chen SQ. Effect of chitosan molecular weight and deacetylation degree on hemostasis. J Biomed Mater Res B Appl Biomater 2008; 84(1):131-137

Yang TL. Chitin-based materials in tissue engineering: applications in soft tissue and epithelial organ. Int J Mol Sci 2011; 12(3):1936-1963

Zhang YL, Gao B, Liu XW. Topical and effective hemostatic medicines in the battlefield. Int J Clin Exp Med 2015; 8(1):10-19

Zimmerman LH. Causes and consequences of critical bleeding and mechanisms of blood coagulation. Pharmacotherapy 2007; 27(9 Pt 2):45S-56S

9. Index

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10. Appendix

Table 1: Topical hemostatic agents (modified from Camp, 2014; Schreiber and Neveleff, 2011)

Type		Comments
ABSORBABLE INTERNAL	Passive	• Application of material to form physical barrier to blood loss • Provides surface for blood clotting Commercially available hemostats include porcine gelatin (GELFOAM®, SURGIFOAM®), bovine collagen (Avitene™, INSTAT®), oxidized regenerated cellulose (SURGICEL®), polysaccharide spheres , beeswax
	Active	• Utilizes thrombin • Concentrated localization of thrombin to enhance fibrin clot formation Commercially-available hemostats include pooled human thrombin (EVITHROM®), recombinant thrombin (Recothrom®)
	Flowables	• Composed of both passive (e.g. gelatin) and active components (e.g. thrombin) • Block blood loss and promote fibrin clot formation Commercially-available hemostats include active (thrombin) and passive (gelatin matrix) components (FLOSEAL®, SURGIFLO®)
	Fibrin sealants	• Generally contain both fibrinogen and thrombin • Concentrated delivery of fibrinogen and thrombin promotes formation of fibrin clot • Increased rates of blood clotting Commercially-available hemostats include pooled human plasma (EVICEL®, TISSEEL™), patient's own plasma with bovine collagen/thrombin (Vitagel™) or patient's own plasma to create fibrinogen/thrombin (CryoSeal®, RAPLIXA®)
	Adhesives	• Diverse synthetic sealants • Common mechanism of sealing tissue Commercially-available hemostats include cyanoacrylates (DERMABOND®), synthetic skin (SurgiSeal®, LiquiBand®) and tissue (OMNEX®) sealants, glutaraldehydes (BioGlue®), polyethylene glycol polymers (CoSeal™, DuraSeal™, Progel®)
TEMPORARY EXTERNAL		• Promotes effective hemostasis • A number of mechanisms promoting hemostasis, some independent of natural clotting cascade (e.g. chitosan derived materials) • Designed for external use • Temporary application Commercially-available hemostats include chitosan (HemCon®, OMNI-STAT), kaolin (QuikClot®) • Designed for external use only

Table 2: Properties of an Ideal Hemostatic Agent (Peng, 2010; Snyder and Sigal, 2013)

Effective	• The agent should stop bleeding reliably and consistently across a variety of wound types and surfaces • The agent should work independently of host coagulation function in order to stop bleeding in patients with clotting dysfunction or those patients being treated with anticoagulants
Safe	• The agent (and its metabolites) should be non-toxic and pose no risk of metabolic, infectious, immunologic or oncologic complications. • The agent should not interfere with any metabolic pathways that would produce significant biologic dysfunction • The agent should be easily removable and/or biodegradable/absorbable to prevent any interference with subsequent biologic processes once agent has been removed
Easy to use	• The agent should be easily stored, ideally at room temperature • The agent should have a long shelf-life to maintain effectiveness for extended periods • The agent should be useable without the requirement for premixing of components in order for rapid application • The agent should require minimal training to use
Cost effective	• The agent should be relatively inexpensive and affordable

Table 3: OMNI-STAT Hemostatic Hospital Products

OMNI-STAT Hemostatic Granules	• Pouch containing 0.1 oz (3 g) of hemostatic granules. Formal offers quick application (just pour onto the bleeding site) and the ability to easily fit a range of wound types and shapes.
OMNI-STAT Hemostatic Gauze	• Pouch containing folded 4" x 4" (10 x 10 cm) woven fabric dressing coated on both sides with OMNI-STAT hemostatic granules.

Table 4: Clotting times (seconds)

	OMNI-STAT®	Control
Test #1	26	1020
Test #2	28	840
Test #3	32	806
Test #4	36	600
Average	**30.5**	**816.5**
Standard deviation	4.4	149.1

Table 5: Clinical studies of OMNI-STAT on wound debridement

Reference	Design & methods	Main outcomes	Main results
Snyder & Sigal (2013)	• Open-label, controlled observational study • Open wounds of various aetiologies (n=40) including venous leg ulcers, diabetic foot ulcers and mixed ulcers • Sharp debridement applied and then treated with chitosan-impregnated gauze (OMNI-STAT)	• Time required to achieve hemostasis • Secondary outcome: patient assessment of pain • Secondary outcome: appearance of wound bed (improvement of granulation tissue) after 7 days	• Time to hemostasis reduced by 4 minutes with OMNI-STAT ($p<0.0001$) • Improvement in granulation tissue in chitosan-impregnated dressing compared with control • Pain score during hemostasis decreased for OMNI-STAT compared with gauze controls • Pain score on dressing removal after 7 days decreased for OMNI-STAT group compared with gauze controls

Table 6: Clinical evaluations of OMNI-STAT on traumatic hemorrhage

Reference	Methodology	Main results
Pozza & Millner (2011)	Case series (n=21) **Gunshot wounds:** • Treated with OMNI-STAT	• Hemostasis achieved at first application in 18 cases • Hemostasis achieved in 3 cases after further applications
Tan & Bleeker (2011)	Case series (n=7) **Gunshot wounds to arm, leg and buttocks** • Persistent bleeding from buttock wound • Packed with OMNI-STAT Gauze	• Bleeding stopped quickly after use of OMNI-STAT Gauze • Removed after 24 hours with no further bleeding
	Multiple injuries from IED blast • Tear wounds and arterial bleed from groin • Emergency bandage applied but leaked • Treated with OMNI-STAT Gauze	• Bleeding stopped quickly after application of OMNI-STAT Gauze • Transfer to operating room with no bleeding
	Trauma from road traffic accident • High energy trauma resulting in venous bleeding from neck • Bleeding not stopped with application of normal pressure bandage	• Bleeding stopped quickly after application of OMNI-STAT Gauze • Transfer to hospital with no bleeding
Crunkhorn et al (2013)	Case report (n=1) **Life-threatening head and neck bleed** • Patient known to have malignant peripheral nerve sheath sarcoma originating from parapharyngeal space • Treated with OMNI-STAT granules	• Bleeding successfully controlled

Table 7: Clinical studies of OMNI-STAT on traumatic hemorrhage

Reference	Design & methods	Main outcomes	Main results
Hatamabadi et al (2015)	• Prospective, randomised controlled open-label study • Penetrating trauma wounds (including stab wounds with knives, glass, motor vehicle accidents) (n=160) • Wound where bleeding was a concern included • Treatment was with either standard pressure gauze (n=80) or OMNI-STAT-coated gauze (n=80)	• Time to achieve hemostasis • Volume of blood loss after beginning of treatment	• Hemostasis achieved within 5 minutes: 32.5% of control group and 51.3% of OMNI-STAT group • Using OMNI-STAT-coated gauze significantly reduced time to hemostasis ($p=0.01$) • Blood loss significantly lower in OMNI-STAT group ($p<0.05$)

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