ORIGINAL ARTICLE

Efficacy of a Dry Fibrin Sealant Dressing for Hemorrhage Control After Ballistic Injury

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Objective: To determine if a dry fibrin sealant dressing (DFSD) will provide superior hemostasis when compared with regular gauze in a ballistic injury animal model.

Design: A nonsurvival randomized goat study.

Setting: A federal biomedical research institute.

Subjects: Eighteen anesthetized Angora goats.

Interventions: Uncontrolled hemorrhage was induced by a complex ballistic extremity injury. Control of hemorrhage was achieved by applying and holding pressure with the DFSD or regular gauze for 2 minutes. The dressings were left in place for 1 hour.

Main Outcome Measures: Total blood loss, mean arterial pressure, ballistic injury, and mortality were recorded after 1 hour.

Results: The injuries were equivalent for the 2 groups. No animal mortality was seen. After 1 hour, the mean (±SEM) blood loss was 124±64 mL in the DFSD-treated group and 377±64 mL in the gauze dressings–treated group (P=.01). Twenty minutes after injury, the mean arterial pressure was 95.0 mm Hg (±SEM, ±4.7 mm Hg) in the DFSD-treated group and 70.0±5.0 mm Hg in the gauze dressings–treated group. The difference persisted for the remainder of the study (P=.01).

Conclusion: The DFSD was superior to gauze in decreasing blood loss and maintaining blood pressure while retaining the simplicity of standard dressing application.

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THE CONTROL of hemorrhage is a critical step in first aid and field trauma care. Unfortunately, the materials and methods available to stop bleeding in prehospital care (gauze dressings, direct pressure, and tourniquets) have not changed greatly in 2000 years.[1] Even in good hands they are not uniformly effective, and the occurrence of excessive bleeding or fatal hemorrhage from an accessible site is not uncommon.[2]

The dry fibrin sealant dressing (DFSD) was developed to overcome these difficulties. It consists of dry, powdered human thrombin and fibrinogen compressed onto a removable backing. When pushed into a wound it coagulates on contact. A prototype was demonstrated to be effective in controlling hemorrhage from a linear incision in exposed femoral arteries.[3] However, it was not known if the DFSD would effect hemostasis in the face of a more complex ballistic injury. The wounding process creates a large, open, complex wound associated with extensive bleeding and shock. We measured the ability of the DFSD to reduce bleeding and shock when compared to conventional treatment with a gauze bandage, both applied with equivalent direct pressure. This randomized, prospective study was conducted to determine if the DFSD was superior to standard gauze for maintaining blood pressure and decreasing blood loss after a ballistic extremity injury.

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RESULTS

A total of 18 goats were used in this study, with 9 goats in each treatment group. All animals survived the study period without difficulty. A large exit wound (>10 cm) was present in 8 of 9 goats in each treatment group. Because the DFSD was

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SUBJECTS AND METHODS

EXPERIMENTAL ANIMALS

Eighteen adult male Angora goats weighing a mean (±SEM) 46.6±6.8 kg were used in this study. All animals were maintained in an Association for Assessment and Accreditation of Laboratory Animal Care–accredited facility; the protocol was approved by the Institutional Animal Care and Use Committee of William Beaumont Army Medical Center, El Paso, Tex. All animals received humane care in strict compliance with the *Guide for the Care of Laboratory Animals* (National Institutes of Health publication 86-23, revised 1985). Anesthesia was induced with 2.4% thiopental sodium and maintained with isoflurane. Deep anesthesia was maintained throughout surgical preparation, wounding, and the hour of observation.

EXPERIMENTAL PROCEDURE

Surgical preparation consisted of the placement of an 8F catheter in the right common carotid artery for blood pressure monitoring. The left thigh was carefully shaved and wrapped in plastic, allowing accurate collection of shed blood into a flexible plastic container. The blood pressure was monitored before injury and every 10 minutes thereafter through the common carotid artery catheter connected to a monitor (Propaq 104, Protocol Systems Inc, Beaverton, Ore).

After surgical preparation, pairs of goats were randomized to allocate 1 animal each into the 2 treatment groups. The anesthetized goats were then wounded with a .308-caliber high-velocity projectile entering the lateral thigh and exiting medially with the intent of creating a large exit wound. Within 5 seconds of wounding, the animals were treated with the chosen dressing applied to the entrance and exit wounds. All dressings were applied by one of us (J.H.). The attempt was made to apply all dressings in a uniform manner. After 2 minutes of direct pressure, the dressings were tied in place with muslin backing and the animals were observed for 1 hour.

The DFSD (American Red Cross Holland Laboratory, Rockville, Md) consisted of human fibrinogen, 1800 mg, human thrombin, 5000 IU, and calcium chloride, 440 mg, all compressed onto a silicone backing. The DFSD was produced to have a size of 10.0×17.5 cm, equal to the standard US Army wound dressing that served as the control. The muslin backing from the gauze dressing was used to tie the DFSD in place. **Figure 1** is a picture of both dressings.

Fluid resuscitation, in response to hypotension, was not performed. Total blood loss was calculated by recording the volume of shed blood and clots, added to the difference in weight of wet and dry dressings. After 1 hour, the animals were humanely killed with an intravenous dose of pentobarbital sodium, 60 mg/kg, a necropsy was performed, and the extent of injuries was documented.

DATA ANALYSIS

Total blood loss and the blood loss per kilogram of body weight were analyzed using the 2-sample *t* test. Mean blood pressure data were analyzed by the analysis of variance (GLM procedure, SAS Institute, Cary, NC).[4] The statistical procedure takes into account the repeating nature of blood pressure measurements over time. Data are reported as the mean±SEM.

designed to stop bleeding from accessible sites and the intent of the study was to induce injuries with large exit wounds, the 2 animals with exit wounds smaller than 4 cm were removed from further consideration in the analysis of the study. A necropsy of the ballistically injured thighs revealed the following: the femoral artery was lacerated in all goats, a comminuted fracture of the femur was present in 7 of 8 goats in each group, and the femoral vein was lacerated in 7 of 8 goats in each group.

The DFSD reduced both total blood loss (124±64 vs 377±64 mL, P=.01) (**Figure 2**) and blood loss per kilogram of body weight (1.3±0.6 vs 3.8±0.6 mL, P=.02) (**Figure 3**). Total blood loss was 67% less in the DFSD-treated group (Figure 2). As shown in **Figure 4**, the mean blood pressure did not differ between the groups before injury. At 10 minutes postinjury, mean blood pressure declined in the DFSD-treated group (P=.04) and the gauze dressing–treated group (P=.01) compared with preinjury levels. No difference was observed between the 2 groups at 10 minutes. By 20 minutes, the mean blood pressure increased (P=.05) in the DFSD-treated group to the preinjury level, where it remained through 60 minutes. In the gauze dressing–treated group, mean blood pressure did not increase significantly (P>.10) above the 10-minute postinjury level at any time. At each time point after 10 minutes, mean blood pressure was higher in the DFSD-treated group than in the gauze dressing–treated group, and the cumulative effect of treatment on blood pressure was significant (P=.01).

COMMENT

Control of hemorrhage is critical to the survival of trauma patients undergoing prehospital and inpatient care. Mortality data from Vietnam indicates that 10% of combat deaths were due to uncontrolled extremity hemorrhage.[5] Up to one third of the deaths from exsanguination during the Vietnam War could have been prevented by the use of effective field hemorrhage control methods.[5] Although civilian trauma mortality statistics do not provide exact numbers for prehospital deaths from extremity hemorrhage, case and anecdotal reports indicate similar occurrences.[2] These data suggest that a substantial increase in survival can be effected by the prehospital use of a simple and effective method of hemorrhage control.

Liquid fibrin sealants have been used for years as an operating room adjunct for hemorrhage control.[6-10] The first mention of tissue glue used for hemostasis dates back to 1909.[11] The widespread use of fibrinogen and thrombin was common in the last year of World War II but was abandoned because of the transmission of hepatitis.[12] Currently, single donor fibrin sealants are widely used clinically, not only for hemorrhage control but in

Figure 1. *The gauze (left) and dry fibrin sealant (right) dressings used in the study. Each dressing measures 10.0×17.5 cm.*

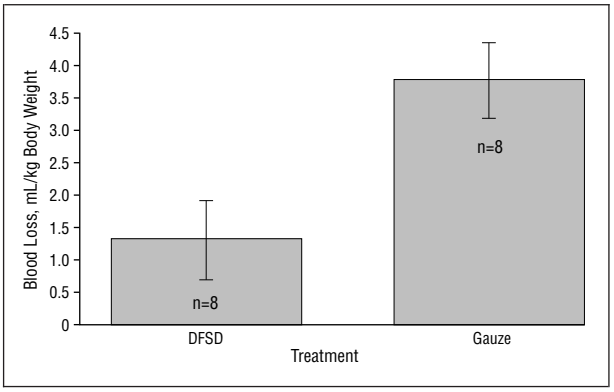

Figure 3. *The mean(±SEM) total blood loss per kilogram of body weight after ballistic injury. The difference between the 2 groups was significant (P=.02). The groups are described in the "Subjects and Methods" section of the text. DFSD indicates dry fibrin sealant dressing.*

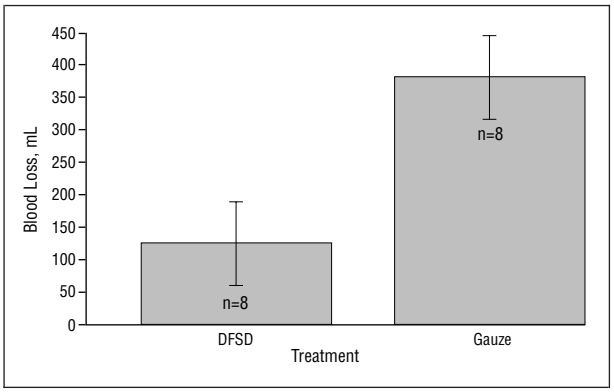

Figure 2. *The mean(±SEM) total blood loss after ballistic injury. The difference between the 2 groups was significant (P=.01). The groups are described in the "Subjects and Methods" section of the text. DFSD indicates dry fibrin sealant dressing.*

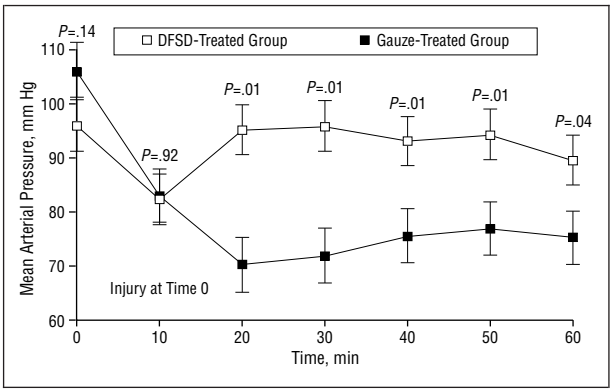

Figure 4. *The mean arterial pressure (±SEM) after ballistic injury in goats treated with either dry fibrin sealant dressing (DFSD) or gauze for 60 minutes. Significance levels for within time point comparisons are shown. The groups are described in the "Subjects and Methods" section of the text.*

various surgical situations.[13,14] Even more extensive use is limited by the strict requirements for temperature control, availability of thawed blood components, and the need for mixing of components. Additional problems with the standard fibrin sealants stem from the transfusion risk of human cryoprecipitate,[15] the low and variable amounts of fibrinogen in the cryoprecipitate (10-30 mg),[16] and hypotensive[17] and antibody[18] responses to bovine thrombin. The American Red Cross and others have developed plasma protein purification methods that seem to eliminate the hepatitis risk,[19] and these products are being considered for approval by the Food and Drug Administration.

A dry fibrinogen-thrombin dressing (TachoComb, Hafslund Nycomed Pharma, Linz, Austria) is available for operating room use in many European countries.[20] Present formulations of this dressing use bovine thrombin. The fibrinogen-thrombin dressing partially accomplishes our goals of no premixing and ease of use, but a requirement for storage at 4°C and prewetting with saline solution precludes field use.

Dry fibrin sealant dressings obviate all the previously described problems by using a dry powder composed of pure human thrombin, fibrinogen, and calcium. These components are found naturally at the site of any wound, but the DFSD applies the naturally occurring proteins in a much higher concentration.[21] The dressing is not temperature sensitive, requires no blood bank support or premixing, has a low disease transmission risk, and provides a high concentration of fibrinogen. The use of the DFSD is the same as any conventional gauze dressing: simply unwrap the dressing, place it on the wound, and apply pressure for 1 to 2 minutes. A fibrin clot that stops bleeding from small, medium, and large vessels as well as soft tissue wounds will form almost instantly.

In our study, total blood loss was decreased by 67% in the DFSD-treated group. No attempt was made to isolate or clamp vascular structures before application of the DFSD, demonstrating that surgical exposure of bleeding vessels is not necessary for hemostasis. Time to hemostasis seemed almost instantaneous in the DFSD-treated group, explaining the reduced blood loss and the return to preinjury mean arterial pressure 20 minutes after wounding. Bleeding was prolonged in the group treated with a gauze bandage, accounting for the increased blood loss and decreased blood pressure throughout the study period. These clinically significant differences were obtained without fluid resuscitation.

Results similar to ours were obtained in the 2 other studies dealing with DFSD. The data of Larson and colleagues[3] closely parallel ours, revealing decreased blood loss and preserved blood pressure in a surgically created wound

treated with a DFSD. In a similar study of bilateral porcine femoral artery lacerations, Jackson and colleagues[22] showed unimpeded blood flow in the lacerated artery along with improved hemostasis in the group they treated with the DFSD. Additionally, they replaced fibrinogen with IgG in the bandage formulation to make a placebo bandage. As expected, this noncoagulating bandage exhibited no hemostatic activity. There are 3 studies of DFSDs using different animal models and methods. All show that the DFSD significantly decreases blood loss.

We have shown in a ballistic extremity injury model with large complex exit wounds that the use of the DFSD results in reduced blood loss and maintenance of blood pressure when compared with gauze wound dressings. This prehospital method of hemorrhage control is simple, fast, and requires no special training. Through its simplicity, the DFSD allows application of advanced technology for hemorrhage control to the injured patient. When fielded in final form, we see this as a forward projection of advanced hemorrhage control outside the operating room, providing urban and military casualties rapid, definitive hemorrhage control.

The opinions expressed herein are the private views of the authors and are not to be construed as official or as reflecting the views of the US Department of the Army or the US Department of Defense.

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REFERENCES

1. Zimmerman L, Veith I. *Great Ideas in the History of Surgery*. San Francisco, Calif: Norman Publishing; 1993:31.
2. Rocko JM, Tischler C, Swan KG. Exsanguination in public: a preventable death. *J Trauma*. 1982;22:635.
3. Larson MJ, Bowersox JC, Lim RC, et al. Efficacy of a fibrin hemostatic bandage in controlling hemorrhage from experimental arterial injuries. *Arch Surg*. 1995; 130:420-422.
4. *SAS/STAT Users Guide*. 4th ed. Cary, NC: SAS Institute Inc; 1990.
5. Bellamy RF. The causes of death in conventional land warfare: implications for combat casualty care research. *Mil Med*. 1984;149:55-62.
6. Garza JL, Rumsey E. Fibrin glue and hemostasis in liver trauma: a case report. *J Trauma*. 1990;30:512-513.
7. Kram HB, Junco TD, Clark SR, et al. Techniques of splenic preservation using fibrin glue. *J Trauma*. 1990;30:97-101.
8. Ochsner MG, Maniscalco-Theberge ME, Champion HR. Fibrin glue as a hemostatic agent in hepatic and splenic trauma. *J Trauma*. 1990;30:884-887.
9. Matthew TL, Spotnitz WD, Kron IL, et al. Four years experience with fibrin sealant in thoracic and cardiovascular surgery. *Ann Thorac Surg*. 1990;50:40-44.
10. Jakob H, Campbell CD, Qiu ZK. Use of fibrin sealant for reinforcing arterial anastomoses. *J Vasc Surg*. 1984;1:171-180.
11. MacPhee MJ, Salz R, Sierra D, eds. *Current Trends in Surgical Tissue Adhesives: Proceedings of the First International Symposium on Surgical Adhesives*. Lancaster, Pa: Technomic Publishing Co; 1995.
12. Kendrick DB. *Blood Program in WW II*. Washington, DC: Office of the Surgeon General, Department of Army; 1989:363-368.
13. Spotnitz WD. Fibrin sealant in the United States: clinical use at the University of Virginia. *Thromb Haemost*. 1995;74:482-485.
14. Lerner R, Binur NS. Current status of surgical adhesives. *J Surg Res*. 1990;48: 165-181.
15. Soland EM, Pitt E, Klien HG. Safety of the blood supply. *JAMA*. 1995;274:1368-1373.
16. Ness PM, Perkins HA. Cryoprecipitate as a reliable source of fibrinogen replacement. *JAMA*. 1979;241:1690-1691.
17. Berguer R, Staerkel RL, Moore EE, et al. Warning: fatal reaction to the use of fibrin glue in deep hepatic wounds. *J Trauma*. 1991;31:408-411.
18. Rapaport SJ, Zivelin A, Minow RA, Hunter CS, Donnelly K. Clinical significance of antibodies to bovine and human thrombin and factor V after surgical use of bovine thrombin. *Am J Clin Pathol*. 1992;97:84-91.
19. Reiss RF, Oz MC. Autologous fibrin glue: production and clinical use. *Trans Med Rev*. 1996;10:85-92.
20. Schiele U, Kuntz G, Riegler A. Haemostyptic preparations on the basis of collagen alone and as fixed combination with fibrin glue. *Clin Materials*. 1992;9: 169-177.
21. Hess JR, Holcomb JB, MacPhee MJ. Hemorrhage control with a dry powdered thrombin and fibrinogen bandage. *Neth Milit Med Rev*. August 1996:122-124.
22. Jackson MR, Friedman SA, Carter AJ, et al. Hemostatic efficacy of a fibrin sealant–based topical agent in a femoral artery injury model: a randomized, blinded, placebo controlled study. *J Vsc Surg*. In press.

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Cholesterol and Coronary Heart Disease: The 21st Century

Scott M. Grundy, MD, PhD

Recent clinical trials have demonstrated that reductions of serum low-density lipoprotein (LDL) levels substantially decrease the risk for coronary heart disease. These trials confirm other lines of evidence that high levels of LDL are a critical atherogenic factor. Aggressive lowering of LDL levels in high-risk patients promises to significantly reduce morbidity and mortality from coronary heart disease in the first third of the 21st century. However, several additional measures will be required to marginalize coronary heart disease in the 21st century. Other lipoprotein abnormalities and other risk factors, eg, cigarette smoking, hypertension, and diabetes mellitus, must be controlled to obtain the full benefit of LDL-lowering therapy. Moreover, the health care delivery system must be reorganized to put more emphasis on prevention. Although much can be achieved through application of current knowledge in prevention efforts, further advances through new research will be required to remove coronary heart disease as a major cause of death in the United States. *Arch Intern Med. 1997;157:1177-1184*

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