

Hemostatic Agent Microporous Polysaccharide Hemospheres (MPH) Does Not Affect Healing or Intact Sinus Mucosa

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Objectives/Hypothesis: Absorbable hemostatic agents are used routinely following sinus surgery. Recent studies suggest that current biomaterials, such as FloSeal Matrix Hemostatic Sealant (Fusion Medical Technologies, Mountain View, CA) may interfere with mucosal regeneration. This study was designed to evaluate the effects of Microporous Polysaccharide Hemospheres (MPH, Medafor, Inc., Minneapolis, MN), a novel rapidly-absorbing hemostatic powder, on healing and intact sinus mucosa.

Study Design: Prospective, controlled study using the rabbit model.

Methods: Both maxillary sinuses of 14 New Zealand white rabbits were surgically opened. The mucosa of 10 rabbits were stripped bilaterally, and the left sinus of each was then treated with either MPH or FloSeal. The mucosa of four additional rabbits were incised but otherwise remained undisturbed. Again, the left sinus of each of the four additional rabbits was treated with either MPH or FloSeal. The right sinus served as an untreated control (stripped or intact) in both arms of the study. Animals were recovered and euthanized 2 weeks later. Specimens were examined by a blinded pathologist using light microscopy.

Results: Untreated regenerated mucosa showed expected areas of sparse cilia, mild serous gland reduction, and fibrosis. MPH-treated sinuses showed no significant changes compared to respective controls, and no MPH substance was identified. In contrast, regenerating mucosa treated with FloSeal showed extensive loss of cilia, inflammation, and fibrosis. Residual FloSeal particles were present within the sinus cavity and grossly incorporated within healing mucosa. Unexpectedly, intact mucosa exposed to FloSeal showed similar findings.

Conclusions: Absorbable hemostatic materials have starkly different effects on mucosal healing. Unlike other agents, MPH is rapidly cleared and has no negative effects on healing or intact sinus mucosa.

Key Words: Endoscopic sinus surgery, paranasal sinus, absorbable biomaterials, postoperative hemostasis, rabbit.

Laryngoscope, 118:1265–1269, 2008

INTRODUCTION

Absorbable hemostatic agents are now used routinely following endoscopic sinus surgery (ESS). Similar to traditional non-absorbable packing, biomaterials provide necessary postoperative hemostasis, but offer the advantage of improved patient comfort as they do not require removal. Although “biodegradable,” currently available agents take weeks to completely resorb, thereby exposing the regenerating mucosal and submucosal tissues to foreign material for extended periods of time. Animal studies evaluating the effects of these agents on healing sinus mucosa have repeatedly shown that absorbable biomaterials negatively influence the regeneration process of sinus mucosa and are actually frankly incorporated within the healing mucosa itself.^{1,2} The associated inflammatory response is believed to impair normal mucosal regeneration and contribute to the formation of scar tissue. In fact, recent investigations in humans have demonstrated a significantly increased risk of synechiae formation with the use of absorbable biomaterials following sinus surgery.^{3–5} The ideal packing agent for ESS, therefore, remains obscure.

Microporous Polysaccharide Hemospheres (MPH, commercially available as Arista and Hemaderm; Medafor, Inc., Minneapolis, MN) is a novel absorbable agent that has been shown to be effective for hemostasis in cardiac, urologic, and dermatologic surgery.^{6–9} Other currently available hemostatic agents function by either providing clotting components (e.g., fibrin glues) or a surface for clotting to be stimulated (for example, collagen, gelatin sponge, oxidized cellulose). MPH particles are produced from purified potato starch and act as a molecular sieve to quickly extract fluids from blood. This osmotic action causes the microporous

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Editor's Note: This Manuscript was accepted for publication February 8, 2008.

Financial Support: This project was funded in part by an educational grant from Medafor, Inc.

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DOI: 10.1097/MLG.0b013e31816c7bc9

particles to swell and concentrate serum proteins, platelets, and other formed elements on their surfaces. The spherical particles with diameters ranging from 30 to 100 μm and their coating of compacted cells create a scaffolding for the formation of a fibrin clot. Importantly, MPH is fully resorbed and enzymatically cleared rapidly from the wound site within only 24 to 48 hours. MPH is now available in a formulation for ESS that has been approved by the U.S. Food and Drug Administration.

This study was designed to evaluate the effects of MPH on healing and intact sinus mucosa using a rabbit model. For comparison, we used FloSeal Matrix Hemostatic Sealant (Fusion Medical Technologies, Mountain View, CA), a commonly used bovine-derived gelatin matrix containing a thrombin component which is resorbed over 6–8 weeks. The use of FloSeal in healing sinuses has been studied previously in several animal and human studies.^{1,4–5}

MATERIALS AND METHODS

Fourteen New Zealand white rabbits (3–5 kg each) were obtained from a commercial vendor and acclimatized for several weeks. The rabbits were anesthetized, and both right and left maxillary sinuses were surgically opened through a midline incision using a previously established surgical technique.¹⁰ In 10 rabbits, the mucosa of both maxillary sinuses was stripped. The left maxillary sinus in five of these animals was treated with MPH and the left maxillary sinus in the other five was treated with FloSeal. The right maxillary sinus in each of these animals was irrigated with normal saline and served as an internal mucosa-stripped control. In the mucosa-intact arm of the study, the maxillary sinuses of the remaining four rabbits were opened and the anterior wall mucosa was incised but the remainder of the mucosa was left undisturbed. MPH was applied to the left antrum in two animals, and FloSeal was placed in the other two. The right sinuses were once again untreated and irrigated with normal saline to serve as mucosa-intact controls. Animals were recovered and humanely euthanized 2 weeks later. Specimens were examined under light microscopy and scored by a blinded pathologist. The results of each group were pooled for uniformity. This study was approved by the Institutional Animal Care and Use Committee at Saint Louis University.

Surgical Procedure

Animals were preanesthetized with ketamine/xylazine (10/3 mg/kg SQ). Intravenous access was obtained by placing an indwelling catheter in the right marginal ear vein. Rabbits were intubated and placed on isoflurane anesthesia (1%–3%) using intermittent positive-pressure ventilation. Vital signs were obtained and recorded using intraoperative monitoring equipment. Intraoperative isotonic fluids (0.9% potassium chloride) were provided intravenously at a rate of 12 mL/kg/hour. A midline nasal dorsum incision was made, exposing the underlying nasal bones. Skin and periosteal flaps were elevated laterally to expose the maxillary sinuses. The anterior wall of the right and left maxillary sinuses was then removed using a drill and cutting burr. The osteotomy was enlarged using a rongeur. Depending on which experimental group the rabbit was randomly assigned, the mucosa was removed using a periosteal elevator and forceps or was simply incised anteriorly to afford access to the sinus interior for treatment. Care was taken to leave the natural outflow tract undisturbed in all cases. The left sinus was then treated with either FloSeal or MPH according to package insert instructions. The right maxillary sinuses in all animals were similarly exposed, irrigated with 5 mL of normal saline, and left untreated to serve as internal controls for both arms of the study. The overly-

ing periosteum and skin were closed in a single layer with running 4.0 nylon sutures and local anesthetic (2% bupivacaine) was injected into the edges of the incision. Systemic analgesia was achieved with buprenorphine 0.5 mg/kg subcutaneously every 12 hours for 2 days postsurgery and as needed afterwards. Systemic antibiotics (enrofloxacin 5 mg/kg subcutaneously, once per day) were administered for 5 days. There were no intraoperative or postoperative complications.

Tissue Preparation

After allowing 14 days of healing, the animals were euthanized with intravenous pentobarbital (100 mg/kg). Tissue harvest was performed by removing both maxillary sinuses en bloc with a sagittal saw. Initial tissue preparation included immediate fixation in 3% glutaraldehyde and 1.5% paraformaldehyde in 0.1 mol/L phosphate buffer for 24 hours. Decalcification was performed in 10% ethylenediamine tetra-acetic acid-tris buffer for 4 weeks. The tissue was embedded into glycol methacrylate blocks, and sectioned at 3 μm in the transverse plane to visualize the entire sinus walls in cross-section. Stains were performed with methylene blue alone, methylene blue and basic fuchsin, as well as hemoxlin and eosin (H&E). Slides were then viewed under light microscopy. Sections were examined and systematically graded for the following histologic features: degree of ciliary loss, presence of foreign body, fibrosis of lamina propria, osteoneogenesis of underlying bone, inflammation, and serous gland presence. Evaluation of tissue specimens was performed in a random order by a blinded, independent pathologist.

RESULTS

Gross Examination

Direct visualization of the specimens did not reveal any differences between the MPH-treated sinuses and the untreated sinuses. The sinus mucosa appeared the same, and there was no evidence of any foreign material identifiable within the interior of the MPH-treated sinuses. FloSeal-treated maxillary sinuses were obviously different from controls. The FloSeal-treated sinuses contained significant amounts of FloSeal substance within the sinus cavities, and the mucosa appeared grossly thickened when viewed in cross-section compared to the contralateral untreated sinus (Fig. 1). No polypoid changes or signs of infection were noted in any of the specimens.

Controls

As previously noted, all rabbits in this study had the right maxillary sinus opened but untreated to serve as an internal control, regardless of whether the mucosa was stripped or left intact. Described by others^{1,10–13} and demonstrated in Figure 2A, the normal respiratory mucosa of the maxillary sinus in the rabbit consisted of layered pseudostratified ciliated epithelium with goblet and basal cells on the basal lamina. Numerous blood vessels and serous glands are found deep to the basal lamina. In comparison, the untreated mucosa which regenerated after being stripped, showed areas of sparse and dysmorphic cilia associated with a mostly continuous epithelium. Focal areas of ciliary loss on surface epithelial cells, with “tufts” of normal length and some abnormally shortened cilia spreading laterally to cover adjacent gaps in the ciliary surface were identified (Fig. 2B). There was mild submucosal gland reduction and minimal fibrosis of the

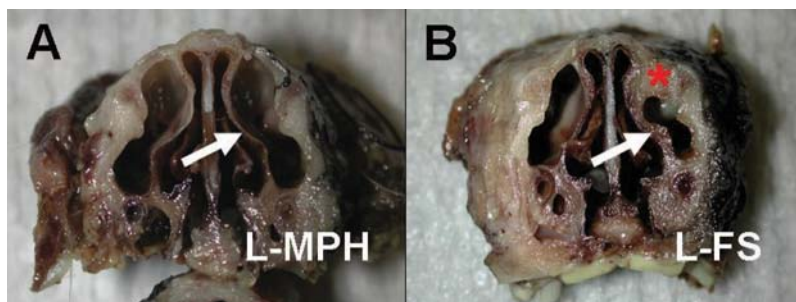


Fig. 1. Sinuses treated with Microporous Polysaccharide Hemospheres (MPH) and FloSeal seen in gross cross-section. There is no difference in MPH-treated sinus (white arrow) and untreated contralateral control. (A) FloSeal-treated side (FS) (B) shows significant residual substance in sinus (*) with mucosal thickening (arrow).

lamina propria. Small foci of reactive bone were also seen. No significant inflammation or foreign body reactions were present.

Sinuses Treated With Microporous Polysaccharide Hemospheres (MPH)

The epithelium of MPH-treated sinuses in the mucosa-intact rabbits was not significantly different from untreated intact rabbit maxillary sinus mucosa. No foreign material or foreign body reaction was noted in any MPH-treated sinuses. Similar to the untreated mucosa-stripped specimens, the stripped MPH-treated sinuses also showed minor ciliary changes, mild submucosal gland reduction, and fibrosis with foci of osteoneogenesis (Fig. 3). On blinded evaluation, the mucosa-intact and mucosa-stripped specimens that had been treated with MPH were indistinguishable from their respective, untreated controls in any of the histologic features studied.

FloSeal-Treated Stripped Mucosa Specimens

Pathologic examination of FloSeal-treated stripped mucosa specimens showed disrupted and disorganized epithelial regrowth with very sparse cilia. Foreign body material was seen on both sides of the epithelium (intraluminal and submucosal), with incorporation of the foreign material into the lamina propria. Granuloma formation was also noted around the foreign body as illustrated in Figure 4. There was severe fibrosis of the lamina propria and a dense acute and chronic inflammatory infiltrate was seen throughout. This significantly increased the thickness of the sinus wall when compared to nontreated controls. Extensive osteoneogenesis was identified along with a dearth of serous glands. Evaluation with H&E staining demonstrated prominent eosinophilia as a component of the inflammatory reaction (Fig. 5). This was a consistent

feature that was not identified with the other staining techniques.

FloSeal-Treated Mucosa-Intact Sinuses

In comparison to untreated mucosa intact controls, sinuses in which FloSeal was applied to intact mucosa displayed an abnormal and metaplastic epithelium with a large decrease of cilia. A moderate degree of submucosal fibrosis with loss of serous glands, osteoneogenesis, and chronic inflammation of the underlying lamina propria were seen. Residual FloSeal substance was seen intraluminally, but foreign body particles were also readily identified deep to the surface epithelium along with a chronic inflammatory infiltrate (Fig. 6). Eosinophilia was once again noted with H&E staining. Although less extensive, the changes noted in the FloSeal-treated mucosa-intact specimens were similar to those observed in the sinuses which were stripped and then treated with FloSeal. This was a very unexpected finding.

DISCUSSION

Bioabsorbable hemostatic materials are engineered to be resorbed by the host over time. The prolonged presence of an absorbable agent during the initial phases of wound healing is suspected to be a major factor in the incorporation of the material into regenerating mucosa which may interfere with normal healing.¹ Persistence of any material within the sinuses through the early recovery period also complicates postoperative debridements which are customarily performed 5 to 14 days following routine ESS. We hypothesized that unlike FloSeal which takes weeks to resorb, MPH, by virtue of its composition, mechanism of action, and rapid absorption profile, would not interfere significantly with mucosal healing in the sinuses. We did not suspect that either agent would

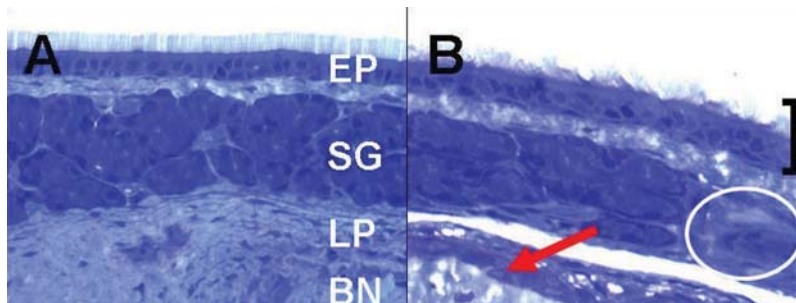


Fig. 2. (A) Normal rabbit mucosa stained with methylene blue (200× original magnification) showing ciliated epithelium (EP), serous glands (SG), lamina propria (LP) and normal bone (BN). (B) Untreated regenerated mucosa after stripping shown with methylene blue stain (200× original magnification) is adjacent. Abnormal and tufted cilia (], osteoneogenesis (arrow) and reduction in serous glands (circle) are shown.

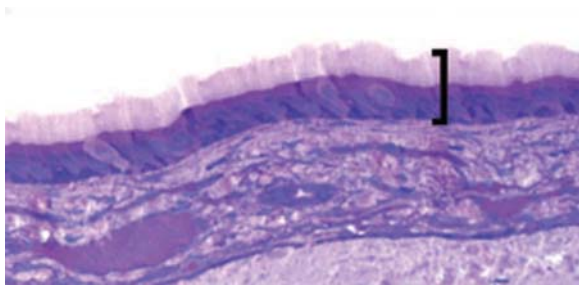


Fig. 3. Methylene blue and basic fuchsin stain (200× original magnification) showing stripped mucosa treated with Microporous Polysaccharide Hemospheres (MPH) which are similar to untreated stripped controls (compare to Fig. 2B).

impact intact sinonasal mucosa, although this specific question had not been addressed by any prior studies on biomaterials to date.

This study confirms that MPH is rapidly and completely cleared when placed within traumatized sinus cavities. There was no gross or microscopic evidence of MPH substance in either the mucosa-intact or mucosa-stripped arms of the study at the 2-week endpoint. Importantly, there were no histologic signs of incorporation of MPH into regenerating mucosa in any of the specimens exposed to this material. Further, histologic examination revealed no significant changes in the morphology of the regenerating epithelium exposed to MPH when compared to untreated stripped mucosal controls. MPH does not appear to negatively affect intact or healing sinus mucosa in the rabbit model. In fact, its presence in healing sinuses is associated with markedly less reactionary fibrosis and inflammation than longer lasting agents such as FloSeal.

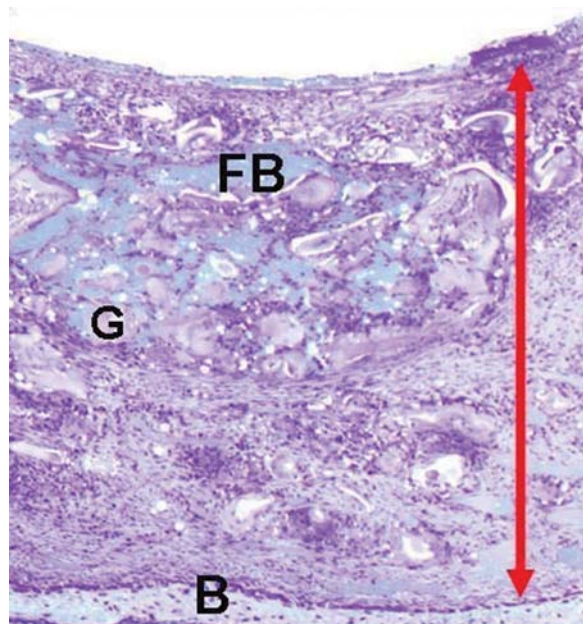


Fig. 4. FloSeal-treated stripped-mucosa (methylene blue stain, 100× original magnification) demonstrating extensively thickened mucosa (arrows). Significant osteoneogenesis (bone = B), granuloma formation (G), and foreign body (FB) are noted.

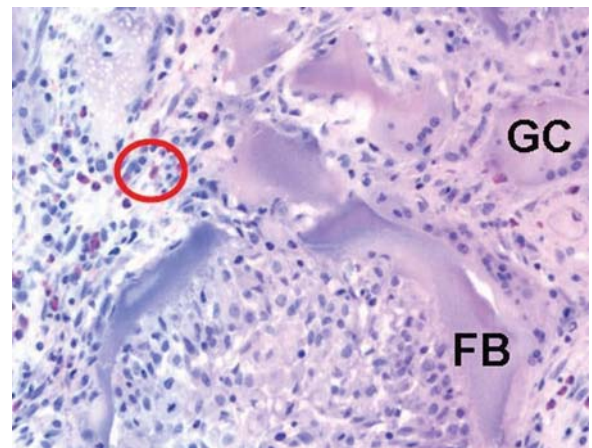


Fig. 5. FloSeal-treated stripped mucosa (original magnification 400×) stained with hematoxylin and eosin (H&E) exhibiting prominent eosinophils (circle), giant cells (GC), and incorporated foreign body (FB).

While MPH has been studied in other areas of the body,⁶⁻⁹ there are no previous studies evaluating the use of this substance in the sinonasal tract. In comparison to other available hemostatic agents that are derived from human or bovine sources, MPH which is made from purified potato starch, is hypoallergenic and carries no inherent risk of disease transmission.⁹ MPH comes in a ready-to-use container and does not require any time-consuming preparation, heating, or premixing.

Maccabee et al.¹ previously investigated long-lasting absorbables, FloSeal and Merogel (Medtronic-Xomed Surgical Products, Jacksonville, FL) using the rabbit model. They found that both substances significantly interfered with the re-epithelialization process and were frankly incorporated into healing sinus mucosa. Osteoneogenesis, fibrosis, and inflammation were demonstrated histologically in their experiments as well. Unlike the methodology used by this group, we stained all specimen slides with H&E in addition to other stains. Evaluation with H&E staining permitted identification of prominent eosinophilia as a component of the inflammatory reaction within

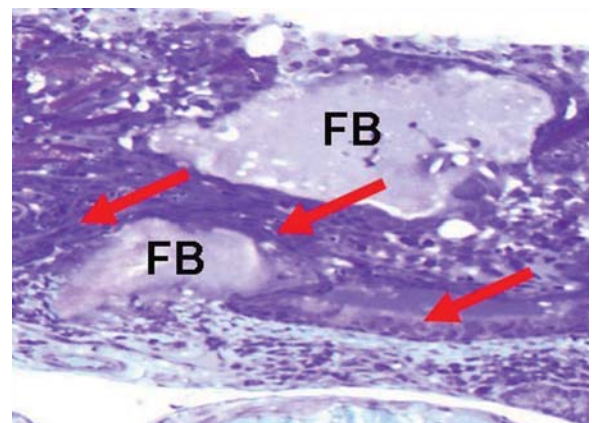


Fig. 6. FloSeal-treated mucosa-intact specimen (methylene blue stain, 200× original magnification) demonstrating foreign body (FB) on both sides of the epithelium (arrows).

all of the specimens treated with FloSeal. This novel finding suggests that there may be an allergic response in addition to the foreign body reaction involved with this substance in the rabbit. It is unknown whether the same cell populations would be present in humans. Given that FloSeal is an animal-product derivative (as are most bio-absorbables), it is certainly possible that an allergic process could occur in human subjects as well.

Whereas previous research efforts have focused on the impact of biomaterials on regenerating mucosa, our study is the only one in the literature to examine the interaction of biomaterials with intact sinus mucosa as well. Our study revealed that FloSeal can also cause an intense inflammatory reaction and become incorporated within the respiratory epithelium, even when it is applied to *intact* sinus mucosa. This was an unexpected but very significant finding. The ability of FloSeal to incite an intense inflammatory reaction in the face of an intact mucosal barrier would appear to be less related to its resorption kinetics and more related to an innate “proinflammatory” or irritating effect of this substance on the host tissues. As noted, in addition to extensive submucosal fibrosis and gland reduction, foreign body reaction, and eosinophilia, foreign body particles were also identified below the epithelium in the FloSeal-treated sinuses where the mucosa was left intact. The mechanism for this is unclear, but it likely represents the host’s defense systems attempting to absorb and degrade the foreign material which is unable to be removed by normal mucociliary clearance.

Recently, various authors have raised concerns over the routine use of FloSeal as a hemostatic agent following ESS. A blinded study by Chandra et al.^{4,5} found that while achieving excellent hemostasis, the application of FloSeal following ESS in human patients was associated with a higher incidence of postoperative granulation tissue and synechiae formation. Shrime et al.³ also found increased synechiae with the use of FloSeal. The results of our study further amplify concerns over the use of this substance for endonasal applications. Further clinical data are needed. If absorbable hemostatic agents with slow absorption kinetics such as FloSeal are to be used following ESS, it would seem prudent to institute frequent saline irrigations and thorough postoperative debridement(s) to diminish the amount and duration of exposure of foreign materials to healing sinus mucosa. Next generation biomaterials such as MPH, which are rapidly and completely resorbed, appear to offer significant and distinct advantages over currently available options.

A major limitation of this study is that it used an animal model, and therefore results cannot be directly extrapolated to humans. Unlike in the clinical setting, there were no postoperative irrigations or debridements performed, and the biomaterials were applied to nondiseased sinuses. The study endpoint of 2 weeks is relatively short and it is accepted that the histologic changes noted during this time frame may continue to evolve or potentially even reverse over time. Despite these limitations, however, the results of this controlled study comparing MPH to FloSeal demonstrated that MPH has significantly

less adverse effects on regenerating and intact sinonasal mucosa. Based on the encouraging findings of this work, clinical trials investigating the effect of MPH in human subjects following ESS are warranted.

CONCLUSION

Absorbable hemostatic materials have starkly different effects on mucosal healing and intact sinus mucosa in the rabbit model. Unlike other previously studied absorbable biomaterials, MPH is rapidly and completely resorbed and is not incorporated into regenerating sinus mucosa. This starch-based material does not appear to have any negative effects on healing or intact sinonasal mucosa, and this preliminary study supports its further use.

Acknowledgments

The authors would like to thank Wanda Morganthaler and Nancy Roth for surgical assistance and care of animals.

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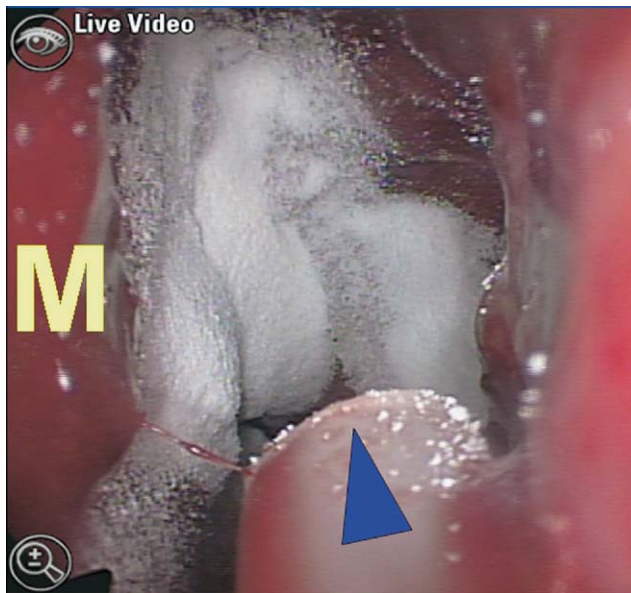


Figure 2 Endoscopic view of applicator (*triangle*) applying MPH powder into the left middle meatus (M = left middle turbinate) at the conclusion of sinus surgery.

icant postoperative bleeding that required an ER visit, hospital admission, or nasal packing/cautery was encountered. At the one week debridement, no gross MPH substance was detected in any of the sinus cavities. Synechiae formation was noted in eight (12.3%) of 65 patients during the study period. Of these, only two (3.1% overall) were grade 2 and required lysis, whereas the majority (6 of 8) were grade 1 and not clinically significant. There were no adverse reactions.

DISCUSSION

The use of MPH for hemostasis has been reported in a variety of specialties, but this is the first description of its use in otolaryngology. Available hemostatic agents function by either providing clotting components (eg, fibrin glues) or a surface for clotting to be stimulated (eg, collagen, gelatin sponge, oxidized cellulose). MPH particles have a diameter of 30 to 100 μm and act as a “molecular sieve” by extracting fluids from blood. This concentrates platelets and other elements that promote the formation of a fibrin clot. MPH powder is in a ready to use container that does not require any preparation, heating, or mixing. In comparison to other biomaterials that are derived from animal sources, MPH, which is made from purified potato starch, is hypoallergenic and carries no inherent risk of disease transmission.⁴

Based on this initial study, MPH appears to be a safe hemostatic agent that works very quickly in sinus cavities. Its unique composition, mechanism of action, and resorption profile offer significant advantages over other biomaterials. Most notably, MPH is rapidly and completely cleared when placed within postsurgical sinus cavities, which limits its exposure to healing mucosa. The adhesion

rates observed in this preliminary study are favorable in comparison with those reported in the literature for ESS performed without the use of any bioabsorbables.⁵ Although promising, further data are needed to critically examine the potential risk of adhesion formation with the use of this product. Controlled studies to compare it against traditional nonabsorbable packing and to no packing at all are required to evaluate the efficacy and impact of MPH on surgical outcomes after ESS.

CONCLUSION

This is the first description of the use of hemostatic powder MPH after endoscopic sinus surgery. MPH appears to be an easy to use, fast-acting agent that is rapidly cleared from the sinuses. Its unique composition, mechanism of action, and clearance profile offer significant advantages. Further studies to examine the efficacy and potential risk of synechiae formation with the use of this product after sinus surgery are needed.

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AUTHOR CONTRIBUTION

Entire work.

FINANCIAL DISCLOSURE

None.

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