

# New haemostatic agents, blood substitutes and the implications for military medicine

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STANCHING HAEMORRHAGE following wounding in battle has depended in the first instance on early “buddy” care and medic assistance. After evacuation, ongoing resuscitation is performed in a regimental aid post, followed by rapid evacuation to a forward hospital. The difficulty of placing a level 3 surgical facility near the front line of battle in the dispersed asymmetrical guerrilla-style urban and remote war scenarios that exist in Iraq and Afghanistan presents complex challenges for military planners. The scenario of fast-moving military units with no clearly defined warfront and random attacks at any time, with the possibility of blocked support lines, is likely to cause delays in casualties reaching surgical support. From their experience in the current Iraq conflict, Clasper and Rew have argued for careful placement of scarce surgical resources, rather than wide dispersal, and for more reliance on an efficient evacuation chain.<sup>1</sup>

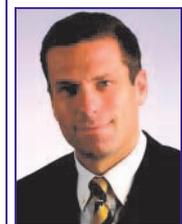
## Abstract

- ◆ The importance of rapidly stanching severe haemorrhage is known. Battle-wound-induced severe haemorrhage is difficult to treat in a combat situation.
- ◆ Newly developed wound dressings that promote blood clotting and halt major life-threatening bleeding are currently being trialled by the US Army and the US Marine Corps in Iraq and Afghanistan.
- ◆ Topical products include QuikClot, Chitosan, and the Rapid Deployment Hemostat (RDH) bandage.
- ◆ Intravenous recombinant factor VIIa (NovoSeven) can stop some cases of severe bleeding due to coagulopathy.
- ◆ Further clinical trials are necessary to establish the role of these products in the civilian setting.
- ◆ We recommend that evaluation of selected haemostatic agents commence in appropriate ADF medical facilities. We also briefly review the potential for new blood substitutes and telerobotic surgery in the military setting.

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Experience in the Second World War and the Korean and Vietnam conflicts clearly demonstrated that rapid resuscitation and use of blood transfusion saves lives in serious trauma. The increased survival rate of civilian trauma patients can clearly be attributed to an aggressive approach to resuscitation and blood transfusion.<sup>2</sup>

“Hot” blood transfusion based on the blood group on “dog tags” was used successfully by the US Rangers in Somalia.<sup>3</sup> This technique is valuable, provided the blood is virologically and bacteriologically safe. Australian Defence Force (ADF) personnel are screened for HIV and hepatitis before deployment. Nevertheless, the ADF uses refrigerated, screened and typed blood for ADF personnel.

There is also no doubt that timely surgical control of haemorrhage saves lives. “Damage control” surgery has become the guiding philosophy in trauma surgery for severely injured people since the advantage of this approach was demonstrated in the treatment of abdominal gunshot wounds.<sup>4,5</sup> Staged laparotomy, with initial temporary closure of injured bowel segments, surgical control of haemorrhage and packing of the abdomen, is followed by one or more laparotomies to restore bowel integrity. This concept is now

the template for damage control surgery, and these concepts are spreading to other areas of emergency surgery.<sup>6,7</sup> Correcting acidosis, hypothermia, anaemia, coagulopathy and hypotension are all critical components of advanced trauma care, and can be achieved most successfully when damage control surgery is practised. Coagulopathy is an important clinical problem that occurs after significant blood loss or when the core body temperature drops below 32°C. Severe trauma may also be complicated by a disseminated intravascular coagulation picture, which often represents a consumptive coagulopathy and may play an important role in the development of multiorgan failure.<sup>8</sup>

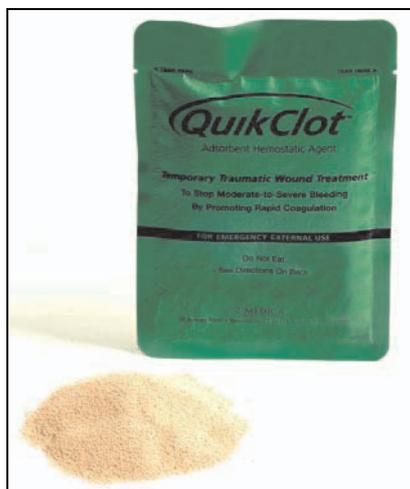
There is also debate about the optimal level of blood pressure following penetrating trauma, with strong evidence from civilian practice that relative hypotension leads to better survival than correction of hypotension.<sup>9</sup> How this translates to the military setting, particularly when there are delays in surgery, is unclear.

Under battlefield conditions, several questions arise regarding the effective treatment of casualties with severe bleeding who are in danger of exsanguination. How well can haemorrhage be stopped by haemostatic dressings until definitive surgery is available? Can early surgery be delayed by using new topical and systemic haemostatic products, and how applicable are these to the military situation? Are there other forms of blood substitution available? What is the role of early surgical intervention? Can the use of haemostatic dressings reduce blood loss following trauma surgery? Could telero-botic surgery play an important role in the treatment of soldiers with severe haemorrhage? These questions are addressed in this review.

## Haemostatic agents

A variety of substances have been developed to be applied in the form of a haemostatic dressing that aims to stop bleeding at the entrance or exit point of the injury. All these substances induce coagulation, with different intervention points within the coagulation system.

### 1: QuikClot



*Sterile zeolite volcanic mineral granules poured into a bleeding wound absorb water content of blood through microscopic holes in the granules, thus concentrating the clotting factors and blood cells and creating a stable clot.*

### 2: American Red Cross haemostatic dressing



*This dressing contains microfibrillar collagen, thrombin, oxidized cellulose, and poly-N-acetyl-glucosamine. Allergic reaction is a potential problem.*

## QuikClot

QuikClot (manufacturer, Z-medica, Newington, CT) (Box 1) consists of a proprietary formula of zeolite volcanic mineral granules, and is marketed as being able to stop high-volume bleeding from open wounds. It has US Food and Drug Administration (FDA) approval.

QuikClot sterile granules are poured into a wound, and absorb the water content of blood through microscopic holes in the granules. This concentrates the clotting factors and blood cells. QuikClot creates a stable clot that can be removed by irrigation and suction.

QuikClot has been tested in an experimental animal model. A complex soft tissue and vascular groin injury was created in swine to create uncontrolled haemorrhage. Multiple dressing types were trialled, and the QuikClot dressing improved survival and decreased bleeding.<sup>10</sup> The granules are non-allergenic.

Use of QuikClot leads to an exothermic reaction. The temperature rises more sharply when the QuikClot granules encounter water compared with blood. The temperature rises within 30–60 seconds and lasts several minutes, with a peak between 42°C and 44°C for about 30 seconds. There are inadequate data to support use of QuikClot in body cavities.<sup>10</sup>

QuikClot dressings are being trialled by the US Marine Corps in Afghanistan and Iraq, and have already been incorporated in the new Marine Corps individual first aid kit. QuikClot is also being used with a new pressure bandage called CinchTight.<sup>11</sup> The cost of QuikClot is about US\$20 per unit.

## American Red Cross haemostatic dressing

In a model of severe venous and hepatic injury in swine, nine dressing types were trialled, and the American Red Cross haemostatic dressing, which contains microfibrillar collagen, thrombin, oxidised cellulose and poly-N-acetyl-glucosamine (manufacturer, CSL Ltd, Parkville, VIC; distributed by Bioplasma) (Box 2), was effective in reducing post-treatment blood loss and in increasing the proportion of animals in which haemostasis was obtained.<sup>12</sup> Allergic reaction is a potential problem.

This product is being trialled in Iraq and is not commercially available.

### Rapid Deployment Hemostat bandage

The Rapid Deployment Hemostat (RDH) bandage (manufacturer, Marine Polymer Technologies, Cambridge, MA) consists of fully acetylated poly-*N*-acetyl glucosamine (p-GlcNAc) applied to a gauze bandage. It has been approved by the US FDA as a dressing for treating bleeding after extremity trauma.

The dressing has been modified for internal use and was tested as an adjunct to standard laparotomy in a pig model of severe liver injury. Anaesthetised animals were rendered hypothermic and coagulopathic, and one group was observed after surgery that included packing of the liver.

The second group had resuscitation and surgery. The mortality, blood loss and fluid requirements were significantly reduced by the use of the RDH bandage.<sup>13</sup>

The cost of this product is not available, and the bandage is still being evaluated for clinical application.

### Chitosan bandage

Chitosan bandage (manufacturer, HemCon Inc, Tigard, OR) was developed by the Oregon Medical Laser Center through a grant from the US Army Medical Research and Materiel Command. The FDA approved the bandage in November 2002.

Chitosan is a biodegradable carbohydrate found in prawns and lobster shells and many other animals. It bonds with blood cells to form a clot, and has some antimicrobial effect. Interestingly, chitosan is not hazardous to those allergic to prawns. Pusateri et al tested the chitosan bandage in a model of severe liver injury in swine, and found it reduced haemorrhage and improved survival.<sup>14</sup>

This dressing is currently being trialled by the US Army. The cost of the bandage is about US\$90–\$100 for a 10 cm by 10 cm square.

### Recombinant factor VIIa

Recombinant factor VIIa (rFVIIa, 'NovoSeven'; manufacturer, Novo Nordisk Pharmaceuticals Pty Ltd, Baulkham Hills, NSW) (Box 3) was developed for the treatment of bleeding in haemophiliac patients with inhibitors to factors VIII and IX. It enhances thrombin production on already activated platelets. Its application has been extended to other patients with profuse bleeding who have impaired thrombin production. This includes patients with thrombocytopenia and

### 3: Recombinant factor VIIa



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platelet function deficiencies.<sup>15</sup> rFVIIa seems to enhance haemostasis at the site of injury without systemic activation of the coagulation cascade.<sup>16</sup>

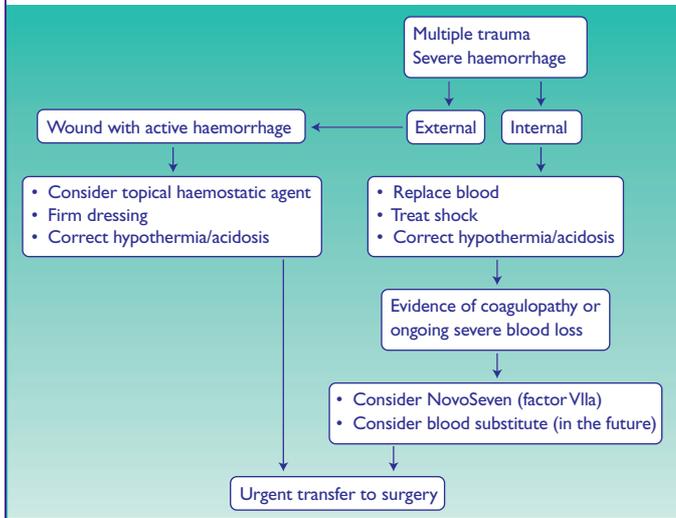
rFVIIa has been used in an experimental model of liver injury in anaesthetised swine. Administration of rFVIIa after a 10% reduction in mean arterial pressure due to avulsion of the left lobe of the liver decreased bleeding and prolonged survival. There was no thrombosis in vital organs.<sup>17</sup> One study showed a reduction in blood loss after administering rFVIIa to pigs with grade V liver injuries and dilution coagulopathy. Increasing the dose did not increase the haemostatic effect.<sup>18</sup> In another study, shorter prothrombin time and higher mean arterial pressures were reported in a swine liver injury model following administration of rFVIIa.<sup>19</sup>

rFVIIa can be used for treating uncontrolled massive haemorrhage in the preoperative setting, and it may play a role as an adjunct to surgical haemostasis in trauma patients and in patients with severe postoperative bleeding following general surgery.<sup>16</sup> In a retrospective study, rFVIIa was used in trauma patients with exsanguinating haemorrhage, and it was concluded that rFVIIa contributed to the control of haemorrhaging in three of five patients. It failed in two patients with overwhelming shock and acidosis.<sup>20</sup> rFVIIa has also been used safely to control surgical bleeding following elective cardiac, abdominal and thoracic surgery, and in trauma patients with uncontrolled bleeding. Significant reductions in blood loss were reported.<sup>21</sup> The activity of rFVIIa is reduced by hypothermia and is dramatically affected by low pH. Therefore, its efficacy may be reduced in patients with acidosis.<sup>22</sup> Martinowitz et al reported rFVIIa (median dose, 120 µg/kg; range, 120–212 µg/kg) resulted in cessation of bleeding in seven massively bleeding, multitransfused, coagulopathic trauma patients after failure of conventional measures. Five of the seven patients died, but this was thought to be due to the severe injuries and shock.<sup>23</sup>

Several randomised blinded studies of rFVIIa are under way for hepatectomy, upper gastrointestinal haemorrhage, transplantation and intracerebral haemorrhage.<sup>15</sup> There have been five international conferences on rFVIIa in Denmark in the past 10 years. Many thousands of administrations of this product have now occurred. Thrombotic complications do not appear to be a significant problem. The Israeli and US defence forces are using this product. Further careful evaluation of rFVIIa is required to determine its optimal dose and role in the management of exsanguination in critically ill trauma patients.

rFVIIa has helped to save lives after severe exsanguination and therefore should be available for use in the ADF for

#### 4: Proposed algorithm for the application of new haemostatic products in trauma patients in the military setting



severely injured ADF members, particularly in remote settings where surgery is not readily available or to use as a supplement to surgical haemostasis where there is severe and uncorrected coagulopathy.

The cost of NovoSeven is \$1128.75 for a 1.2 mg vial, \$2257.50 for a 2.4 mg vial and \$4515 for a 4.8 mg vial. The doses used in trauma patients are generally 90–200 µg/kg, which amounts to about \$10 000 for a 90 kg soldier.

### Blood substitutes

Modified haemoglobin solutions, perfluorocarbon emulsions, and liposome-encapsulated haemoglobin are the three types of blood substitutes that have been under development. The first two have reached phase III clinical trials, and the third is in preclinical testing.<sup>24</sup>

Low volume resuscitation with a polymerised bovine haemoglobin-based oxygen carrying solution (HBOC-201) was trialled in a porcine model of controlled haemorrhage. HBOC-201 provided adequate tissue oxygenation for survival in this model, with no long-term organ dysfunction identified.<sup>25</sup> Another study of HBOC-201 in a porcine model of controlled haemorrhagic shock found that hypotensive resuscitation with HBOC-201 restores tissue oxygenation and reverses anaerobic metabolism at significantly lower volumes than other resuscitation fluids.<sup>26</sup> These studies suggest that HBOC-201 would be an effective primary resuscitation fluid in remote military or rural settings. However, careful clinical evaluation will be required before it is more widely introduced.

### Telerobotic surgery

Robotic surgery provides the potential to undertake more complex and precise tasks with minimal invasion, and is likely to have a major effect on the way surgery is practised.<sup>27</sup> Robot-assisted surgery is already used in cardiac surgery, general surgery, urological surgery, and neurological surgery. The virtual reality systems and telepresence used in the robotic surgery technology could be used for remote surgery, and may therefore have application in military surgery.

An injured soldier could be placed on a critical care pod and transported to a vehicle, where telerobotic surgery, with the assistance of a medic using telepresence and a robotic surgeon, could be carried out. These systems also have great training potential using virtual reality systems.<sup>28</sup> The sensation of touch, tissue characteristics, and tension are being incorporated into these systems. It is still early days for the evolution of these systems in managing acute patients, and the use of the haemostatic agents will obviate the need for such “immediate” surgery on the battlefield.

### Discussion

Battle wound dressings have not changed over several centuries of warfare. However, a revolution in initial wound management is occurring in Afghanistan and the Persian Gulf with the advent of dressings that are designed to stop life-threatening haemorrhage.

Oozing versus major arterial and venous haemorrhage are very different surgical problems that often co-exist in trauma patients. The haemostatic dressings and rFVIIa may have an important role in stopping ongoing oozing that can be a source of significant blood loss and a technical challenge for the surgeon. It appears from reading the descriptions of haemostatic dressings that they can also stop large-volume arterial and venous haemorrhage, although it is not clear how much pressure should be applied. Theoretically, the use of haemostatic dressings may reduce tourniquet time on a wounded limb, with the dressing being applied after the application of the tourniquet, which can then be released. The use of these agents following experimental liver trauma indicates that haemostatic dressings may have a wider role in reducing blood loss following trauma surgery.

Haemostatic dressings also need to be trialled in humans for control of internal haemorrhage, such as that resulting from solid organ injury. The absorbability of the dressing will need to be established if it is to be used internally.

Prospective randomised controlled trials can only be performed when there are adequate numbers of patients. This may be feasible in a civilian setting in major trauma centres in Australia. The ADF is planning to trial haemostatic dressings as part of the JP2060 Future Capability Development.

## Conclusions

There are clearly several options for the choice of haemostatic wound dressings, and further testing will be required to establish their individual suitability. The Chitosan and QuikClot dressings are more durable and less expensive than the Red Cross haemostatic dressing. In Box 4, we propose an algorithm for the introduction of these agents into the ADF.

Timely surgical control of haemorrhage saves lives and remains a fundamental component of trauma care. Advanced haemostatic dressings, rFVIIa and blood substitutes do not replace the need for surgical control of haemorrhage, but may help to avoid life-threatening exsanguination haemorrhage and to stabilise the patient until surgical care is undertaken. These agents may also be suitable in desperate cases of severe bleeding when there is general ooze not well suited to surgical control. New haemostatic agents may have great potential to improve the survivability and outcome from penetrating injuries with haemorrhage in war. Improved blood substitute products may also have an important role on the battlefield for extending resuscitation time to surgery by attenuating the effects of blood loss and shock.

Prospective controlled trials of these new therapies should be undertaken to firmly establish their clinical application. However, the imperative of saving the lives of wounded soldiers on the battlefield has already prompted the widespread and apparently successful application of haemostatic dressings in the Iraq war. We await the peer-reviewed evaluation of these trials. We believe that it is now time to carefully evaluate the usefulness of selected haemostatic wound dressings and rVIIa in the ADF, particularly in remote settings where a medic or medical officer can apply these dressings or administer rVIIa as an aid to stabilisation of the patient when surgery will be delayed. It is likely that these new haemostatic wound dressings, topical agents, rVIIa, and blood substitutes such as HBOC-201 will have a major life-saving role, both on the battlefields of the future and in the civilian setting.

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