Renal Injury and the Application of Polysaccharide Hemospheres: A Laparoscopic Experimental Model

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Abstract

Background and Purpose: Microporous polysaccharide hemospheres (MPH) are hemostatic beads engineered from purified plant starch. MPH accelerates the natural clotting cascade by concentrating clotting factors and proteins on their surface while absorbing aqueous and low molecular weight components from blood. The purpose of this study was to determine the efficacy of MPH in achieving hemostasis in the setting of laparoscopic renal injury.

Materials and Methods: In four domestic pigs, 16 laparoscopic renal trocar injuries were created (8 each of 12 and 5 mm). A standard hand-assisted laparoscopic approach was used to each kidney so that two lesions per kidney were randomly created. MPH was applied to each treatment lesion with light pressure maintained for 60 seconds. Four of the 16 lesions, two each of 12 and 5 mm, were allowed to bleed as controls. Hemostasis was defined as no active bleeding or oozing. The animals were sacrificed at the conclusion of the procedure.

Results: The mean time to hemostasis for the 12-mm MPH and control lesions was 196.2 ± 53.3 and 372.0 ± 225.6 seconds, while the average blood loss was 8.3 ± 3.7 and 12.0 ± 4.9 g, respectively. For the 5-mm MPH and control lesions, the average time to hemostasis was 100.2 ± 24.8 and 247.0 ± 134.4 seconds, while the average blood loss was 8.3 ± 3.8 and 9.0 ± 0.7 g, respectively. The median number of applications of the MPH for the 5- and 12-mm injuries was 1 and 2, respectively.

Conclusions: MPH provided a rapid and effective means of hemostasis for laparoscopic renal parenchymal injuries in this model. Additional evaluation is warranted, however, before general application is advisable.

Introduction

THE FIELD OF LAPAROSCOPIC SURGERY has experienced exponential growth as training and experience have increased over the past decade.¹ The potential benefits to the patient of less postoperative pain, less blood loss, shortened hospitalization and convalescence, improved cosmesis, and earlier return to normal activity make consideration of these techniques attractive to surgeons and patients.² Although bleeding is generally considered a standard risk of surgery, during laparoscopy, this can have dramatic effects on the successful outcome of the procedure. While it is the ambition of every surgeon to limit blood loss and prevent hemorrhage, inadvertent injuries to parenchymal organs can oc-

cur.³ In a multi-institutional review of 2407 laparoscopic procedures, Fahlenkamp and associates² reported a 4.4% complication rate; bleeding accounted for 39% of these complications.

One of the most preventable complications in laparoscopic surgery is trocar or access injury, which can be devastating.^{4,5} Bhoyrul and colleagues⁴ reported 355 trocar injuries, attributed to overpenetration of the trocar into the abdominal cavity with 182 of these injuries defined as visceral. The successful intraoperative management of these iatrogenic injuries is important for the success of the procedure and for the patient.

Conventional techniques to achieve hemostasis in the open surgical setting, such as pressure, ligature, or cautery,

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FIG. 1. Molecular exclusion demonstration of the selective porosity of the microporous polysaccharide hemisphere microbead. Components of blood are selectively absorbed into the bead while the osmotic swelling and the exclusion of the other components of blood form a lattice that accelerates the natural clotting cascade.

are modestly effective in the setting of minimally invasive procedures.^{1,6} Laparoscopic surgeons are challenged by the limitations of instrumentation, visualization, space constraints, and accessibility, which can severely impede the ability to adequately control bleeding. To assist the surgeon in the management of intraoperative bleeding, topical hemostatic agents have been developed that provide valuable tools for both open and laparoscopic surgeons.

Successful hemostasis has been anecdotally reported with a variety of these materials. Fibrin glue, microfiber hemostatic collagen, intercorporeal suture techniques, argon beam coagulation, monopolar and bipolar electrocautery, laser and tissue welding, gelatin matrices, granular mineral hemostatic agents, hydrogels, and glutaraldehyde mixtures have all been used to achieve laparoscopic hemostasis.⁷⁻¹² Each has a unique risk and benefit profile as well as potential side effects. The ideal hemostatic agent would be nonimmunogenic, inexpensive, readily available, easy to deploy, and biodegradable, with no residual radiographic signature.

Microporous polysaccharide hemispheres (MPH, Medafor Inc., Minneapolis, MN) are biologically inert, plant-based polysaccharides, synthesized into spherical microporous particles (10–200 micron spheres) that are highly effective in achieving topical hemostasis.¹³ The particles act as molecular sieves that selectively absorb water and low molecular weight compounds from the blood and concentrate clotting factors and platelets on the surface, thereby, accelerating the natural clotting cascade (Fig. 1).

The passive mechanism of hemoconcentrating endogenous clotting factors while initiating particle swelling from osmotic forces provides a natural scaffolding on which a fibrin matrix can form (Fig. 2). The clot formed by the expanded MPH beads, platelets, and clotting proteins is more resilient than a purely natural clot.¹⁴ The MPH-enhanced clot is enzymatically broken down into small water-soluble fragments, leaving no trace or radiographic evidence of deployment within 12 hours of application.^{13,14}

The purpose of this experiment was to determine the effectiveness of MPH in the intracorporeal laparoscopic environment for trocar injury to the renal parenchyma and to test the usefulness of a new, specially designed laparoscopic applicator.

Materials and Methods

The protocol was approved and performed in accordance with guidelines established by the Institutional Animal Care and Use Committee in compliance with the *Federal Animal Welfare Act, the Guide for the Care and Use of Laboratory Animals*, National Research Council.

The experimental model consisted of four pathogen-free domestic pigs that weighed between 20 and 25 kg. Each animal

FIG. 2. Scanning electron micrograph of the interaction of microporous polysaccharide hemispheres with human blood and associated protein matrix. Note the fibrinous interconnections between the polysaccharide beads.

was used as a multiple injury model with the creation of four separate lesions per animal, or two per kidney. The lesions were formed using a specially modified 5-mm and 12-mm Endopath Bladeless Trocar (Ethicon Endo-Surgery Inc, Cincinnati, OH), which allowed the creation of uniform and reproducible lesions (Fig. 3). A total of 16 lesions were created, eight each with the modified 12 mm and 5 mm trocars.

The MPH was deployed by a 20-cm, specially designed suction applicator (Fig. 4) through a 12-mm laparoscopic port. The device, loaded with 0.5 g of MPH in the distal end, allowed precise delivery of the material to the wound by providing suction to keep the material in place while engaging

FIG. 3. The 12-mm Endopath Bladeless Trocar, modified for laparoscopic injury through the hand gel port. Note the broad ledge near the tip to ensure lesion reproducibility in terms of depth and circumference.

FIG. 4. Specially designed laparoscopic suction applicator. The distal tip holds an adjustable amount of material that is protected from contamination by the outer sheath. The material is loaded onto the tip, while the side hole in the proximal portion is covered to maintain suction through the instrument. After deployment, the suction is broken, leaving the material at the site of injury.

the source of bleeding. When suction was broken, via a side finger hole, the material remained on the bleeding surface and was released by the applicator.

MPH was applied to each lesion, except for the control lesions, and pressure maintained for 60 seconds before release. To standardize comparison with the control lesions, pressure was maintained on the control lesions with the modified trocars after creation for 60 seconds as well. Hemostasis was defined as no oozing or bleeding from the site of injury.

Each animal underwent an identical surgical procedure, first on the left and then on the right kidney, varying only in the size of the lesion and number of MPH applications necessary to achieve hemostasis.

Sedation was achieved with a mixture of tiletamine and zolazepam (Telazol, Wyeth, Madison, NJ), 5 mg/kg; xylazine (Rompun, Bayer Corp., Shawnee Mission, KS), 2 mg/kg; and glycopyrrolate (Robinul, Wyeth, Madison, NJ) 0.06 mg/kg, intramuscularly, followed by endotracheal intubation and anesthesia maintenance with inhalational isoflurane 1% to 3% in 100% oxygen. Normal saline intravenous fluid was administered to maintain a mean arterial pressure of greater than 60 mm Hg.

Each animal was sterilely prepped and draped in the supine position. A 7-cm incision was made in the anterior abdominal wall at the level of the umbilicus. A 100-mm Gel-Port (Applied Medical, Rancho Santa Margarita, CA) was then placed, and a CO₂ pneumoperitoneum of 15 mm Hg was achieved.

One 12-mm trocar was placed under direct vision at the left midclavicular line subcostally and another at the left axillary line lateral to the midpoint of the incision to allow access to the left kidney. The animal was then placed in a modified decubitus position. The kidney was exposed by mobilizing the bowel medially, and the surgical site was carefully dried with a surgical sponge and weighed before creation of each lesion.

In a randomly selected order, either a 5-mm or 12-mm lesion was created so that each kidney had one of each lesion. The control lesions were always created last, so that if exsanguination occurred, it would not interfere with the completion of the experiment.

The MPH was then applied to each lesion and, if there was any rebleeding or oozing, another application of MPH was delivered. The time from the removal of the MPH applica-

tor or modified trocar (for the control lesions) until complete hemostasis was achieved was recorded for each lesion. The postlesion sponge weight was used as an approximation of blood loss with 1 g roughly equivalent to 1 mL of blood. After hemostasis was apparently achieved, each lesion was observed for 5 minutes with the pneumoperitoneum pressure at 5 mm Hg. MPH application was repeated, as necessary.

Each animal was maintained for 30 min after successful hemostasis of the last lesion. This was to ensure that there was adequate mean arterial pressure and no acute rebleeding episodes. Following this, each animal was euthanized with intravenous sodium pentobarbital 7.8% in isopropyl alcohol at 100 mg/kg, and the kidneys harvested for histopathologic examination.

The significance of the time to hemostasis and the amount of blood loss was determined by the two-sample *t* test. The comparison of the number of applications of MPH was performed using the Wilcoxon rank sum test. Groups with a *P* value of less than 0.05 were reported as significant.

Results

The lesions were created in the upper and lower pole of each kidney in approximately the same location for each animal. No animal exsanguinated from either the experimental or control lesions. The amount of blood loss from each lesion and the collection of the four lesions per animal were not enough to affect any of the animal's measurable hemodynamic parameters. A mean arterial pressure (MAP) of 60 mm Hg was maintained for each animal.

The mean time to hemostasis for the 5-mm MPH and control lesions were 100.2 ± 24.8 and 247.0 ± 134.4 seconds, respectively. The 12-mm MPH and control lesions had a longer time until complete hemostasis was achieved, 196.2 ± 53.3 and 372.0 ± 226.0 seconds, respectively. The hemostasis time was shorter for the MPH-treated 5-mm injuries, which was statistically significant compared with the 12-mm treated lesions ($P = 0.005$). No more than 4

minutes was needed to achieve hemostasis in any MPH-treated lesion. The results are summarized in Table 1.

The mean number of applications for the MPH to the 5-mm and 12-mm lesions was 1.0 ± 0.0 and 1.7 ± 0.5 , respectively. This value was significant between the two treatment groups ($P = 0.025$). No more than two applications of MPH were needed to achieve complete hemostasis in any treatment group. The 5-mm lesions were all controlled with just a single application of MPH, suggesting that the amount of MPH delivered to the lesion was effective. Larger lesions needed more MPH.

The average amount of blood loss after the creation of each MPH-treated lesion until the time of hemostasis was 8.3 ± 3.8 g for the 5-mm and 8.3 ± 3.7 g for the 12-mm injuries. Although the amount of blood loss was not different between the two groups ($P = 1.0$), one 5-mm lesion had profuse bleeding associated with its creation (16 g blood loss), likely because of injury to a large renal arterial branch. The mean blood loss from the control lesions until hemorrhage stopped was 9.0 ± 0.7 g and 12.0 ± 4.9 for the 5-mm and 12-mm lesions, respectively. When looking at the amount of blood loss from all MPH-treated lesions compared with the control lesions, 8.3 ± 3.6 g versus 10.0 ± 3.4 g, the control lesions had more blood loss. This relationship, however, was not statistically significant ($P = 0.436$).

All animals survived the experiment without incident or appreciable changes in their individual hemodynamic parameters. The histologic findings were consistent with acute renal injury, with no signs of surrounding tissue changes from the MPH material. There was no histopathologic evidence of global renal congestion or dysfunction in this acute injury model.

Discussion

The advancement and application of laparoscopic techniques make the emergence of laparoscopic procedures more common and accepted in modern urologic practice. Reports

TABLE 1. SUMMARY OF RESULTS

Lesion	Animal	Lesion sequence	Applications of MPH	Time to hemostasis (min)	Blood loss (g)
12 mm	1	2	1	1:33	5
	1	4	Control	3:32	8
	2	2	2	3:31	9
	2	4	Control	8:51	15
	3	1	2	3:24	6
	3	3	2	3:16	15
	4	1	2	3:58	6
	4	3	1	3:55	9
5 mm	1	1	1	2:22	16
	1	3	1	1:47	7
	2	1	1	1:50	7
	2	3	1	1:20	7
	3	2	1	1:26	7
	3	4	Control	2:32	8
	4	2	1	1:16	6
	4	4	Control	5:42	9

MPH = microporous polysaccharide hemispheres.

from the largest series of laparoscopic procedures cite a complication rate between 4.4% and 6.9%.^{1,2} One of the most devastating complications that can occur is bleeding—not only in terms of the morbidity associated with the physiologic changes of acute blood loss, but also because of the impaired visualization of the surgical field. Even minor bleeding can jeopardize a procedure because of the light absorption of the hemoglobin and associated tissue staining.^{4,7}

Inadvertent injury to the kidney can occur during access or in the performance of other intra-abdominal procedures.^{1,2,4,5} While solid organ injury may represent only a minor nuisance for surgeons during an open procedure, these occurrences can present considerable challenges for surgeons during laparoscopy. Positive pneumoperitoneal pressure can limit venous bleeding during laparoscopy, but aggressive suction can make the injury worse. Laparoscopic management is limited by exposure, the availability and orientation of the ports and instrumentation, and the prompt access to and ease of application of hemostatic agents. To our knowledge, this report represents the first description of laparoscopic intracorporeal use of MPH to facilitate renal parenchymal hemostasis.

Hemostatic agents have been used in surgery since 1909 when Bergel first described the use of dried human plasma to control bleeding.¹⁵ Over the past century, many products have been developed to facilitate and improve hemostasis. These include antifibrinolytics, fibrin sealants, matrix hemostats, and topical hemostatic agents. The application of these materials to renal parenchyma is well reported for use during laparoscopic partial nephrectomy (LPN). Any injury to the kidney represents an important consideration, because the kidney is one of the most vascular tissues in the human body, reflecting its role in plasma filtration.¹⁶

The design of our experiment used a multiple injury porcine model. The type of model for hemostatic study is an important consideration, given the cost of research. Small mammals, although readily available and cost efficient, do not lend themselves well to this area because of efficient natural clotting mechanisms. Tuthill and colleagues⁶ used a heparinized rat model to evaluate the clinical effectiveness of Gelfoam with thrombin, fibrinogen without thrombin, and a fibrin sealant in response to a heminephrectomy injury. The control animals exsanguinated after renal blood flow was reestablished, while the fibrin sealant demonstrated the most efficient hemostatic control. The tendency toward exsanguination in heparinized animals is also supported by the work of Petratos and coworkers.¹⁷

Our injury model was not as extensive as a heminephrectomy, but to prevent premature death of the animal, all control lesions were created last. The small animal model may have been well suited for their experiments, but the applicability to inadvertent renal injury is not as obvious. We elected to use pigs, which anatomically and functionally mimic humans while providing a large abdominal cavity that allows excellent exposure for laparoscopic experimentation.

The MPH was very effective in accelerating the natural clotting cascade in the porcine model. The MPH was able to achieve complete hemostasis in every test lesion. The time to hemostasis never exceeded 4 minutes for any of the lesions. This theoretically would enable the surgeon to rapidly

repair any vascular solid-organ injury and return to the laparoscopic procedure. The one 5-mm trocar injury in which brisk bleeding was encountered was still able to be controlled with a single application of MPH; however, because of the nature of the injury to the intrarenal vasculature, more blood was lost initially, increasing the overall blood from that lesion compared with others. The rapid nature of the bleeding displaced some of the MPH, which eventually sealed the lesion by a hemostatic plug from the swelling and mechanism of action of the MPH. Importantly, MPH is supplied as a readily available dry powder that does not require reconstitution or mixing. This is in contrast to other hemostatic agents. The time necessary to prepare a substance for application in the setting of LPN may not be a concern, because the level of anticipation, need, and urgency can be predicted, which may not be the case in the acute unexpected situation.

The topical application of BioGlue (CryoLife Inc., Kennewick, WA), which has been used in LPN as well as in the face of acute laparoscopic splenic injury, requires a dry field. In other words, acute bleeding with any vigorous source is not well managed by this agent.⁸ MPH can be applied to an actively bleeding source because of its unique mechanism of action. The 12-mm lesions did need more applications of MPH to achieve hemostasis than the 5-mm lesions, which may be a reflection of injury severity or size. It was our experience, however, that the MPH was able to achieve complete hemostasis in all test lesions. While other topical agents have demonstrated hemostatic proficiency in human LPN situations, the potential side effects of these other agents must be considered.^{8,9,11,16}

Antifibrinolytics, such as aminocaproic acid, tranexamic acid, and aprotinin, work by binding plasminogen and interfering with the subsequent conversion to plasmin. Plasmin breaks down fibrin clots into fibrin degradation products, impairing hemostasis. These agents are largely used as stabilizing agents in fibrin sealants or systemically and have limited topical application.¹⁵ Aprotinin is derived from bovine lung and has the potential to cause antibody formation in humans. In rats, tranexamic acid has been reported to cause convulsions, hyperexcitability and death, but in humans, this has not occurred to date.^{15,18}

Fibrin sealants are derived from plasma proteins, usually representing a combination of fibrinogen (factor I), fibrin stabilizing factor (factor XIII), thrombin (converts fibrinogen to fibrin), and aprotinin.¹⁹ These sealants use vapor-heated, freeze-dried, pooled human fibrinogen, factor XIII, bovine aprotinin, human thrombin, and calcium chloride.^{18,19} Human thrombin has generally replaced bovine sources in these preparations, because in 126 cases since 1955, patients exposed to bovine thrombin have acquired thrombin antibodies.^{20–22} In addition, Hino and coworkers²³ reported three cases of iatrogenic parvovirus B19 transmission associated with commercial sealants.

Evicel (Ethicon Inc., Somerville, NJ) is an entirely human product that uses tranexamic acid rather than bovine aprotinin. Although potential bovine product reactions are avoided, there are still concerns about tranexamic acid.¹⁵ Perhaps the largest impediment to this therapy in the acute laparoscopic setting, other than getting the material to the site of injury, is the prolonged preparation time of up to 40 minutes to reconstitute these products.²⁴

Matrix hemostats, such as FloSeal (Baxter Healthcare, Deerfield, IL), use a special bovine collagen gelatin matrix that is cross-linked by glutaraldehyde.²⁵ Like fibrin sealants, they require preparation with thrombin before application. Surgiflo (Ethicon Inc., Somerville, NJ) is conceptually similar to FloSeal, except that the porcine gelatin matrix is mixed with bovine thrombin at the institution. The major difference between these agents and the fibrin sealants is the need for active bleeding as a source of fibrinogen.

BioGlue is bovine serum albumin cross-linked by glutaraldehyde that targets tissue proteins independent of the clotting cascade. This resolute material can be prepared rapidly, but it is much less biodegradable than the other matrix hemostats.²⁶ Other topical hemostatic agents are gelatins such as Gelfoam (Pharmacia Corp, Kalamazoo, MI) and Surgifoam (Ethicon Inc, Somerville, NJ), oxidized cellulose such as Surgicel (Ethicon Inc, Somerville, NJ), microfibrillar collagen such as Avitene (C.R. Bard Inc, Murray Hill, NJ) and Collastat (Kindall Company, Boston, MA), and granular minerals such as QuickClot (Z-Medica Corp., Wallingford, CT).

The gelatin products trap platelets in uniform pores to facilitate the clotting cascade, and often these products are soaked in thrombin before use. Typically, these agents are unable to tamponade bleeding and are often disrupted with movement or agitation. Oxidized cellulose materials help form a lattice for clot formation and do not actually enhance the clotting process.²⁷ Microfibrillar collagen stimulates platelets and the intrinsic clotting cascade, yet laparoscopic application remains a hindrance to usefulness.

QuickClot is composed of zeolite, a microporous crystalline aluminosilicate, which adsorbs fluid in an exothermic reaction and acts by concentrating clotting factors on its surface.²⁸ Intracorporeal use has been associated with infection and, more importantly, necrosis and third-degree thermal injury of surrounding tissues.¹²

A considerable barrier to the application of any topical agent in the laparoscopic environment is the delivery mechanism. In this experiment, we used a specially designed applicator with suction to keep the MPH dose engaged at the tip. This suction helped to engage the site of injury and, when the suction was broken, allowed the material to stay on target. While the powder did occasionally spill into the abdominal cavity, this did not limit visibility and, because of its reported rapid absorption, would not be expected to be a problem.¹³

Because MPH is derived from a plant source, the risk of disease transmission or allergic reaction is minimal. The readily available source provides a means to keep the overall cost of production low. MPH at the time of this experiment was named Hemoderm, which came in 2 g bellows. It is currently marketed with FDA approval as Arista AH and comes in a box of five in 1 g, 3 g, and 5 g bellows. Each application of the MPH was 0.5 g in the laparoscopic applicator for a cost of approximately \$25 per application. Unlike QuickClot, the tenacious clot formed by the hemoconcentration of the natural clotting factors and the swelling of the microbead during absorption of the aqueous components of blood is not associated with any exothermic reaction or injury.

MPH has been described as a highly effective topical hemostatic agent in the management of prolonged access bleed-

ing of patients receiving dialysis, of punch biopsies of porcine liver, and in the setting of open porcine partial nephrectomies.^{13, 29,30} Our goal was to examine the efficiency of MPH in the laparoscopic setting for renal parenchymal injuries. The material worked very rapidly and was able to achieve hemostasis in all of our test lesions in less than 4 minutes.

Despite these results, there are limitations to this study that warrant consideration. There were only four animals used in this preliminary study, thus limiting the power of the study. Because this was a pilot study to gain experience with this new material and establish a baseline for further experimentation, however, we think the number of lesions were sufficient. Each animal was used as a multiple injury model, which can influence the results.

The control lesions were always created last, and despite maintenance of MAP, this could have limited the impact of the control injury. The control lesions did eventually stop bleeding, which indicated the recuperative nature of the model and the hearty response of the porcine model to renal injury. This phenomenon could also be attributed to the tamponade effect of pneumoperitoneal pressure. We are currently testing the material in the setting of supraphysiologic hemostatic pressure as well as in the anticoagulated model.

The present study was not blinded, and the MPH was not compared with any other agent. The experimental design did not allow for the surgeon to be blinded, because this was an initial trial to demonstrate the usefulness of a new device and product.

Conclusion

MPH offers an exciting alternative that may soon be added to the surgical armamentarium for treatment of acute intracorporeal hemorrhage. Before widespread acceptance can be recommended, however, further research is needed, with longer survival studies and direct comparisons with other hemostatic agents.

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Abbreviations Used

PN = laparoscopic partial nephrectomy

MAP = mean arterial pressure

MPH = microporous polysaccharide hemispheres