

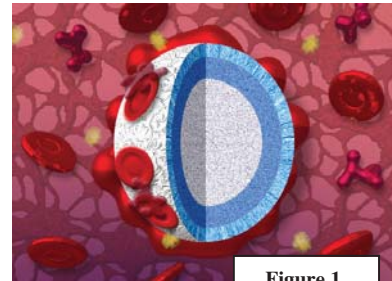
## **Microporous Polysaccharide Hemospheres Provides Effective Topical Hemostasis in a Human Modified Bleeding Time Incision Model**

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### **Summary:**

Topical bleeding from surgical and traumatic wounds contribute to substantial blood loss and patient morbidity. Several topical hemostatic agents are available which either provide clotting components (e.g., fibrin glues) or provide a surface for clotting to be stimulated (e.g., collagen, gelatin sponge, oxidized cellulose). A new microporous polysaccharide hemisphere (MPH) product (TraumaDex™: Medafor Inc, Minneapolis, MN) works by a unique mechanism. The polysaccharide microspheres have a porous surface that effectively absorbs water and low molecular weight compounds from blood, concentrating platelets and clotting proteins at the bead surface, thereby enhancing endogenous clotting mechanisms. We investigated the efficacy of this topical hemostat in a modified bleeding time study in human subjects. Twenty-nine healthy human volunteers had two small surgical incisions placed on their non-dominant forearm. One site was treated with the TraumaDex™ and the other site acted as control. Time to hemostasis and quality of wound healing was evaluated. The MPH treated wounds stopped bleeding five minutes faster (84 seconds on average, compared to 381 seconds) than the control site ( $p < 0.001$ ). Immediate hemostasis was achieved in 23 out of 29 (79%) of the subjects treated with MPH. Wound healing, as measured by length of scar and width of induration at seven days showed no significant difference between the TraumaDex-treated group and the control. In conclusion, this novel topical hemostatic agent (TraumaDex) significantly speeds thrombosis of skin lacerations with no visibly apparent inhibition of wound healing. Investigations of the application of MPH technology for topical hemostasis in surgical wounds and traumatic bleeding continue.



**Figure 1.**

### **Introduction:**

Topical bleeding represents a major cause of blood loss in surgical and non-surgical trauma patients. This can lead to blood transfusions with their inherent risk of complications (transfusion reactions and transfusion transmitted disease) as well as significant expense. To circumvent the need for transfusion, several hemostatic agents have been developed and fall into two categories: those that add clotting elements to generate clots (fibrin sealants and thrombin glues), and those that act as a surface on which endogenous coagulation factors react to generate clots (e.g., gelatin foam, microfibrillar collagen, oxidized regenerated cellulose). These agents have varying degrees of efficacy, some carrying a potential risk of infection or allergic reaction, adhesion formation,

prolonged preparation time, and considerable expense. TraumaDex™ (Medafor Inc, Minneapolis, MN) is a novel microporous polysaccharide hemisphere product that promotes blood clotting by a unique mechanism. It is made from purified potato starch and formed into 30-100 micron spheres with a microporous surface (Figure 1). These pores, applied directly onto an actively bleeding wound, act to rapidly dehydrate blood and concentrate clotting proteins, red blood cells, and platelets to promote instantaneous clot formation. At the same time the microsphere surface also promotes clotting. Figure 3 demonstrates fibrin gel adhering to the microspheres in a scanning electron micrograph. The polysaccharide microspheres are quickly degraded by endogenous amylase and pyrase, leaving no substance to act as a nidus for infection or adhesion formation. The raw material and production costs make TraumaDex considerably less expensive than other hemostatic agents. In addition, thromboelastograph (TEG) analysis demonstrates that when TraumaDex was added to citrated blood, clot formation was faster (Figure 4).

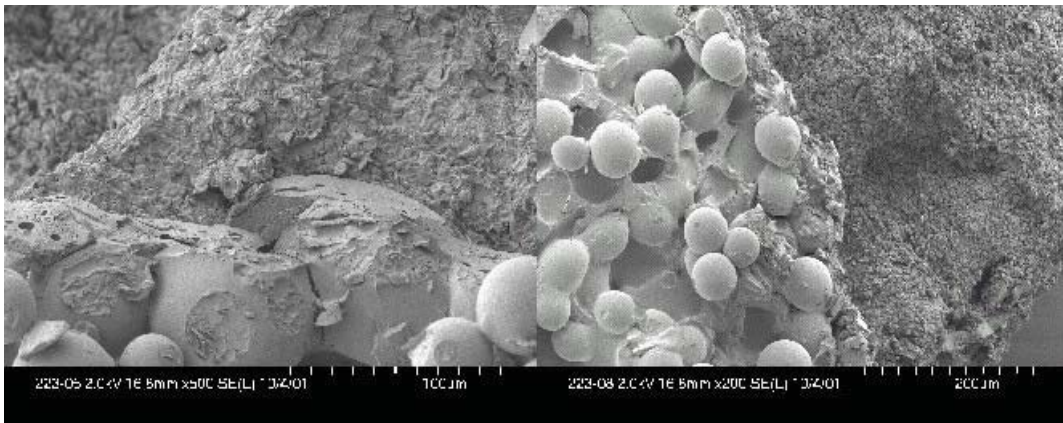


Figure 3. SEM photo of Degradable Microporous Polysaccharide Hemospheres.

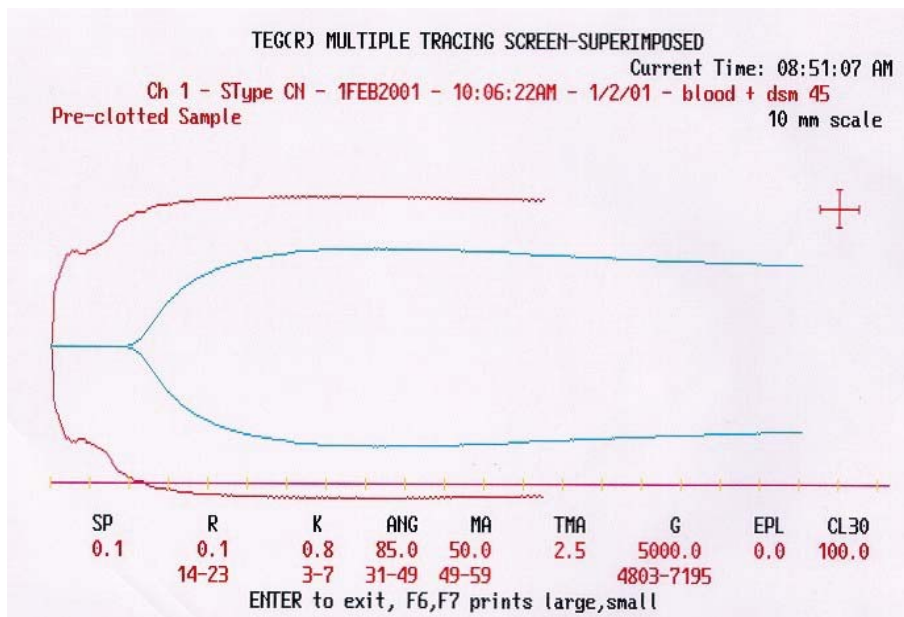


Figure 4. Thromboelastograph (TEG) Analysis of Citrated Blood With and Without TraumaDex Added.

### Materials and Methods:

The study design and protocol were reviewed and approved by the institutional research board. Twenty-nine healthy volunteers gave written informed consent. Exclusion criteria included: age less than 18 years, pregnancy, ongoing infection, history of bleeding/clotting diathesis, use of anticoagulant medications, any bruises, scars or recent cuts on the area of forearm to be studied. The average age of volunteers was 36 years and 77% were male.

**Modified Bleeding Time.** The primary outcome of this study was time to hemostasis as measured by a modified bleeding time analysis. With patients in the sitting position the volar surface of the non-dominant forearm was swabbed with alcohol and the skin was allowed to dry. Two Surgicutt (International Technidyne Corporation, Edison, NJ) devices were used simultaneously to produce two incisions (5 mm x 1 mm deep) in the skin 5 cm below and parallel to the antecubital fossa (Figure 6). TraumaDex was applied to either medial or lateral incision sites with different subjects to avoid site specific differences in bleeding time. After blotting off excess blood from both sites with gauze, a single dose of approximately 25 mg dry TraumaDex beads was directed into the study incision (no sham substance was placed in the control site). Immediately following application of TraumaDex, gentle pressure was applied over both sites for 30 seconds. The time to hemostasis at both sites was recorded by a second investigator with a stopwatch. At 15 second intervals the quality of bleeding from each site was visually evaluated and scored based on degree of bleeding until hemostasis was reached. Bleeding time was evaluated for up to 10 minutes, and in case of failure (defined as the wound not achieving hemostasis after 10 minutes) the investigator used other methods to stop bleeding (typically additional pressure over the wound). The study subjects remained in the procedure area for 15 minutes after bleeding stopped to observe for any re-bleeding or reactions to the TraumaDex beads. No complications occurred in our study subjects. The secondary outcome was determination of any differences in wound healing between the control and treatment group. At seven days following application, subjects returned for visual inspection of the two scars. Measurements of scar length, width of skin induration, and whether the scar was raised or not was noted. Two subjects did not return for follow-up.

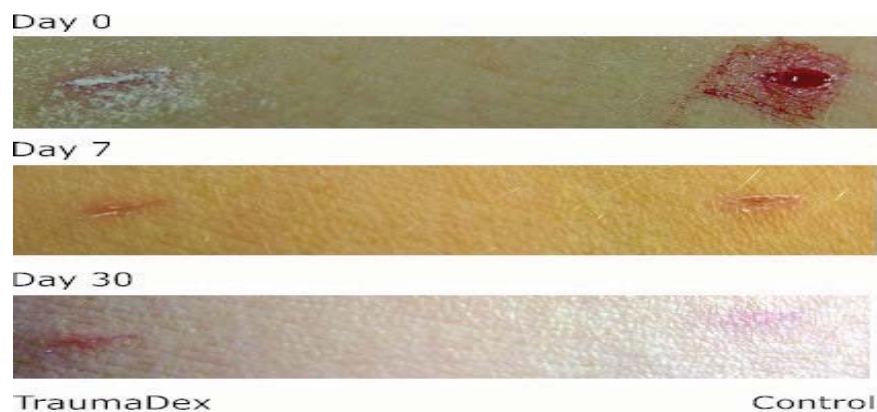


Figure 6. Photos of Incisions With TraumaDex Treatment and Control.

### Results:

Application of TraumaDex beads to a bleeding time incision demonstrated a dramatic reduction in bleeding time in humans. In all but two of the subjects, TraumaDex application caused immediate hemostasis. This degree of hemostasis was never observed at the control site, where the fastest time to hemostasis was 180 seconds. In 4 out of 29 subjects, TraumaDex-treated wounds attained immediate hemostasis, but had slow oozing thereafter. In none of the subjects

were any side effects from TraumaDex treatment observed. Time to hemostasis was significantly lower at the TraumaDex treated site with an average time to hemostasis of 84 seconds (95% CI: 32-136), compared with 381 seconds (95% CI: 334-428) for the control site (paired t-test,  $P < 0.0001$ ). In addition, the 95% confidence interval for differences between the two groups was between 216-378 seconds. Thus, treatment with TraumaDex decreased bleeding time by five minutes ( $297 \pm 81$  seconds) compared to the control site. Analysis of wound healing at seven days revealed no statistical difference in size of scar or skin induration. Scar size was 3.8 mm (95% CI: 3.5-4.1) at the control site and 3.8 mm (95% CI: 3.6-4.1) at the TraumaDex site. Similarly, the width of induration of the skin was 1.5 mm (95% CI: 1.4-1.7) and 1.8 mm (95% CI: 1.2-2.4) for control and experimental sites, respectively ( $p = \text{NS}$ ).

### **Discussion:**

Microporous polysaccharide hemospheres dramatically reduced time to hemostasis in a human bleeding time model. The addition of TraumaDex to the wound resulted in an immediate cessation of bleeding. Gentle pressure alone had no similar effect on control sites. There was no visible difference in wound healing or scar formation between the control and study sites. Delayed slight oozing did occur in four of the TraumaDex sites. This may be due to ineffective application. In one subject the TraumaDex treated site oozed for greater than 10 minutes whereas the control site clotted in 3 minutes. It is unclear whether this represents an effect of the TraumaDex or possible anatomic difference between the two sites on this subject's forearm, such that a larger venule may have been lacerated by the incision. Bleeding from traumatic and surgical wounds represents an important cause of patient morbidity. Significant blood loss may require blood transfusion with the inherent risk of transfusion-transmitted disease, and added expense. Several other topical hemostatic agents, including fibrin glues and thrombin, have limited efficacy, may be difficult to use, have allergic or infectious potential, and are expensive. Other products, which serve as a substrate to activate thrombosis and hemostasis, demonstrate variable efficacy, difficulty with application and decreased efficacy in heparinized patients. The MPH technology (TraumaDex™, Bleed-X™, HemaDerm™, Arista AH™) represents a series of hemostatic agents with a novel mechanism of action. In addition to providing physical support for clot formation, the MPH absorbs water from the local environment and hyper-concentrates platelets and coagulation factors. This instantly places platelets and clotting proteins in direct contact, promoting thrombus formation. The MPH beads swell as they dehydrate the blood, further acting as a hemostatic plug. The product is made from purified potato starch and has virtually no infective or sensitization risk and is relatively inexpensive.

### **Conclusion:**

Microporous polysaccharide hemospheres (TraumaDex™) effectively accelerated time to hemostasis in this model of bleeding in healthy adults. In addition, this agent appears to have no negative impact on visible wound healing at seven days. The use of MPH may represent an important advancement in the management of topical bleeding with significant advantages over other hemostatic agents.

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