A Comparison of Avitene Ultrafoam versus Gelfoam With and Without Thrombin to Effectively Control Bleeding

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Introduction

Topical hemostatic agents are used to stop bleeding in a wide range of surgical procedures. Many of the products currently available are not effective in controlling blood loss as quickly as desired, therefore, it has become common to soak hemostatic agents with thrombin, the enzyme that catalyzes the conversion of fibrinogen to fibrin. The preparation of thrombin requires additional preparation time and exposes the patient to a potentially hazardous reaction to the drug. The use of topical bovine thrombin preparations has occasionally been associated with the formation of antibodies against bovine thrombin and/or factor V which in some cases may cross react with human factor V, potentially resulting in factor V deficiency. Patients with antibodies to bovine thrombin preparations should not be re-exposed to these products to avoid abnormalities in hemostasis (Thrombin-JMI package insert, GenTrac, Inc., Middleton, Wisconsin 53562). The purpose of this study was to compare the effectiveness of two hemostatic agents Gelfoam, a gelatin derived from porcine skin, and Ultrafoam, a collagen which is made of lyophilized Avitene flour and water. A comparison was also made of both products soaked in thrombin. The studies were conducted in a highly controlled swine spleen laceration model, which provides data amenable to statistical analysis.

Methods

Small incisions were made in the retracted spleen of anesthetized juvenile Yorkshire pigs of either sex. The extent of the wound was controlled by placing a #11 scalpel blade in a right angle clamp so that 4mm of blade was exposed. A wound 4mm deep and 8mm in length could then be made in the ventral surface of the spleen starting at the tail and proceeding towards the head of the spleen. The number of wounds per spleen ranged from 8 to 18, the scalpel blade was changed after 10 wounds.

The wound was left to bleed for 20 seconds, and then wiped clean with gauze. The test article (approximately 1.3cm x 1.3cm) was placed on the wound, tamponaded with finger pressure for 20 seconds, then the pressure was removed and the site was observed for breakthrough bleeding for two minutes. If breakthrough bleeding was observed within two minutes, pressure was reapplied for 20 seconds and the cycle was repeated. The endpoint was the number of tamponades to achieve no breakthrough bleeding. Thrombin was added by soaking the sample in a thrombin solution until fully saturated.

The following samples were paired during testing (20 pairs each): Ultrafoam versus Gelfoam, Ultrafoam-thrombin versus Gelfoam-thrombin, Ultrafoam versus Gelfoam-thrombin. A pair was defined as two samples tested one after the other and adjacent to one another on the spleen. For each pair, the first sample tested was alternated from pair to pair. Each pair was tested in most cases two or three times on each animal.

Statistical Analysis

The frequency of the number of tamponades for each product type within the paired group was analyzed using the Fisher’s exact test and The Stuart-Maxwell test (both one-tailed) at alpha 0.05. It was expected that Ultrafoam without thrombin would need fewer tamponades than Gelfoam without thrombin due to collagen’s propensity to attract platelets (expect better than), but would require more tamponades than Gelfoam with thrombin since thrombin effectively converts fibrinogen to fibrin (expect no worse than). These paired groups were analyzed separately. Therefore, a one-sided test based on expected results was appropriate.

The SAS software package was used for calculating the Fisher’s exact test for each paired group. For n x n (“x” means multiplication) contingency tables (foam type x number of tamponades), Fisher’s exact test yields the probability of observing a table that gives at least as much evidence of association as the one actually observed, given that the null hypothesis is true. The hypergeometric probability (p value) of every possible table is computed (from the SAS/STAT User’s Guide, release 6.03 edition). If ½ x the two-tailed p value (which is the one-tailed p value) was less than or equal to 0.05, the frequency distributions were considered significantly different.
The Stuart-Maxwell test, which is a generalization of the McNemar test, was manually calculated using Table 8.5 and formulas 8.18 and 8.19 on page 120 of “Statistical Methods for Rates and Proportions”, Joseph L. Fleiss, 2nd edition, published by John Wiley & Sons, New York, NY. The Stuart-Maxwell test involves determining the number of pairs with the same result and differing results, and calculating the value of the Stuart-Maxwell chi-square at 2 degrees of freedom for matched pairs with 3 mutually exclusive outcomes. The one-tailed alpha value was 0.10 (two-tailed value of 0.05 x 2). For the purposes of this calculation, the 3 outcomes were 1, 2, or 3 tamponades. In 2 cases (1 Gelfoam without thrombin and 1 Ultrafoam without thrombin) a sample that required 4 tamponades was treated as a 3 in order to allow the use of the Stuart-Maxwell test.

Results

In the Ultrafoam vs. Gelfoam pairs, the frequency (%) of Ultrafoam samples requiring 1, 2, 3, or 4 tamponades was 55, 25, 20, and 0 respectively (Fig. 1). Gelfoam exhibited 30, 60, 5, and 5 respectively (Fig. 1). The Ultrafoam distribution was skewed to 1 tamponade. The Gelfoam distribution was skewed to 2 tamponades. The tamponade frequency distribution for Ultrafoam was significantly different than the tamponade frequency distribution for Gelfoam according to the Fisher’s exact test (one-sided p value>=0.035). The Stewart-Maxwell test indicated the tamponade frequency distributions were borderline significantly different (one-sided p value>=0.054). This indicated that in this model, Ultrafoam without thrombin performed significantly better than Gelfoam without thrombin.

In the Ultrafoam-thrombin/Gelfoam-thrombin pairs, the frequency (%) of Ultrafoam-thrombin samples requiring 1, 2, 3, or 4 tamponades was 85, 10, 5, and 0 respectively (Fig. 2). Gelfoam-thrombin exhibited 85, 15, 0, and 0 respectively (Fig. 2). Both frequency distributions were skewed to 1 tamponade. There was no significant difference between the Ultrafoam-thrombin and Gelfoam-thrombin tamponade frequency distributions according to both the Fisher’s exact test (one-sided p value>=0.500) and The Stewart-Maxwell test (one sided p value>=0.274). Thus thrombin improved the performance of Gelfoam but not Ultrafoam. This suggested a comparison of Ultrafoam without thrombin with Gelfoam with thrombin would be appropriate.

The frequency (%) of Ultrafoam samples requiring 1, 2, 3, or 4 tamponades in the Ultrafoam/Gelfoam-thrombin pairs was 80, 15, 0, and 5 respectively (Fig. 3). Gelfoam-thrombin exhibited 85, 15, 0, and 0 respectively (Fig. 3). Both frequency distributions were skewed to 1 tamponade. There was no significant difference between the Ultrafoam and Gelfoam-thrombin tamponade frequency distributions according to both the Fisher’s exact test (one-sided p value>=0.500) and The Stewart-Maxwell test (one sided p value>=0.303). This indicated that in this model, Ultrafoam without thrombin was as effective as Gelfoam with thrombin.
Discussion

Overall, the tamponade frequency distributions were similar for all samples with the exception of Gelfoam without thrombin. Ultrafoam without thrombin, Ultrafoam with thrombin, and Gelfoam with thrombin all exhibited tamponade frequency distributions that were skewed to 1 tamponade. Gelfoam without thrombin exhibited a tamponade frequency distribution that was skewed to 2 tamponades. Ultrafoam without thrombin has a comparable performance to Gelfoam with thrombin and addition of thrombin to Ultrafoam does not improve its performance. This suggests that Ultrafoam is effective in producing an intrinsic generation of thrombin from native blood components.

The hemostatic performance of Ultrafoam without thrombin in this study is supported by the widespread clinical use of Avitene Microfibrillar Collagen Hemostat (flour). Avitene flour is routinely used without thrombin to stop blood loss in many different surgical applications. Ultrafoam is made from lyophilized (freeze-dried) Avitene flour and water, and has a similar microfibrillar structure. The microfibrillar structure could provide an increased surface area for activation of the intrinsic clotting pathways of the blood. A second possibility is that the microfibrillar structure of collagen provides a mechanical and chemical stimulus for platelet activation leading to release of procoagulant substances from platelet granules. Determination of the mechanism of the observed effect is beyond the scope of this study.

Conclusions

The results of this study show that Ultrafoam is an effective hemostat comparable in performance to Gelfoam-thrombin. Because the performance of Ultrafoam is not improved by the addition of thrombin, it does not require the addition of thrombin to achieve effective hemostasis.

References

7. Murphy DJ, and Clough CA; A New Microcrystalline Collagen Hemostatic Agent. Surgical Neurology 2: 77-79 (1974)