Efficacy of hemostatic matrix and microporous polysaccharide hemospheres

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ABSTRACT

Background: Microporous Polysaccharide Hemospheres (MPH) are a new plant-derived polysaccharide powder hemostat. Previous studies investigated MPH as a replacement to nonflowable hemostatic agents of different application techniques (e.g., oxidized cellulose, collagen); therefore, the purpose of this study was to determine if MPH is a surrogate for flowable hemostatic agents of similar handling and application techniques, specifically a flowable thrombin-gelatin hemostatic matrix.
Methods: Hemostatic efficacy was compared using a heparinized porcine abrasion model mimicking a capsular tear of a parenchymal organ. MPH (ARISTA, 1 g) and hemostatic matrix (Floseal, 1 mL) were applied, according to a randomized scheme, to paired hepatic abrasions (40 lesions per group). Hemostatic success, control of bleeding, and blood loss were assessed 2, 5, and 10 min after treatment. Hemostatic success and control of bleeding were analyzed using odds ratios and blood loss using mean differences.
Results: Hemostatic matrix provided superior hemostatic success relative to MPH at 5 (odds ratio: 0.035, 95% confidence interval: 0.004–0.278) and 10 min (0.032, 0.007–0.150), provided superior control of bleeding at 5 (0.006, <0.001–0.037) and 10 min (0.009, 0.001–0.051), and had significantly less blood loss at 5 (mean difference: 0.3118 mL/min, 95% confidence interval: 0.0939–0.5296) and 10 min (0.5025, 0.2489–0.7561).
Conclusions: These findings corroborate other MPH investigations regarding its low-level efficacy and suggest that MPH is not an appropriate surrogate for hemostatic matrix despite similar application techniques. The lack of a procoagulant within MPH may likely be the reason for its lower efficacy and need for multiple applications.

1. Introduction

Absorbable hemostatic agents have become an important part of the surgical armamentarium to manage intraoperative bleeding. The use of these agents is believed to reduce hospital resources and use of blood products (i.e., packed red blood cells, fresh frozen plasma, and platelets) [1]. Given the essential need of these agents to improve surgical practice,

new hemostatic agents are continually developed. One new class of absorbable hemostatic agents is polysaccharide spheres produced from plant-derived starch. This new class includes microporous polysaccharide hemospheres (MPH).

Murat et al. [2] first described the hemostatic agent as a plant-derived starch. MPH has a porous surface, which absorbs water and low molecular weight compounds, <40,000 Da, from the blood to concentrate blood solids [2]. The use of MPH is documented in a series of animal models [2–9]. These studies use noncoagulopathic animal models and compare MPH with other low-end hemostatic agents, for example, oxidized cellulose and collagen pad. MPH has not been compared in a clinically relevant animal model with a flowable hemostatic matrix agent of similar handling characteristics and application techniques.

Prior et al. [10] first described flowable hemostatic matrix as a combination of fibrillar collagen, bovine thrombin, and autologous plasma. Recent investigations, however, demonstrated that the most effective flowable hemostatic matrix is a combination of human thrombin and bovine gelatin [11]. The effectiveness of this hemostatic matrix is believed to be due to the unique gelatin shape and properties. This flowable hemostatic matrix has been demonstrated to be effective in several human studies across multiple surgical specialties [12–14]. Given the lack of comparative studies between MPH and agents of similar handling characteristics and application technique, this study compares the hemostatic efficacy of MPH and a flowable hemostatic matrix in a heparinized porcine abrasion model. This surgical model mimics a capsular tear of a parenchymal organ experienced during surgery. The null hypothesis is that the agents will have equal hemostatic efficacy.

2. Methods and materials

2.1. Hemostatic agents

Microporous polysaccharide hemospheres (MPH) are ARISTA AH (Medafor, Inc, Minneapolis, MN). MPH is produced by the reaction of epichlorohydrin with a highly purified potato starch solution that is then irradiated for sterility. In a prospective, multicenter, randomized, controlled clinical study, MPH was noninferior to a collagen hemostatic pad. Flowable hemostatic matrix is Floseal VH S/D (Baxter Healthcare Corporation, Deerfield, IL). The hemostatic matrix is composed of human-derived thrombin and bovine-derived gelatin. In three prospective, multicenter, randomized, controlled clinical studies, hemostatic matrix was superior to a collagen hemostatic pad prepared with thrombin [12–14].

2.2. Heparinized porcine hepatic abrasion model

A heparinized porcine hepatic abrasion model was used to mimic intraoperative capsular tears. The model is a literature-accepted animal model to compare hemostatic agents [11,15,16] and is representative of an appropriate application of each hemostatic agent based on previous published uses [3,11]. All animal activities were performed according to the Guide for the Care and Use of Laboratory Animals and the United States Animal Welfare Act in an institution accredited by the Association for Assessment and Accreditation of Laboratory Animal Care International (AAALAC) following Institutional Animal Care and Use Committee approval.

A total of six female Yorkshire pigs were used for this study for ease of handling and husbandry. Each animal was preoperatively medicated with ketamine (20 mg/kg, intramuscularly [IM]), xylazine (2 mg/kg, IM), and atropine (0.05 mg/kg, IM), after which each was mask induced using isoflurane (up to 5% of inhaled air) in a 2:1 nitrous oxide to oxygen carrier. Peri- and intra-operatively, all pigs received a continuous rate infusion of crystalloid solution. Each animal was heparinized to at least two times greater than their baseline activated clotting time to mimic the clinical situation throughout the study. This level of heparinization gives a clinically relevant activated clotting time of ≥200 s [8].

Once at a surgical plane, a celiotomy was performed to expose the liver lobes without compressing the hepatic vasculature. The consistent hepatic vascular architecture that lacks a vasoconstriction response provides consistent and reproducible bleeds [17]. A series of two hepatic abrasions, 1 cm diameter and 0.3–0.4-cm deep, were created using a hand drill fixed with sandpaper. Bleeding of each lesion was scored as 0, 1, 2, 3, 4, or 5, which represented "no bleeding," "ooze," "very mild," "mild," "moderate," and "severe," respectively. A lower bleeding score was equated to a greater control of bleeding.

The series of abrasions were treated with either MPH or the hemostatic matrix according to a randomized scheme not seen by the surgical investigator until the time of treatment. Each hemostatic agent was prepared according to the manufacturer's instructions for use. A total of 1 g of MPH and a total of 1 mL of the hemostatic matrix were applied once to each assigned lesion. After application, each agent was approximated to the bleeding site using gauze and digital pressure for 2 min. The gauze was then removed, and the treated lesions were assessed at 2, 5, and 10 min after treatment according to the previously mentioned standardized score by the same surgical investigator who created the lesions. Treated lesions were simultaneously and equally irrigated after the 5 min assessment to remove excess material. Only one surgical investigator created, treated, and assessed the lesions throughout the study to ensure consistency.

A bleeding score of 0 and 1 were considered as hemostatic success. Blood loss from each lesion was measured using preweighed gauze held to each lesion for 1 min then reweighed. Grams of blood loss were then converted to milliliters per minute, where 1 g equaled 1 mL.

2.3. Statistical analysis

The study was designed with the goal that 80 lesions (40 per group) would be evaluated and sufficient to detect a difference in rates of 75% versus 35% (i.e., 40%) with an alpha of 0.05 and a power of 90%. A 40% difference in efficacy is deemed clinically meaningful based on previous studies [11,15,16]. The statistical analysis was performed using SAS (SAS Institute Inc, Cary, NC).

For bleeding score, logistic regression was used to evaluate the treatment effect at 2, 5, and 10 min after treatment using SAS procedure LOGISTIC in the following two ways: assuming a binomial model on percent hemostatic success with a score ≤1 and assuming a proportional odds model on observed control of bleeding. In doing so, the odds ratio for "MPH" and/
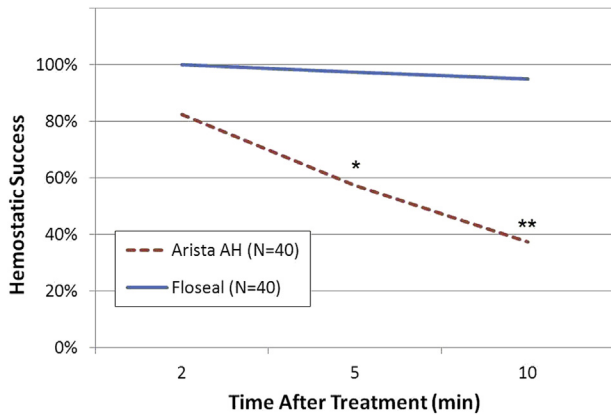
Fig. 1 — Floseal (hemostatic matrix) provides and maintains greater hemostasis than ARISTA AH (absorbable hemostatic particles) in a heparinized porcine hepatic abrasion model of a capsular tear. Statistical significance is based on a binomial odds ratio (* 0.035, 95% CI: 0.004–0.278; ** 0.032, 0.007–0.150; n = 40 per group per time point).

or "hemostatic matrix" and its 95% confidence intervals (CIs) were computed at each time point after treatment.

For blood loss, a general linear model was used to evaluate the treatment effect at 2, 5, and 10 min after treatment using SAS procedure MIXED. In doing so, the mean difference for "MPH"-"hemostatic matrix" and its 95% CIs were computed at each time point after treatment. Independent variables for all models included treatment group, pig, liver lobe (medial, right, or left), and initial bleeding score (at 0 min, untreated).

3.   Results

Six pigs were used to create and treat a total of 40 lesions per group. The volume of product applied proved sufficient for the size of lesion created for both treatments. The hemostatic success of hemostatic matrix was 17.5%, 40%, and 57.5% greater than MPH at 2, 5, and 10 min after application, respectively (Fig. 1).

Based on the odds ratio for hemostatic success, hemostatic matrix was statistically superior to MPH at 5 (odds ratio: 0.035, 95% CI: 0.004–0.278) and 10 min (0.032, 0.007–0.150) after application (Table 1). No covariate effects were significant, and all were removed to compute the odds ratios and their confidence limits (Table 1).

Similarly, based on the odds ratio for control of bleeding, hemostatic matrix was statistically superior to MPH at 5 (0.006, <0.001–0.037) and 10 min (0.009, 0.001–0.051) after application (Fig. 2). The pig effect was significant at 5 and 10 min and was maintained in this analysis; all other covariate effects were not significant and were removed to compute the odds ratios and their confidence limits (Table 1). The odds ratios could not be performed at 2 min in both analyses because hemostatic matrix had a 100% success, which leads to dividing by zero when the odds ratio is calculated. In comparison, MPH provided 82.5% success at 2 min.

Based on the mean difference of blood loss, MPH had a greater rate of blood loss than hemostatic matrix 2 min after application (mean difference: 0.1655 mL/min, 95% CI: −0.0088 to 0.3398) and significantly greater at 5 (0.3118, 0.0939–0.5296) and 10 min (0.5025, 0.2489–0.7561) (Table 2). The pig effect was significant at 10 min in this model; all other covariate effects were not significant and were removed to compute the mean differences and their confidence limits.

4.   Discussion and conclusions

This study used a heparinized porcine hepatic abrasion model to compare the hemostatic success, degree of bleeding, and blood loss of lesions treated with MPH and hemostatic matrix. Hemostatic matrix provided greater hemostatic success, control of bleeding, and less blood loss than MPH. Based on the statistical analysis performed, hemostatic matrix was at least 29 times more likely to provide hemostatic success than MPH at 5 min after application and 31 times more likely at 10 min after application. Overall, the performance of hemostatic matrix was superior to that of MPH in this animal model; as such, the null hypothesis of equal hemostatic efficacy is rejected.

This difference is likely due to the different mechanism of action of each hemostatic agent. The mechanism of action of

Table 1 — Floseal (hemostatic matrix) provides superior hemostatic success and superior control of bleeding than ARISTA AH (absorbable hemostatic particles).

Statistical analysis	Time point after treatment (min)	Pig effect P value	Lobe effect P value	Baseline effect P value	Odds ratio (MPH/hemostatic matrix)	95% confidence limit	
						Lower	Upper
Hemostatic success	5	0.1672	0.2827	0.2195	0.035	0.004	0.278
	10	0.3064	0.7042	0.2198	0.032	0.007	0.150
Control of bleeding	5	0.0403	0.1280	0.4391	0.006	<0.001	0.037
	10	0.0033	0.4309	0.3345	0.009	0.001	0.051

Significance is based on a binomial model on percent hemostatic success and a proportional odds model on observed degree of bleeding. Covariate effects that were not significant were removed to compute the odds ratios and their confidence limits. The odds of success is defined as probability of success divided by one minus this probability. The odds ratio, then, is the ratio of the odds of success for any two treatments. If the odds ratio is equal to one, then the two treatment groups are equal. If the odds ratio is less than one, then hemostatic matrix is favored.
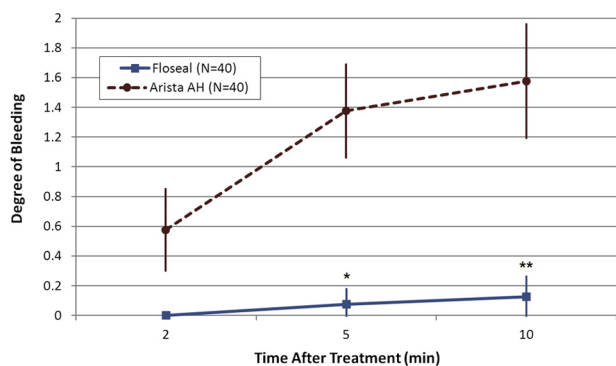
Fig. 2 – Floseal (hemostatic matrix) provides greater control of bleeding than ARISTA AH (absorbable hemostatic particles) in a heparinized porcine hepatic abrasion model of a capsular tear. Statistical significance is based on a proportional odds ratio (* 0.006, 95% CI: <0.001–0.037; ** 0.009, 0.001–0.051; n = 40 per group per time point). (Error bars represent one plus or minus the standard error based on normal approximation.)

MPH is to concentrate blood solids to form a hemostatic plug [2], whereas hemostatic matrix activates platelets and actively converts fibrinogen to fibrin by delivering thrombin to the bleeding site [12–14]. In doing so, hemostatic matrix gelatin conforms to wound surfaces by absorbing tissue fluid to create a tamponade effect [18]. The combination of these three mechanisms of action is likely the reason for its greater efficacy in this study and as reported by other investigators who have used hypocoagulopathic, hypothermic, or hemodilute animal models [11,18,19].

MPH induces coagulation through platelet plug formation by concentrating blood solids. Platelet plug formation is vulnerable to patient-specific conditions, that is, hypothermia and coagulopathy. Platelet adhesion is unequivocally demonstrated to be defective in hypothermic patients (33°C–37°C) [20,21]. Platelet function is also negatively impacted in heparinized patients due to the inactivation of thrombin. Concurrent with our findings, MPH is not documented to be effective in heparinized patients or animal models.

In a study by Björses and Holst [8], MPH had a 20% (3 of 15) success rate to treat a rodent partial nephrectomy model heparinized to correct for interspecies variation. Ersoy et al. [5]

and Neuffer et al. [22] have also reported that MPH is not effective in severe bleeds. This may be because MPH absorbs proteins up to 40,000 Da as it absorbs tissue fluid. In doing so, α-thrombin (39,000 Da), β-thrombin (28,000 Da), and γ-thrombin (28,000 Da) [23,24] are sequestered into the hemospheres from the bleeding site. Although this sequestration does not inhibit coagulation, it may impede it leading to multiple reapplications.

Ereth et al. [3] investigated the efficacy of MPH relative to collagen sponge in a 6-mm diameter, 5-mm deep hepatic punch biopsy model in swine. In 33% of applications, MPH had to be applied more than once. The authors did not state the volume of MPH applied in each application. Murat et al. [2] investigated the efficacy of MPH relative to oxidized cellulose with bolster suture in a 2.5-cm-deep lower pole partial nephrectomy model in swine. In 25% of applications, 10 g of MPH had to be applied more than once. In a follow-up study by Murat et al. [4], a similar model was performed laparoscopically, in which 33.3% of applications required an additional 1 g application more than once. Humphreys et al. [6] investigated the efficacy of MPH in a 5- and 12-mm trocar lesion of the spleen in swine; no comparator was used. In 42.8% of the 12-mm lesions and 33.3% of the 5-mm lesions, 0.5 g of MPH had to be applied more than once. Beyond the need for multiple applications, several investigators report a short-lived clot.

MPH is epichlorohydrin cross-linked purified potato starch, which is completely degraded by alpha amylase as quickly as 6 h after application [25]. The short lived clot created by MPH may lead to continued postoperative bleeding requiring surgical revision. In comparison, in a prospective, randomized clinical study comparing hemostatic matrix with oxidized cellulose and collagen sponge, use of hemostatic matrix led to a 4.5% (5 of 110 patients) incidence of surgical revision compared with a 13.5% (14 of 104 patients) incidence for low-end hemostats similar to MPH [26]. The difference between treatments was statistically significant (P = 0.04). Concurrent to the level of efficacy demonstrated by other investigators and in this study, such a rapidly absorbed hemostatic agent is most suited for low-level bleeding [5,22].

The fast degradation has minimal effect on treated tissue [27]. Antisdel et al. demonstrated that MPH did not affect the timing or extent of natural sinus mucosa healing relative to a no treatment control after avulsion of the maxillary sinus mucosa in rabbits. As with many absorbable hemostatic agents, MPH is not to be placed in and around foramina of bone, areas of bony confine, the spinal cord, and optic nerve or

Table 2 – Floseal (hemostatic matrix) provides superior reductions in blood loss than ARISTA AH (absorbable hemostatic particles).

Statistical analysis	Time point after treatment (min)	Pig effect P value	Lobe effect P value	Baseline effect P value	Mean difference (mL/min) (MPH-hemostatic matrix)	95% confidence limit	
						Lower	Upper
Blood loss	2	0.4390	0.2020	0.5097	0.1655 (0.1733–0.0078)	−0.0088	0.3398
	5	0.1336	0.1071	0.4328	0.3118 (0.3255–0.0138)	0.0939	0.5296
	10	0.0097	0.2544	0.9582	0.5025 (0.5272–0.0247)	0.2489	0.7561

Significance is based on a general linear model of mean difference in blood loss (mL/min). Covariate effects that were not significant were removed to compute the odds ratios and their confidence limits.

optic chiasm due to mass effect. MPH swells 500% on contact with fluid. For comparison, hemostatic matrix has a maximum swell of 10%–20% within 10 min.

This is the first study comparing the rate of blood loss after treatment of MPH and hemostatic matrix. A limitation of this metric is that the difference in blood loss is seemingly minimal. At 2 min after application, MPH had a 0.16 mL/min greater blood loss than hemostatic matrix, which increased to 0.5 mL/min 10 min after application. Due to the limited intraoperative observation, it is not known whether the increasing blood loss of MPH would plateau or continue to increase, or whether hemostatic matrix would do so beyond 10 min. A longer intraoperative observation period is needed to determine if or when the difference in rate of blood loss stabilizes, converges, or continues to diverge.

This is the second study comparing the hemostatic efficacy of MPH and hemostatic matrix, but the first clinically representative comparison. The uniqueness of a porcine hepatic abrasion model is that the model mimics a clinical lesion and application of the hemostatic agents. Furthermore, the animal model is heparinized to mimic the clinical condition of patients with underlying disease, such as those with renal [28] or hepatic disease [29]. The strength of our study includes the use of randomization, standardized side-by-side lesions, statistical power, and clinical relevancy. The limitation of our study is that the hemostatic agents were only compared in one tissue type. To address this, Björses and Holst [8] compared MPH and hemostatic matrix in a rodent partial nephrectomy model, in which MPH provided a hemostatic success rate of 20% and hemostatic matrix provided 100% success rate. Although a small sample size was used by Björses, the efficacy differences agree between the animal models.

Overall, hemostatic matrix provided superior hemostatic success, control of bleeding, and statistically significant less blood loss than MPH in a heparinized porcine hepatic abrasion model of a parenchymal organ capsular tear. These findings corroborate other MPH investigations regarding its efficacy and suggest that MPH is not an appropriate surrogate for flowable hemostatic matrix despite similar application techniques. A direct clinical comparison, however, is needed to determine the clinical impact of the greater efficacy of hemostatic matrix relative to MPH found in this animal model.

Acknowledgment

Disclosure

K.M.L., H.A., L.L., and A.M. were employees of Baxter Healthcare Corporation at the time of this work. A.G. was an employee of Baxter Innovations GmbH at the time of this work. The study was designed and performed using sound scientific methods and standardized lesions for impartial data collection and comparison.

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