Microporous Polysaccharide Hemospheres (MPH) for Cerebral Hemostasis: A Preliminary Report

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Key words
- Absorbable hemospheres
- Arteriolar bleeding
- Cerebral capillary
- Cerebral hemorrhage
- Cerebral oozing
- Microporous polysaccharide hemospheres (MPH)
- Surgical cerebral hemostasis
- Venous

Abbreviations and Acronyms
MPH: Microporous polysaccharide hemospheres
MRI: Magnetic resonance imaging

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OBJECTIVE: **To report preliminary experience in using Microporous Polysaccharide Hemospheres (MPH; Medafor, Inc, Minneapolis, Minnesota, USA) for cerebral and dural sinus hemostasis.**

METHODS: **Absorbable hemospheres for hemostasis were used in 10 patients (6 men, 4 women, mean age 56.2 years) undergoing cerebral procedures. The indication was corticosubcortical cerebral hemostasis after resection of meningiomas ($n = 5$) and gliomas ($n = 5$). In one case, absorbable hemospheres were applied for generalized oozing over the superior sagittal sinus. The surgical technique, time to bleeding control, and associated complications were recorded.**

RESULTS: **Effective hemostasis, defined as cessation of oozing bleeding, was achieved no later than 2 minutes after topical agent application in all patients except two, in whom the hemostatic application was repeated. Mean follow-up was 12 months. No patient developed allergic reactions or systemic complications in association with hemostatic absorbable hemospheres. There was no case of cerebral hematoma, swelling, or infection after surgery.**

CONCLUSIONS: **In this preliminary study, the direct application of absorbable hemospheres helped to control superficial cerebral bleeding, reducing the use of bipolar coagulation and shortening surgical time. Although use of absorbable hemospheres seems to be safe and effective, further investigations and prospective studies with longer follow-up are strongly recommended to arrive at final conclusions.**

INTRODUCTION

Hemostasis in cranial surgery is one of the most important skills that a neurosurgeon must acquire. Generalized oozing bleeding from multiple surface vessels of the dura mater and brain may be bothersome. Although bipolar cautery may arrest bleeding from the operative field, this method bears the risk of injury to normal nervous tissue, with deleterious neurologic deficits in some cases. Various hemostatic agents and techniques are used by neurosurgeons depending on the type, source, and location of the bleeding.

Arista AH consists of patented Microporous Polysaccharide Hemospheres (MPH) (Medafor, Inc, Minneapolis, Minnesota, USA), a plant-based, flowable powder engineered to dehydrate blood, enhancing clotting on contact (16). The commercial information of absorbable hemospheres states that their use is indicated in surgical procedures as an adjunctive hemostatic agent in the control of capillary, venous, and arteriolar bleeding. Their use facilitates the formation of an elastic, natural clot within a few minutes regardless of the patient's coagulation status. Absorbable hemospheres were first used as a topical dressing based on MPH technology for the control of bleeding wounds from traumatic injuries including cuts, lacerations, and puncture wounds in military scenarios (personal communication). This hemostatic agent has been made available on the market for the past few years, but its use is still limited to cardiovascular (3, 7), orthopedic (6), spleen and liver (9, 10) and renal surgery (2, 14). One research study, completed on a rat brain as a neurosurgical model, refers specifically to its intracranial application (5). This preliminary report was conducted to evaluate the efficiency, safety, and application of absorbable hemospheres in cranial cerebral procedures for superficial cerebral and dural hemostasis.

MATERIALS AND METHODS

Study subjects comprised a consecutive series of 10 patients 28–65 years old undergoing elective cranial surgery with a total of 12 MPH applications. The criterion for intraoperative inclusion of MPH was persistent or excessive bleeding that required more than standard techniques for hemostasis, such as bipolar coagulation and use of cellulose and collagen sponge, or the consideration that these methods were excessively time-consuming or could lead to injury of neural tissue. In each case, the decision to use absorbable hemospheres was made by the surgeon according to his preferences and the individual intraoperative situation.

The primary endpoint was defined as no hemorrhage in the operative field after application of hemostatic hemospheres.

The following data were collected and analyzed for all patients: age, sex, diagnoses, assessment of level of consciousness on admission, operative site, neurosurgical procedures, and length of procedure. Preoperative clinical laboratory tests included *(i)* complete electrolyte panel, *(ii)* liver function tests, *(iii)* full blood count with differential, *(iv)* prothrombin time, and *(v)* partial thromboplastin time. Evaluation of the following was also done: intraoperative source and type of bleeding (arteriolar, venous, or generalized venous oozing), time to bleeding control, and quantity of hemostatic hemospheres used. After surgery, patients were evaluated with the following assessments: laboratory tests (C-reactive protein, eritrosedimentation rate, alkaline phosphatase, blood urea, creatinine, and leukocyte count), neurologic examination, and adverse events at postoperative day 1, 7, and 30. All patients underwent postoperative cranial magnetic resonance imaging (MRI). The neuropsychologist, who was not involved in the initial clinical care of patients, performed the 3-month outcome evaluation.

RESULTS

Between January and August 2009, 10 consecutive patients (6 men, 4 women, mean age 56.2 years) were included in this study. The patients underwent a supratentorial craniotomy for brain tumor, five for cerebral convexity meningiomas and five for corticosubcortical gliomas. The lesion was located in the frontal area in five cases and in the parieto-occipital region in five cases. In all patients, the surgical method involved the use of standard techniques for hemostasis initially (ie, bipolar and suction cautery, oxidized cellulose, and collagen sponge); when these measures failed, were excessively time-consuming (>2 minutes of oozing), were considered risky, or were inadequate, a single dose (2–3 mL) of hemostatic hemospheres was applied directly to the site of bleeding.

Effective hemostasis, defined as cessation of bleeding after topical hemostatic agent application, was achieved no later than 2 minutes in all except two patients with continuous cerebral oozing (**Figure A** and **B**). In these latter cases, the bleeding

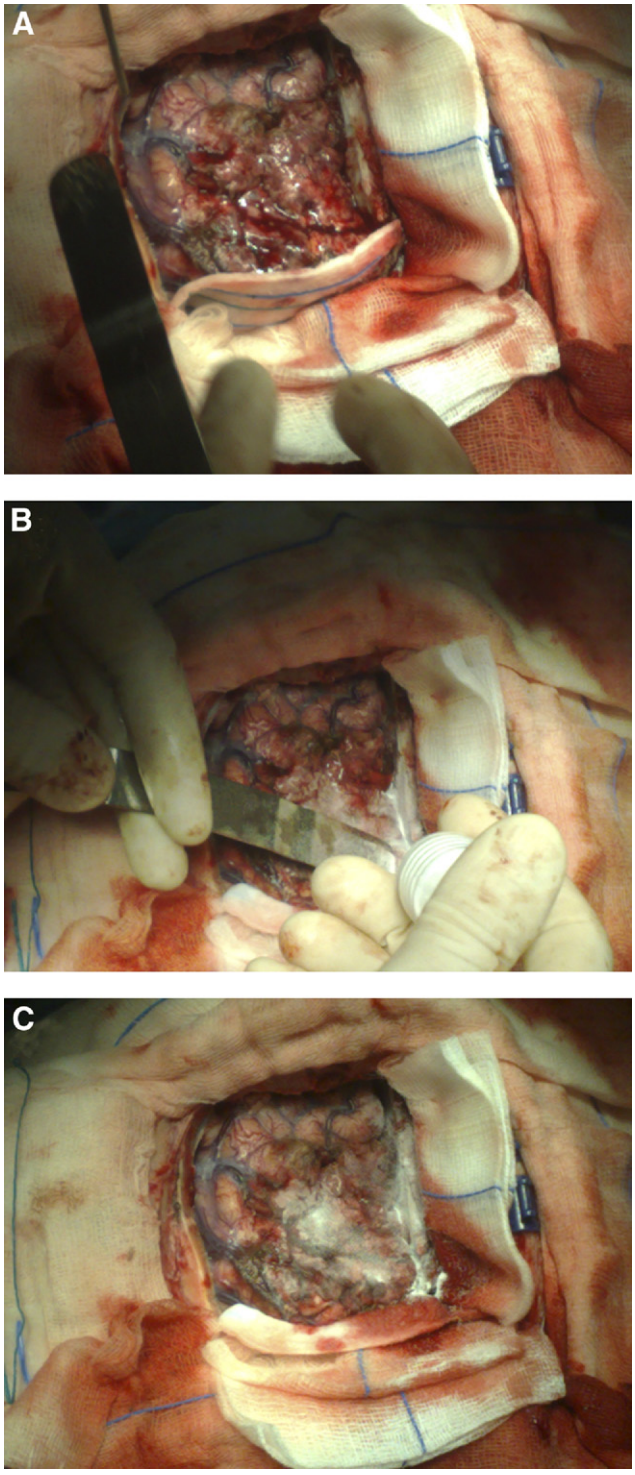

Figure. (A) Photograph depicting diffuse bleeding over the cortex after resection of a meningioma in the central area. **(B)** Application of MPH hemostat over cerebral oozing. **(C)** A cottonoid is applied over the hemostat template; after less than 2 minutes, the cottonoid is removed without irrigation, leaving excess MPH hemostat on site and without evidence of bleeding.

was finally stopped after a new application of MPH. In one case, bleeding occurred from a small tear along the superior sagittal venous sinus. The bleeding could not be repaired by suture; a small piece of oxidized cellulose was placed over the bleeding gap of the venous sinus, and hemostasis subsequently was achieved by additional application of MPH over the cellulose and the rest of the sinus. The conformation of the cellulose prevented the hemostatic hemospheres from entering the underlying venous sinus, avoiding the possibility of sinus thrombosis and embolism.

Mean follow-up was 12 months (range 7–15 months), and clinical and neurologic examinations were performed on day 1 postoperatively, at discharge, and 1 month after discharge. All identified neurologic deficits were already present before surgical intervention or were known as potential complications of the type of operation performed, as in the case of central area meningioma invading the subjacent cortex. In this latter case, the patient developed a new upper extremity motor deficit after a complete resection of the lesion. In all cases, neuropsychologic evaluations were unchanged or improved. No patient developed fever, allergic reactions, or systemic complications such as embolism or distant infections. Neurosurgical wound infections were not recorded.

Postoperative MRI was performed at discharge or after 1 month in all patients. MRI with contrast agent was done after 1–3 months. Normal postoperative conditions were found; there were no signs of acute rebleeding, hematoma, inflammation, perifocal edema, or scar formation attributable to the hemostatic sealant. In one case of malignant glioma, the patient developed status epilepticus 3 days after surgery, with normal postoperative changes on brain computed tomography scan. Seizures were controlled pharmacologically, and the patient was discharged after 20 days. Clinical laboratory test results (mean values) revealed almost no differences between the preoperative data compared with the findings obtained at 1 day, 1 week, and 1 month after surgery.

DISCUSSION

We report here our preliminary experience with the use of MPH for cerebral hemostasis in 10 patients with corticosubcortical cerebral oozing. We observed adequate hemostasis in all patients except two, in whom the hemostatic MPH application was repeated after 2 minutes to stop the persistent oozing. We also used MPH in one case over the dural sinus. MPH is an absorbable hemostatic powder derived from purified plant starch polymer and free of all biologic components (7, 9, 10). When applied directly to the source of bleeding, it begins on contact accelerating the intrinsic clotting cascade and reaching its maximum volume acts as a molecular sieve to extract fluids from blood instantly on contact. This powerful osmotic action causes the particle to swell and concentrates serum proteins, platelets, and other formed elements on its surface (5, 16). The particles and their coating of compacted cells create a scaffold for the formation of a fibrin clot within a few minutes of application.

In clinical studies, MPH has produced no adverse reactions (1, 2, 16), and it is readily absorbed and enzymatically cleared from the tissue within 24–48 hours. In an experimental study (5) comparing commonly used topical hemostatic agents in brain tissue defects, residual material was not present with Arista, contrasting with the presence of residual material in lesions in the Avitene (microfibrillar collagen; Alcon, Inc., Hünenberg, Switzerland), FLOSEAL (gelatin matrix thrombin sealant; Baxter Healthcare Corp., Deerfield, IL, USA), and Surgicel (oxidized cellulose; Ethicon, Inc., West Somerville, NJ, USA) cohorts. Avitene and FLOSEAL have also shown a propensity for causing granuloma formation, but there was no evidence of this with Arista and Surgicel.

In neurosurgery, mechanical measures to stop intraoperative bleeding are limited if difficulties are encountered during bipolar coagulation. Although bipolar coagulation frequently provides control of bleeding, it is time-consuming and leads to a wide enlargement of the working channel (11, 15). Hemostatic agents may be difficult to apply on the walls of the operative cave through a narrow operating channel. MPH has a plastic device applicator, which is a lightweight, long, flexible tube, to provide delivery of the hemostatic powder deep into hemorrhagic wounds and into difficult-to-reach locations. This applicator is similar to the FLOSEAL (4, 8). Capillary ooze is a general problem at the end of tumor removal, but the use of MPH solved the problem expeditiously in all our cases. We injected this agent with a syringe tip, and the powder nature of the MPH enabled the material to conform to any irregular surgical cave geometry. In our opinion, it is less precise for delivery than FLOSEAL (8), given its powder nature. The MPH hemostat is ready to use, however, requiring no mixing, no additional patient blood or other components, and no special handling or storage conditions. Excess granular material not incorporated in the hemostatic clot was carefully removed by application of a cottonoid, without disrupting the hemostatic seal and without normal saline washing. Mainly because it degrades rapidly, MPH does not promote infection or any foreign body reaction as other materials may (12, 13, 17). The cost is similar to other hemostatic agents on the market.

One potential concern when using any biologic hemostatic agent is the risk of virus transmission (12); however, MPH is a nonbiologic hemostat. Also, there is a theoretical danger of aggravating perilesional brain edema when increasing any local powder concentration; such edema may partially result from a direct opening of the blood-brain barrier. In our series, after application of MPH, in less than 1 minute in most cases, the excess material was removed by gentle suction and application of a cottonoid, reducing the concentration of formed clot and leaving a white clear operative field (**Figure C**). A control head computed tomography scan performed after surgery showed absence of abnormal perilesional edema formation in all cases. Control MRI with contrast agent did not show abnormal enhancement.

Of concern with hemostatic medications is the potential of thrombotic complications; there are isolated unpublished case reports of thromboembolic complications secondary to injection of gelatin hemostatic matrix over a bleeding venous sinus tear. In this case, using oxidized cellulose or gelatin sponge as a web to prevent migration of MPH into the venous sinus, we did not observe embolism or sinus thrombosis in the treated patient. The presence of Surgicel over the bleeding sinus tear permitted adequate coherence of the hemostatic powder with effective hemostasis, and, excess of MPH was not removed from the bleeding

site in this case. The difficulty with this strategy in the assessment of MPH efficacy is the confounding effect of the previously applied agents. We mainly used MPH, however, in a single dose (2–3 mL), when superficial oozing was encountered. Because we used bipolar cautery, oxidized cellulose, and collagen sponge concomitantly, we cannot evaluate the sole hemostatic effect of MPH. The difficulty in the assessment of MPH efficacy with this strategy is the confounding effect of the previously applied agents. We found MPH particularly useful in cases of arteriolar bleeding at the cortex. Instead of using bipolar coagulation, we found the powder nature of MPH controlled hemostasis adequately.

After evaluation in a multicenter clinical trial, MPH has received CE certification, and it has recently been approved for clinical use by the U.S. Food and Drug Administration (FDA) (5, 10) for most types of surgery, including cardiovascular (3), orthopedic (6), nose and throat (1), and general surgery (9) applications. Safety and biocompatibility after direct application of MPH to neural tissue has been shown in preclinical studies (2, 5, 7 14). Inflammatory reaction to MPH in the brain was reported to be equivalent to the reaction of other commonly used neurosurgical hemostatic agents with a short median time to biodegradation compared with the other implanted hemostatic materials (5). In this preliminary report of 10 cases, there was no evidence of any immune-mediated coagulopathy after exposure to hemostatic powder, and there were no adverse events related to the direct application of the hemostatic agent to the brain.

MPH marketing materials advertise hemostatic properties "regardless of the patient's coagulation status," which, in our opinion, is not true because it cannot be tested specifically. The hemostatic efficacy of MPH in the setting of known hypercoagulable states, such as cancer, meningiomas, or other coagulopathies, cannot be examined. Although superficial cerebral application of MPH seems to be safe and effective, further investigations, longer follow-up periods, and prospective trials are strongly recommended to arrive at final conclusions.

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