Avitene™ Microfibrillar Collagen Hemostat for Adjunctive Hemostasis in Surgical Procedures: A Systematic Literature Review

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Abstract: Adequate hemostasis during surgical procedures is essential for successful patient outcomes and reduced healthcare resource utilization. Topical hemostatic agents can act as catalysts for the clotting cascade or as a scaffold to promote platelet activation or aggregation. Although an ever-increasing number of topical absorbable hemostatic agents are now available for perioperative use, health care providers are disadvantaged by the lack of comparative data on feasibility, clinical effectiveness, advantages, and limitations of each in specific surgical settings. This knowledge is important for appropriate product choice when patient characteristics, type of surgical procedure, type of bleeding, and product availability may differ widely. This manuscript provides the first comprehensive overview of Avitene™ Microfibrillar Collagen Hemostat (MCH), a bovine collagen-based absorbable hemostat that has been widely used for over four decades in the United States and abroad. MCH is indicated as an adjunct to hemostasis across a broad spectrum of surgical specialties and has been shown to achieve hemostasis with positive patient outcomes and a favorable safety profile in many applications, including hepatic, orthopedic, splenic, oral, and otolaryngologic surgery. Although published clinical data regarding the use of MCH in cardiovascular surgery is limited, evidence suggests moderate use in this specialty. The information contained in this systematic review will help health care providers understand the clinical use and effectiveness of the product to determine appropriate use in differing bleeding scenarios across multiple surgical specialties. Future studies may include comparative functional and cost analyses to explore the economic advantages of using absorbable hemostatic agents compared with each other or with conventional techniques of hemostasis, when appropriate.

Keywords: Avitene, hemostasis, surgery, topical, hemorrhage, microfibrillar collagen

Plain Language Summary
Control of excessive bleeding during surgery is a difficult but important task. Products called hemostats can be placed on a bleeding site during surgery to help the body’s own processes for clotting. Each patient is different, and each surgery is performed for a different purpose. Because so many different hemostats are available for surgeons to use, knowing which product to use during each surgery is difficult. This review was completed to provide information on the use of one specific product, Avitene™ Microfibrillar Collagen Hemostat (MCH). MCH is made from collagen, a protein found in skin and other connective tissues. If MCH is left in the body after surgery, it will absorb in less than 90 days. MCH has been widely used for many decades in the United States and other countries, and has been shown to work quickly and safely to control bleeding when conventional methods of hemostasis are ineffective during many different types of surgery. In the future, studies may help to compare the costs of using MCH and other absorbable hemostats with the costs of other methods designed to control bleeding.
Introduction

Purpose
Avitene™ MCH has been available for clinical use for several decades. There exists a body of literature summarizing MCH in surgical settings that demonstrate that, despite newer materials being introduced into the marketplace, MCH continues to serve as a standard for hemostatic performance. This paper summarizes the literature around MCH use in a variety of surgical bleeding scenarios.

Overview of Hemostasis
Some degree of bleeding is common in all surgical procedures; excessive blood loss can lead to significant morbidity or mortality. Successful perioperative hemostasis can reduce the risks of severe complications such as peripheral circulatory failure and resultant stroke or myocardial infarction, arterial or venous thromboembolism, symptomatic hematoma, and death.1,2 Transfusion of blood products in the absence of successful hemostasis is reported to be associated with an increased risk of acute lung injury, circulatory overload, and allergic and/or anaphylactic reactions.3,4 Less common risks include immune, hemolytic, and non-hemolytic reactions to transfused blood products as well as infection.4 The economic impact of uncontrolled bleeding can be substantial when considering prolonged surgery time, reoperations or other postoperative interventions, and prolonged intensive care unit (ICU) or hospital length of stay. Recent estimations of the hospital costs of bleeding-related complications and transfusions resulting from inpatient surgery ranged from US $2,805 to $17,279 depending upon the type of surgery.5

Conventional techniques to control major bleeding during surgery include application of pressure, suturing, ligation, cautery, or other mechanical and energy-based mechanical means. Especially for diffuse hemorrhage or uncontrolled local bleeding during surgery, use of topical hemostatic agents are useful as adjunctive therapy when conventional methods are insufficient or impractical (eg, in instances of coagulopathies and/or platelet dysfunction or for use in parenchymal tissues or bony surfaces).6 The type of topical hemostatic agent used in the surgical setting is determined by specific patient characteristics, type of surgical procedure, type of bleeding, and product availability.3 Biologically active hemostatic agents such as thrombin or products containing fibrinogen act as catalysts for the clotting cascade, while mechanical (passive) hemostatic agents, form a barrier to bleeding and act as a scaffold to promote clotting by platelet activation and aggregation.3,6 Absorbable hemostats are regulated as Class III devices and include porcine or bovine gelatin, bovine collagen, starch, oxidized regenerated cellulose (ORC), and other components.

Understanding the clinical effectiveness and advantages or limitations of absorbable hemostatic products is critically important to ensure appropriate clinical use for superior patient outcomes, which may subsequently reduce healthcare resource utilization. This systematic review of published clinical data on the use of MCH, a bovine collagen-based absorbable hemostatic agent that is widely indicated for all types of surgical specialties, aims to summarize the clinical impact of this product and to offer areas for future study.

Methods
A systematic language literature search was conducted using the Cochrane Central Register of Controlled Trials, MEDLINE/PubMed database, and Embase database with no date limitations. Keywords used for the search included collagen, Avitene, hemostasis, haemostasis, hemostatic agent, surgery, and surgical. Results were limited to human studies published in the English language. Additional reports were manually identified by references cited in the relevant publications. Emphasis was placed on randomized controlled studies where possible. Characteristics of the included clinical evaluations are summarized in Table 1.

Product Description
Avitene™ MCH flour was approved in 1976, with multiple form factors coming into the market after. MCH is absorbable and is prepared as a sterile, porous, pliable, water-insoluble partial hydrochloric acid salt of purified bovine corium collagen.8 Although early publications characterize MCH as microcrystalline, the US Food and Drug Administration prefers to describe MCH as microfibrillar. Advantages of MCH include tight adhesion to bleeding surfaces with limited swelling, fast induction of hemostasis, and low tissue reaction.11

Design and Formulation
MCH is commercially available in multiple forms: as a flour-like formulation provided loose (Avitene™ MCH Flour) or preloaded in 1 g volume into a syringe (SyringeAvitene™); as non-woven sheets provided flat (Avitene™ Sheets) or preloaded for endoscopic delivery through standard trocars and cannulae (EndoAvitene™); or
Table 1 Characteristics of Included Clinical Evaluations of Avitene™ Microfibrillar Collagen Hemostat

| First Author | Year | Type of Study/Publication | Patient Characteristic, Sample Size | Setting | Conclusion |
|--------------|------|---------------------------|-------------------------------------|---------|------------|
| Wilkinson TS | 1973 | Clinical evaluation/feasibility | 10 Skin graft donor sites in 8 patients | Single center | Avitene™ MCH reduced time to cessation of visible bleeding and mean volume of blood absorbed with no healing disorders. |
| Vistnes LM | 1974 | Clinical evaluation/feasibility | 15 Skin graft donor sites from 10 patients | Single center | Treatment with microcrystalline bovine collagen (MBC) significantly reduced blood loss. |
| Morgenstern L | 1977 | Case series | 36 Patients with hepatic bleeding of diverse etiology | Single center | Intractable bleeding from the liver surface was treated successfully with Avitene™ MCH. |
| Morgenstern L | 1982 | Editorial | – | – | No instance of subhepatic abscess or infection with use of microfibrillar collagen in the gallbladder bed. |
| Craig C | 1977 | Controlled clinical evaluation/feasibility | 31 Iliac crest bone graft donor sites from 29 patients | Single center | A significantly lower bleeding rate was observed after treatment with Avitene™ MCH than after manual compression with dry sponges. No clinically significant immune response was observed. |
| Harris WH | 1978 | Comparative study | 45 Total hip replacements | Single surgeon at a single center | Avitene™ MCH was effective in reducing bleeding from cancellous bone and did not interfere with bone healing. No cutaneous sensitivity to Avitene™ MCH was observed. |
| Ritter MA | 1978 | Controlled clinical evaluation | 160 Total-condylar total-knee replacements performed in 160 patients | Single center | MCH reduces blood loss and decreases the need for blood replacement with no increase in wound complication or infection rates. |
| Lee BY | 1982 | Controlled clinical evaluation/feasibility | 20 Rotation flaps or primary closures performed for the repair of pressure sores in 18 male spinal cord-injured patients | Unknown | MCH use reduced total hemovac drainage immediately postoperative (versus no agent). |

| Splenic Surgery |
|-----------------|
| Giuliano AE | 1981 | Retrospective case series | Splenic salvage performed in 33 patients | Single center | Use of Avitene™ MCH alone or in combination with other agents successfully achieved hemostasis in 25 of 33 patients. |
| Morgenstern L | 1974 | Case report | Iatrogenic splenic injury in one patient | Single center | Complete hemostasis to avert splenectomy was achieved with Avitene™ MCH. |
| Morgenstern L | 1977 | Case series | Iatrogenic splenic injury in 15 patients | Single center | Hemostasis was achieved in 13 of 15 patients to successfully avert splenectomy. |
| Pachter HL | 1981 | Case series | Treatment of splenic injuries in 27 consecutive patients | Single center | Splenorrhaphy was successfully accomplished in 24 of the 27 patients by primary suture repair often in conjunction with Avitene™ MCH. |

(Continued)
as a soft, pliable sponge (Avitene™ Ultrafoam™ Collagen Sponge). MCH is applied directly to the bleeding surface and when possible, should be compressed with dry sponges immediately after the application of the dry product. Because the product is highly adherent to any physiological surface, care must be taken to ensure accurate application with dry instruments or forceps.

### Indications for Use and Mechanism of Action

MCH is used in surgical procedures as an adjunct to hemostasis when control of bleeding by ligature or conventional procedures is ineffective or impractical. MCH is indicated across surgical specialties, including neurosurgery and urology. MCH is not administered according to a standardized dosing regimen; product labeling recommends use of the minimal amount of product needed to achieve hemostasis. Application of pressure over the product with a dry sponge is recommended for a period of time that varies with the force and severity of bleeding. After 5–10 minutes, the excess MCH may be removed by teasing and irrigation, and any breakthrough bleeding can be treated with additional product. When placed in contact with a bleeding surface, MCH enhances platelet adherence to the collagen fibrils, promoting platelet aggregation and the release of clotting proteins, such as platelet factor 3 and ADP, and activating Hageman factor to form fibrin and to promote hemostasis. The effect on platelet adhesion and aggregation is not inhibited by heparin in vitro. In addition, MCH was found effective in heparinized dogs and in eight of nine fully heparinized human subjects.

Adverse effects have been reported following use of absorbable hemostatic agents in bony or neural spaces when the agent exerts pressure on sensitive structures after absorption of blood. Although no drug interactions have been described with the use of absorbable hemostatic agents, drug-induced alterations in hemostasis that affect the clotting process have been reported with use of absorbable hemostatic agents.

### Clinical Evaluation of Avitene™ MCH

In 1973, Wilkinson et al were the first to report a reproducible, objective model to clinically evaluate hemostatic capability of MCH using skin graft donor sites of uniform size, thickness, and capillary supply.

| First Author | Year | Type of Study/Publication | Patient Characteristic, Sample Size | Setting | Conclusion |
|--------------|------|---------------------------|------------------------------------|---------|------------|
| Luetje CM    | 1977 | Case report               | Control of bleeding from iatrogenic injury in postauricular tympanoplasty in one patient | Single center | Use of Avitene™ MCH controlled hemostasis and allowed completion of the tympanoplasty in an otherwise routine fashion. |
| Morgan PR    | 1978 | Case report               | Control of hemorrhage following removal of a glomus tympanicum tumor in one patient | Single center | Use of Avitene™ MCH resulted in rapid hemostasis with minimal clot bulk. |
| Wirthlin MR  | 1980 | Case series               | Control of bleeding at the donor site of free gingival graft procedures as well as 2 other bleeding sites in 6 patients | Unknown | Rapid cessation of bleeding occurred at all 8 sites following application of Avitene™ MCH. |
| Saroff SA    | 1982 | Controlled clinical evaluation/feasibility | Control of bleeding from palatal donor site of free soft tissue autografts in 20 patients | Unknown | Avitene™ MCH treatment achieved rapid hemostasis with no effect on the rate or quality of healing. |
| Taylor MT    | 1980 | Case series               | 61 Consecutive patients with anterior epistaxis | Single center | Avitene™ MCH was successful in controlling anterior epistaxis in 44 of 61 patients (72%). Associated morbidity was minimal. |

Abbreviation: MCH, microfibrillar collagen hemostat.
Immediately after skin graft excision, MCH flour (experimental product) and furacin gauze pad (control product) were applied to each donor site under standardized and controlled conditions. Additional filter paper discs applied over the MCH and furacin gauze at regular intervals were air-dried for elution and spectrophotometric evaluation of hemoglobin content. Quantitation of blood absorbed by each disc was normalized to each patient’s hemoglobin level. Other endpoints included time elapsed to cessation of visible bleeding, foreign body reactions, disordered healing, residual extraneous collagen, and sensitivity to bovine antigens. Under these conditions, application of MCH reduced both time to cessation of visible bleeding (experimental: 1 min; control: 15.7 min) and mean volume of blood absorbed (experimental: 0.058 mL per unit area; control: 0.286 mL per unit area; \( p < 0.025 \)). No significant effect was observed on the quality or speed of healing versus control, and sensitivity tests confirmed only weak antigenicity of collagen in this setting and patient population. This model for comparative evaluation of hemostatic effectiveness has been used with\(^ {15} \) or without modification to evaluate multiple hemostatic agents in the decades since.

**Use in Hepatic Surgery**

Despite many technical refinements to help improve the safety of hepatic surgery, perioperative bleeding and transfusion requirements remain major factors in increased morbidity and mortality rates as well as prolonged hospital length of stay.\(^ {20-22} \) The extreme vascularity of the liver predisposes this organ to diffuse bleeding following traumatic damage or operative procedures.\(^ {23,24} \) Underlying pathologic conditions or coagulopathies may also complicate successful hemostasis.\(^ {25} \) Morgenstern et al\(^ {26} \) reported a case series of 36 patients with hepatic bleeding of diverse etiology (gallbladder bed following cholecystectomy, superficial lacerations, liver biopsy sites, capsular denudation, hemangioma, hepatic resections, and other cases). In these patients, the degree of bleeding ranged from a constant, uncontrollable ooze to a brisk, potentially lethal hemorrhage. In all but one patient, for which the hepatic laceration could be only partially packed, MCH was effective in securing hemostasis. In at least six patients, use of MCH was considered lifesaving. Although no instances of subhepatic abscess or infection were reported, the authors suggest minimal use of the product to both ensure adequate hemostasis and minimize risk of infection.

This report was the first to describe the effectiveness of MCH in a variety of clinical applications when used adjunctively or as a primary means of topical hemostasis. The authors claim superiority of MCH over other topical hemostats [Surgicel\(^ {®} \) (Ethicon) or Gelfoam\(^ {®} \) (Pfizer)] in terms of mechanism of action, surface adherence, and tolerability even in the presence of severe infection.\(^ {26,27} \)

**Use in Orthopedic Surgery**

Hemostasis is especially important in orthopedic surgical procedures, during which exposed bone surfaces are prone to diffuse bleeding and may be difficult to access. In preclinical studies, adverse effects of various topical hemostatic agents were reported, such as impeded bone healing with bone wax\(^ {28} \) or oxidized cellulose\(^ {19} \) as well as increased incidence of wound infection with Gelfoam\(^ {®} \).\(^ {29,30} \) Because MCH adheres tightly to bleeding surfaces and promotes fast induction of hemostasis, this material is considered ideal for orthopedic applications.

Craig and Asher\(^ {11} \) evaluated the control of bleeding from 31 iliac crest bone graft donor sites in 29 patients by MCH (\( n = 14 \) grafts) compared with Gelfoam\(^ {®} \) with thrombin packs (Pfizer) (\( n = 10 \) grafts) and sponge compression only (\( n = 7 \) grafts). As measured by baseline sampling, no statistically significant differences were observed among the groups in pre- or post-operative hemoglobin concentration and initial blood loss rates. Samples were also taken at 2-minute, 3-minute, and 5-minute intervals following treatment with hemostatic agent or compression only. At each post-treatment interval as well as for the cumulative total of the post-treatment period, administration of MCH and Gelfoam\(^ {®} \) with thrombin resulted in significantly less bleeding than sponge compression only. However, no significant differences were observed between the hemostatic effects of MCH and Gelfoam\(^ {®} \) with thrombin. This study also investigated the possibility of an immune response to bovine antigens in the implanted MCH. Evaluation of mean pre- and post-operative Complement C3 levels and hemagglutinin antibody titers showed no clinically significant difference in immune response among the groups. Lack of immune response in 7 of 11 patients confirmed the low-level antigenicity of MCH; detectable IgE antibody levels in the remaining 4 patients were not clinically significant. Citing supporting results from laboratory studies, the authors claim that MCH does not inhibit bone healing when used in orthopedic surgical procedures.\(^ {11} \)
Harris et al reported similar results following a single-center parallel assessment of bleeding cancellous bone surfaces and the hemostatic effect of gelatin paste (13 total hip replacements), MCH (13 hips), and thrombin-soaked gelatin sponge (11 hips) compared with control (no agent; 8 hips). Again, baseline blood loss rates did not differ between the groups, and at a 3-minute post-treatment interval, all three topical hemostatic agents were effective in reducing bleeding from the cancellous bone compared with control. Though tests of the relative effectiveness of the hemostatic agents in this study were inconclusive due to study design issues, the authors predicted similar percent reductions in bleeding by the gelatin-based hemostatic agents and MCH, with a significantly greater effect of all experimental agents compared with control ($p < 0.01$). In these patients, no cutaneous sensitivity to MCH was observed preoperatively and up to 10 days postoperatively, as assessed by intradermal skin tests, and the hemostatic agents did not appear to interfere with bone healing.

A larger controlled trial assessed hemovac drainage over 48 hours postoperative, number of units of blood replaced, wound complications, and wound infections up to 1 year postoperative in 160 subjects undergoing total-condylar total-knee replacements with ($n = 74$) or without the use of MCH ($n = 86$). No infections occurred in the MCH group; only one postoperative infection occurred in the control group. Only one wound bleed occurred in the MCH group, which was attributed to the subject’s low prothrombin activity. Significantly less hemovac drainage was recorded in the MCH group (402 cc vs 672 cc in the control group; $p < 0.01$), and significantly fewer blood units were replaced in the MCH group (0.25 vs 1 in the control group, $p < 0.001$) compared with control. The author concluded that MCH can statistically reduce blood loss, which decreases the need for blood replacement and the associated risk factors, while not increasing the risk for increased complications or infections.

Lee et al assessed the hemostatic effect of MCH compared with standard intraoperative procedures to secure hemostasis of actively hemorrhaging bone surface after osteotomy. This study was conducted in male spinal-cord injured patients undergoing rotation flap procedures or primary closure for the repair of pressure sores at the ischial, sacral, or trochanteric regions. Two groups of 10 procedures each included seven conventional rotation flaps, two myocutaneous rotation flaps, and one primary closure. In one group of 10 procedures, MCH was applied, while the other group served as matched controls. For each patient, hemovac drain output was measured each day; after 7 days of postoperative follow-up, average total hemovac drainage from the MCH group was 11% less than that of the control group (110 mL over 7 days for MCH; 157 mL for control). Together with data from preclinical studies, these results led the authors to conclude that use of MCH to achieve hemostasis in this application is safe and effective in producing clinically significant reductions in blood loss.

### Use in Splenic Surgery
MCH has been used successfully for hemostasis in emergent surgical procedures, such as organ salvage after trauma or for repair of iatrogenic organ injury during abdominal surgery. Giuliano and Lim described the use of MCH alone or in combination with electrocautery, Gelfoam® plus thrombin, and/or gentle pressure in 25 patients undergoing splenorrhaphy (splenic salvage) following traumatic injury. Of these 25 patients, and 7 more who underwent suture repair of bleeding lacerations or hemiplenectomy, hemostasis was successfully achieved in all, and none required reoperation for control of bleeding or subsequent splenectomy for any reason.

In an early report including a canine experimental study and one human case, Morgenstern describes MCH as an effective and reliable hemostatic agent that is superior to all other agents previously used for superficial splenic injuries. Subsequently, Morgenstern reports the successful use of MCH in 13 of 15 patients to avert splenectomy following iatrogenic injury; in all instances, capsular avulsion occurred during a concurrent operative procedure and bleeding was not resolved with measures such as pressure, electrocoagulation, or other hemostatic substances in general use. In one of the two remaining patients, MCH was ineffective due to complications in product application; the other remaining patient had severe coagulopathy, which ultimately resulted in death. Among the 13 patients in which successful hemostasis was achieved, no reoperation was necessary. Similarly, Pachter et al describe successful splenorrhaphy by primary suture repair, often in conjunction with MCH, in 24 of 27 patients with splenic injury. In these 24 patients, no reoperations were necessary for bleeding, and no postoperative infections occurred. Extensive injury precluded successful splenorrhaphy in the remaining three patients.

These data helped to support the safety of splenorrhaphy with administration of hemostatic agents including...
MCH in selected patients to avoid the complications of splenectomy, such as increased susceptibility to life-threatening infection or venous and arterial vascular complications, and have supported the ongoing efforts to preserve the spleen in victims of trauma and iatrogenic injury.

**Use in Oral and Otolaryngologic Surgery**

MCH has been used extensively in difficult to reach anatomic sites such as nasal or oropharyngeal cavities. A case report published by Luetje describes the successful use of MCH for control of bleeding caused by inadvertent jugular bulb entry during postauricular tympanoplasty, while Morgan successfully achieved hemostasis with MCH following the removal of a glomus tumor in the middle-ear cleft. Wirthlin et al described the application of MCH to the palatal donor site of tissue autografts in six patients undergoing periodontal surgical procedures. The authors conclude that, while only limited data exist for these indications due to the nature of case reports, MCH is an excellent topical hemostatic agent in this surgical setting, requires no special preparation or application techniques, averts the need for additional methods to control bleeding, and frees the surgeon to focus on the recipient site and successful graft placement. Subsequently, Saroff et al reported the successful cessation of postoperative hemorrhage by MCH from the palatal mucosal donor site of free tissue autografts to repair mucogingival defects. Of 20 patients in this study, 10 received MCH as a dressing to cover the palatal donor site (experimental group) and 10 received a conventional periodontal dressing (control group). In the experimental group, visible bleeding ceased after 1 minute on average compared with nearly 20 minutes on average in the control group. After 10 minutes of treatment application, a significant 51% reduction ($p < 0.01$) was observed in the blood flow rate between the experimental and control groups. Additionally, no differences between the groups was observed in the rate or quality of healing nor in degree of pain perceived among the patients, and no postoperative complications occurred.

Taylor reported in 1980 the successful use of MCH to control anterior epistaxis in 44 of 61 patients; following initial control of bleeding by MCH in these 44 patients, rebleeding occurred within 72 hours in only 5 patients. Septal mucosal healing occurred within 4–8 days in the 44 MCH-controlled patients, while healing was slower (≥13 days) in the patients not achieving successful hemostasis. In this study, MCH achieved adequate hemostasis in only two of seven patients with thrombocytopenia, and the remaining five required packing. No complications occurred following the use of MCH, and patient discomfort was limited to nasal stuffiness. The authors concluded that MCH is a simple and effective form of treatment for anterior epistaxis that could be easily utilized in emergency rooms and clinics as an alternative to cautery or nasal packing. Similarly, Wakle described MCH as a valuable tool for emergency room physicians in management of epistaxis and post-tonsillectomy bleeding.

**Use in Cardiovascular Surgery**

Cardiovascular surgical procedures are highly associated with blood loss and the need for transfusions. Prophylactic use of pharmacologic agents such as tranexamic acid and $\varepsilon$-aminocaproic acid appears to be safe, efficacious, and cost-effective, and has gained popularity to control bleeding and reduce the risk of transfusion in cardiac surgery procedures. Despite moderate clinical use of established topical hemostatic agents such as MCH in this setting, the safety and efficacy of many of these agents have not been fully assessed by robust clinical trials. Fibrin sealants, adhesives, or flowable gelatin or collagen (with or without thrombin) may be preferred in cardiovascular surgery applications. Two newer MCH agents have been compared against oxidized cellulose for cardiovascular surgical procedures in recent years; however, the established nature of MCH in clinical practice has not required such a comparative investigation.

**Future Developments**

Opportunities for future study include better understanding of mechanisms and identification of robust hemostatic markers that may indicate bleeding risk during surgery. In a prospective observational study, Kimura et al analyzed the association between perioperative bleeding and the measurement of several hemostatic markers, including platelet, coagulation, fibrinolysis, and vascular functions to elucidate the mechanisms of hemostasis during spinal surgery. Results of the study demonstrate the importance of plasminogen activator inhibitor (PAI)-1, which regulates fibrinolysis, for perioperative hemostasis. In addition, obesity was identified as an important predictor for excess bleeding during surgery, perhaps due in part to platelet dysfunction. Association of perioperative risk and clinical outcomes may help to predict patients with increased risk for excessive bleeding during surgery and may greatly
inform the appropriate or targeted perioperative use of hemostatic agents.

The lack of evidence-based guidelines for absorbable hemostatic use presents a problem for product selection and an opportunity for future study. Ideally, functional evaluation of the available absorbable hemostatic agents would provide evidence for appropriate usage. For example, comparative evaluation in a swine spleen laceration model demonstrated both that the hemostatic effectiveness of Avitene™ Ultrafoam is comparable to that of Gelfoam with thrombin (Pfizer) and that the effectiveness of Ultrafoam is not improved with the addition of thrombin, which carries additional product costs and risks of immunogenicity. Additional cost-comparative studies may help to elucidate the health resource utilization outcomes of topical hemostats such as MCH versus standard of care or other agents when used in various surgical settings and in various patient populations.

Discussion
A myriad of topical absorbable hemostatic agents are available for clinical use; however, scarce clinical evidence exists comparing characteristics such as method of application, ease of use, timing and storage requirements, and clinical effectiveness of these agents. Critical evaluation of published literature can help to determine use and effectiveness of these agents in various surgical settings. Since becoming commercially available in 1973, MCH has shown to produce rapid hemostasis with positive patient outcomes and few reported complications in a wide variety of surgical specialties, including hepatic, orthopedic, splenic, oral, and otolaryngologic surgery. Successful clinical use of MCH in cardiovascular surgery is supported anecdotally, though relevant published literature in this specialty is scarce. In the future, functional evaluation and cost-comparative studies may help to elucidate the economic advantages of topical hemostats such as MCH used to control bleeding in the operating room.

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References
1. Karkouti K, Dattilo KM. Perioperative hemostasis and thrombosis. Can J Anaesth. 2006;53(12):1260–1262. doi:10.1007/BF03021588
2. Kimura A, Ohmori T, Sakata A, et al. Hemostatic function to regulate perioperative bleeding in patients undergoing spinal surgery: a prospective observational study. PLoS One. 2017;12(6):e0179829. doi:10.1371/journal.pone.0179829
3. Samudrala S. Topical hemostatic agents in surgery: a surgeon’s perspective. AORN J. 2008;88(3):S2–S11. doi:10.1016/S0001-2092(08)00586-3
4. Gabay M, Boucher BA. An essential primer for understanding the role of topical hemostats, surgical sealants, and adhesives for maintaining hemostasis. Pharmacotherapy. 2013;33(9):935–955. doi:10.1002/phar.1291
5. Stokes ME, Ye X, Shah M, et al. Impact of bleeding-related complications and/or blood product transfusions on hospital costs in inpatient surgical patients. BMC Health Serv Res. 2011;11:135. doi:10.1186/1472-6963-11-135
6. Emilia M, Luca S, Francesca B, et al. Topical hemostatic agents in surgical practice. Transfus Apher Sci. 2011;45(3):305–311. doi:10.1016/j.transci.2011.10.013
7. Gabay M. Absorbable hemostatic agents. Am J Health Syst Pharm. 2006;63(13):1244–1253. doi:10.2146/ajhp060003
8. Rose N, Stanley W, Holt S, Arnold D. Clinical experiences with microcrystalline collagen hemostatic material. J Am Osteopath Assoc. 1978;78(4):254–262.
9. Lee BY, Thoden WR, McCann WJ, Lewis JM, Madden JL, Clancy T. Microfibrillar collagen hemostat in the surgical management of decubitus ulcers. Contemp Surg. 1982;21(43–44):46.
10. Craig CC, Asher MA. Hemostasis in human iliac crest donor sites with microfibrillar collagen. Spine. 1977;2(4):313–317. doi:10.1097/00007632-19771200-00013
11. Schonauer C, Tessitore E, Barbagallo G, Albanese V, Moracci A. The use of local agents: bone wax, gelatin, collagen, oxidized cellulose. Eur Spine J. 2004;13(Suppl 1):S89–96. doi:10.1007/s00586-004-0727-z
12. Mason RG, Read MS. Some effects of a microcrystalline collagen preparation on blood. Haemostasis. 1974;3(1):31–45. doi:10.1159/000214040
13. Taylor MT. Avitene – its value in the control of anterior epistaxis. J Otolaryngol. 1980;9(6):468–471.
14. Wilkinson TS, Tenerny JH, Zufi D. The skin graft donor site as a model for evaluation of hemostatic agents. Plast Reconstr Surg. 1973;51(5):541–544. doi:10.1097/00006534-19730500-00009
15. Vistnes LM, Goodwin DA, Tenerny JH, Ksander GA, Gruber RP. Control of capillary bleeding by topical application of microcrystalline collagen. Surgery. 1974;76(2):291–294.
16. Kooby DA, Stockman J, Ben-Porat L, et al. Influence of transfusions on perioperative and long-term outcome in patients following hepatic resection for colorectal metastases. Ann Surg. 2003;237(6):860–869. doi:10.1097/01.SLA.0000072371.95588.DA
17. Ibrahim S, Chen CL, Lin CC, et al. Intraoperative blood loss is a risk factor for complications in donors after living donor hepatectomy. Liver Transpl. 2006;12(6):950–957. doi:10.1002/lt.20746
18. Lau WY, Lai EC, Lau SH. Methods of vascular control technique during liver resection: a comprehensive review. *Hepatobiliary Pancreat Dis Int*. 2010;9(5):473–481.

19. Berrevoet F, de Hemptinne B. Use of topical hemostatic agents during liver resection. *Dig Surg*. 2007;24(4):288–293. doi:10.1159/000103660

20. Clark WR, Leather RP. Hemostasis during liver resections. *Surgery*. 1970;67(3):556–557.

21. Coccolini F, Montori G, Catena F, et al. Liver trauma: WSES position paper. *World J Emerg Surg*. 2015;10:39. doi:10.1186/s13017-015-0030-9

22. Morgenstern L, Michel SL, Austin E. Control of hepatic bleeding with microfibrillar collagen. *Arch Surg*. 1977;112(8):941–943. doi:10.1001/archsurg.1977.0137000839005

23. Morgenstern L. Use of microfibrillar collagen. *Surgery*. 1982;92(3):563.

24. Geary JR, Kneeland Frantz V. New absorbable hemostatic bone wax; experimental and clinical studies. *Ann Surg*. 1950;132(6):1128–1137. doi:10.1097/00000658-195012000-00012

25. Himman F, Babcock KO. Local reaction to oxidized cellulose and gelatin hemostatic agents in experimentally contaminated renal wounds. *Surgery*. 1949;26(4):633–640.

26. Lindstrom PA. Complications from the use of absorbable hemostatic sponges. *AMA Arch Surg*. 1956;74(1):133–141. doi:10.1001/archsurg.1956.01280010135018

27. Harris WH, Crothers OD, Moyen BJ, Bourne RB. Topical hemostatic agents for bone bleeding in humans. A quantitative comparison of gelatin paste, gelatin sponge plus bovine thrombin, and microfibrillar collagen. *J Bone Joint Surg Am*. 1978;60(4):454–456. doi:10.2106/00004623-1978600400-00004

28. Ritter MA. A means of reducing postoperative blood loss in orthopaedic surgery: a preliminary report. *Orthop Rev*. 1978;7(10):119–120.

29. Giuliano AE, Lim RC. Is splenic salvage safe in the traumatized patient? *Arch Surg*. 1981;116(5):651–658. doi:10.1001/archsurg.1981.03380170127023

30. Morgenstern L. Microcryostalline collagen used in experimental splenic injury. A new surface hemostatic agent. *Arch Surg*. 1974;109(1):44–47. doi:10.1001/archsurg.1974.01360010030006

31. Morgenstern L. The avoidable complications of splenectomy. *Surg Gynecol Obstet*. 1977;145(4):525–528.

32. Pachter HL, Hofstetter SR, Spencer FC. Evolving concepts in splenic surgery: splenorrhaphy versus splenectomy and postsplenectomy drainage: experience in 105 patients. *Ann Surg*. 1981;194(3):262–269. doi:10.1097/00000658-198109000-00003

33. Morgenstern L. Let the preserver of spleens beware. *Surg Gynecol Obstet*. 1982;154(1):81.

34. Barrett J, Sheaff C, Abuabara S, Jonasson O. Splenic preservation in adults after blunt and penetrating trauma. *Am J Surg*. 1983;145(3):313–317. doi:10.1016/0002-9610(83)90189-7

35. Di Sabatino A, Carsetti R, Corazza GR. Post-splenectomy and hypersplenile states. *Lancet*. 2011;378(9785):86–97. doi:10.1016/S0140-6736(10)61493-6

36. O’Neal HR, Niven AS, Karam GH. Critical illness in patients with asplenia. *Chest*. 2016;150(6):1394–1402. doi:10.1016/j.chest.2016.03.044

37. Johnson LP. A review of the use of Avitene in otolaryngologic surgery. *Otalaryngol Head Neck Surg*. 1980;88(1):7–9. doi:10.1177/0194599880880102

38. Lueyte CM. Control of jugular bulb hemorrhage with microfibrillar collagen. *Ear Nose Throat J*. 1977;56(10):405–406.

39. Morgan PR, Johnson CQ, Morrison WV. Control of hemorrhage in glomus tympanicum surgery. *Ear Nose Throat J*. 1978;57(10):465–467.

40. Wirthin MR, Vernino AR, Hancock EB. The use of a new topical hemostatic agent. *J Periodontol*. 1980;51(4):225–227. doi:10.1902/jop.1980.51.4.225

41. Saroff SA, Chasens AI, Eisen SF, Levey SH. Free soft tissue autografts. Hemostasis and protection of the palatal donor site with a microfibrillar collagen preparation. *J Periodontol*. 1982;53(7):425–428. doi:10.1902/jop.1982.53.7.425

42. Walike JW, Chinn J. Evaluation and treatment of acute bleeding from the head and neck. *Otalaryngol Clin North Am*. 1979;12(2):455–464. doi:10.1016/S0030-6665(20)32479-8

43. Leff J, Rhee A, Nair S, et al. A randomized, double-blinded trial comparing the effectiveness of tranexamic acid and epsilon-aminocaproic acid in reducing bleeding and transfusion in cardiac surgery. *J Ann Card Anaesth*. 2019;23(3):265–272. doi:10.4103/aca.ACA_137_18

44. Vyas KS, Saha SP. Comparison of hemostatic agents used in vascular surgery. *Expert Opin Biol Ther*. 2013;13(12):1663–1672. doi:10.1517/14712598.2013.848193

45. Sirlik M, Eryilmaz S, Yazicioglu L, et al. Comparative study of microfibrillar collagen hemostat (Colgel) and oxidized cellulose (Surgicel) in high transfusion-risk cardiac surgery. *J Thorac Cardiovasc Surg*. 2003;126(3):666–670. doi:10.1016/S0022-5229(03)00042-4

46. Qerimi B, Baumann P, Husing J, Kneubel HP, Schumacher H. Collagen hemostat significantly reduces time to hemostasis compared with cellulose: COBBANA, a single-center, randomized trial. *Am J Surg*. 2013;205(6):636–641. doi:10.1016/j.amjsurg.2012.05.033

47. Avitene™ Microfibrillar Collagen Hemostat Instructions for Use, C. R. Bard, Inc. (Davol). Available from: www.bd.com/en-us/offerings/capabilities/biosurgery/hemostats/avitene-microfibrillar-collagen-hemostat. Accessed May 27, 2021.