Advances in Absorbable Biomaterials and Nasal Packing

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KEYWORDS

• Endoscopic sinus surgery • Biomaterials • Hemostasis
• Chronic rhinosinusitis • Adhesion

BACKGROUND: NASAL PACKING IN ENDOSCOPIC SINUS SURGERY

Endoscopic sinus surgery (ESS) is a continuously developing field that has had many exciting developments in the past 3 decades. Advances in the understanding of functional sinus surgery and mucosal-sparing techniques has driven an interest in the management of the post-ESS nasal and sinus cavity to achieve more rapid postoperative reepithelialization and reciliation. Many surgeons believe that the postoperative treatment regimen is as important as the surgery.

All sinus surgeons have the common objective of achieving excellent hemostasis and postoperative healing that avoids adhesion formation and lateralization of the middle turbinate; however, little agreement exists on how this is best achieved. The use of various interventions, from removable nasal packing, absorbable nasal packing, to no packing at all, is widely debated.

Nasal packing has been the traditional method of controlling ongoing bleeding after surgery to the paranasal sinuses. Additionally, nasal packing has been used to prevent adhesion formation, middle turbinate lateralization, and restenosis after surgery. Unfortunately, removable nasal packing has been rated by patients to be the most unpleasant aspect of the ESS surgical experience.[1,2] Some surgeons advocate not packing the middle meatus,[3] whereas others continue to use this technique to prevent middle turbinate lateralization.[4] Controversy still exists about whether to pack or not.

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This article reviews the literature on the use of absorbable biomaterials and their effects on hemostasis and wound healing, evaluating experiences with 20th century agents and exploring developing trends and 21st century innovations.

Nasal packing was first described in the otorhinolaryngolic literature in 1951[5] and the use of absorbable biomaterials since 1969.[6] Removable nasal packing has been designed to tamponade mucosal bleeding and act as a barrier to adhesion formation. Numerous packing agents are available, including Vaseline-soaked ribbon gauze, fingerstall packs, polyvinyl acetate sponge (Merocel, Medtronic Xomed, Jacksonville, Florida), and various balloon tamponade devices. However, these agents cause considerable discomfort for patients, both in terms of pain and bleeding on removal.[1,2,7–9] Other complications associated with removable nasal packing include septal perforation, pack dislodgement, aspiration, toxic shock syndrome, foreign body granuloma, myospherulosis, obstructive sleep apnea secondary to nasal obstruction, and even death.[10,11] Animal studies investigating the mucosal trauma caused by removable nasal packing have shown a 50% to 70% loss of the ciliated mucosal surface area in the region of the pack.[12] Therefore, a transient impairment of the patient's innate immune system, the mucociliary clearance, may be associated with the use of removable nasal packing.[13]

These drawbacks of removable nasal packing have led to the ongoing development and application of absorbable biomaterials that do not require subsequent removal and still achieve positive effects on hemostasis, promote wound healing, and provide middle turbinate support. Absorbable biomaterials either provide clotting factors or a substrate to stimulate clotting. Other important characteristics of these agents include safety and efficacy, absorption kinetics, composition, usability (including form of the agent and delivery device), and cost. Biomaterials were extensively investigated and researched in the ear, nose, and throat literature well before the evolution of ESS, and this interest continues today. Both human and animal trials have contributed significantly to the understanding of these products and their role in ESS.

In an attempt to simplify the literature on biomaterials, this article is organized into effects on intraoperative hemostasis, postoperative hemostasis, and finally wound healing, in human studies and animal models. **Table 1** summarizes the literature on 20th century biomaterials and lists observations on hemostasis and wound healing in humans.

EFFECT OF 20TH CENTURY BIOMATERIALS ON HEMOSTASIS

Intraoperative Hemostasis

Absorbable porcine gelatin (Surgiflo, Ethicon Inc, Somerville, New Jersey) and thrombin combination; topical antifibrinolytics such as epsilon–aminocaproic acid (Amicar, Lederle Parenterals Inc, Carolina, Puerto Rico) and tranexamic acid (Cyklokapron, Pfizer, Puurs, Belgium); and hyaluronic acid have all been investigated in human studies for their intraoperative hemostatic properties after ESS. Surgiflo hemostatic matrix combined with thrombin is an absorbable porcine gelatin that was investigated by Woodworth and colleagues[14] after sinus surgery in a prospective trial. Results showed that patients experienced rapid hemostasis within 10 minutes, with a median time of 1 minute; however, this study had no control arm.[14]

Only one trial has studied topical antifibrinolytics after ESS. These agents prevent fibrinolysis and stabilize the blood clot. Results showed that topical epsilon–aminocaproic acid was ineffective at producing hemostasis compared with saline; however, tranexamic acid at low dose (100 mg) improved hemostasis significantly ($P<.05$). This observed effect was reduced at higher doses.[15] This study is only the second in the literature to use an objective surgical grade score to monitor hemostatic efficacy.

Table 1
Human studies on 20th century biomaterials

Biomaterial	Study	Study Design	Intraoperative Hemostasis	Postoperative Hemostasis	Adhesions/Wound Healing
Surgiflo/thrombin combination[14]	30 pts	Prospective (uncontrolled)	29/30 in 10 min	29/30 (1 req packing)	No adhesions
Epsilon–aminocaproic acid[15]	10 pts	DB RCT	Ineffective versus saline	10/10 pts	—
Tranexamic acid[15]	10 pts	DB RCT	Better versus saline (P<.05)	10/10 pts	—
Sepragel sinus[17]	20 pts	RCT	Same as no treatment	—	—
Quixil (fibrin glue)[8,16,69]	158 pts[8] 64 pts[16]	DB RCT[8] Prospective (controlled)[16]	Same as Merocel[8]	—	Same as Merocel[16]
Merocel[7,45]	16 pts[7] 61 pts[45]	Cohort[7] SB RCT[45]	—	16/16 pts[7]	No adhesions↓ Adhesions versus no packing (P = .001)[45]
Surgicel Nu-knit[18]	60 pts	RCT	—	60/60 pts, same as gauze and Merocel	—
MeroGel[22,43,44]	37 pts[22]	DB RCT[22]	—	—	Same as Merocel (3/37 adhesions)[22]
	42 pts[44]	SB RCT[44]	—	—	Same as no pack[44]
	35 pts[43]	RCT[43]	—	—	Same as removable pack[43]
Gelfilm[24,46]	115 pts[24]	Prospective (controlled)[24]	—	—	↑ adhesions verus MeroGel (P<.05)[24]
	51 pts[46]	RCT[46]	—	—	↑ granulations versus no pack (P<.05)[46]
Mitomycin C[23,49,50]	55 pts[49] 29 pts[23] 38 pts[50]	3 DB RCTs	—	—	All show same as no pack

Abbreviations: DB, double–blind; pts, patients; RCT, randomized controlled trial; req, required; SB, single-blind; ↑, increased; ↓, decreased.

Fibrin glue (Quixil, Omrix Co., Brussels, Belgium) is a combination of human thrombin and fibrinogen mixed with amino acids and salts, which allows this compound to form an easily applied gel. It was first used in the rhinology literature in the early 1990s, largely for managing cerebrospinal fluid rhinorrhea or for endonasal/transsphenoidal pituitary surgery. Vaiman and colleagues[16] showed that Quixil is effective in producing postoperative hemostasis, although they did not analyze how long it took to achieve.

Hyaluronic acid (Sepragel sinus, Genzyme Biosurgery, Cambridge, Massachusetts) is a viscoelastic gel containing polymers of highly purified forms of hyaluronic acid and has been investigated for immediate hemostasis by Frenkiel and colleagues.[17] Results showed no significant difference in total blood loss between the Sepragel sinus side and the no treatment side; however, a subjective general improvement of hemostasis was noted with the intervention side.

Postoperative Hemostasis

Surgiflo/thrombin combination, Merocel, and oxidized regenerated cellulose (Surgicel Nu-knit, Ethicon Inc, Somerville, New Jersey) have been studied for their effects on hemostasis after ESS. The Surgiflo/thrombin combination caused postoperative bleeding, requiring nasal packing in 1 of 30 patients.[14] Merocel was investigated in 16 patients after ESS, with no reported incidence of postoperative epistaxis.[7] Shinkwin and colleagues[18] compared Surgicel Nu-knit with Vaseline ribbon gauze and Merocel. All packing agents were equally effective with no incidence of postoperative epistaxis in any of the treatment arms.

Of particular interest is the number of patients experiencing postoperative epistaxis without any nasal packing or treatment at all. Athanasiadis and colleagues[15] found no incidence of postoperative epistaxis in 30 patients undergoing ESS. Jameson and colleagues[19] reported no incidence of postoperative epistaxis in 47 patients undergoing ESS without nasal packing. In a large retrospective review of patients after ESS, Orlandi and Lanza[20] challenged the practice of placing any pack at all, both in the immediate perioperative period and postoperatively. Among 165 patients, only 11.2% required nasal packing at the conclusion of operating, and none experienced postoperative epistaxis over 4 years.

Conclusions on Hemostatics

Tranexamic acid is an effective hemostatic option compared with no treatment, and fibrin glue is as effective as Merocel packing on immediate hemostasis. Sepragel sinus does not significantly reduce intraoperative blood loss when compared with no treatment. Additionally, one uncontrolled prospective trial suggests that Surgiflo/thrombin combination is effective in the immediate intraoperative period. In terms of postoperative bleeding, no evidence shows that any agent was more effective than no treatment at all; however, one large retrospective analysis suggests that immediate postoperative and long-term packing are not necessary in more than 90% of patients.

EFFECT OF 20TH CENTURY BIOMATERIALS ON ADHESION FORMATION

Adhesion formation is the most common complication encountered after ESS and can result in occlusion of the sinus drainage pathway. In addition, adhesions can result in recurrent symptoms and subsequent surgical failure. Studies have shown that up to 25% of patients who experience adhesion formation will require revision surgery in the future.[21] The incidence of adhesion formation after ESS is reported

to be between 1% and 36%.[22–24] Therefore, a large body of literature is devoted to reducing the incidence of adhesion formation after ESS, with numerous biomaterials marketed for this effect.

When considering adhesion prevention, one must remember that agents that promote hemostasis through stimulation of the intrinsic coagulation cascade also stimulate inflammation.[25,26] Inflammatory responses are linked to hemostatic activation through a network of humoral and cellular components, including protease factors involved in the clotting and fibrinolytic cascades. Thus, the potential exists for potent coagulation cascade activation, leading to adverse wound healing.

Animal trials have also contributed significantly to the understanding of paranasal sinus wound healing and a large number of trials reflect this. The predominant models used are those involving sheep, rabbits, and mice. Sheep are an ideal model because they are large animals in which routine sinus surgical techniques can be used, and histologically their mucosa is identical to that of humans.[27]

Models of bacterial rhinosinusitis were developed using Merocel to block the maxillary sinus ostia, along with *Bacteroides fragilis* inoculation, resulting in a histologically confirmed, persistent, localized bacterial rhinosinusitis.[28] Finally, rabbits have well-pneumatized sinus cavities, and both their sinonasal anatomy and immunologic reactions are very similar to those of humans, making them a useful animal model for the study of biomaterials.[29]

Sheep Models

Shaw and colleagues[12] examined the effects of ribbon gauze packing and cottonoids on the nasal mucosa in a single-blind randomized controlled trial involving sheep. Nasal packing was left in situ for 10 minutes, followed by removal of packing and the associated mucosa. Blinded histologic analysis was then performed. Results showed that both packing agents produced more than a 50% loss of ciliated mucosal surface area ($P<.005$).

In a double-blind randomized controlled trial, McIntosh and colleagues compared the effects of Merocel (5 days) with no packing in the sheep model. Serial biopsies were taken at 4, 8, 12, and 16 weeks after treatment. Results showed no significant difference in the rate of reepithelialization, total surface ciliation, and overall maturity of cilia between the packed and non-packed sides at any point.[30]

Another further study compared the effects of MeroGel (Medtronic Xomed, Jacksonville, Florida) with no treatment in a sheep model of chronic sinusitis. This study created standardized mucosal injuries after histologic analysis of healing mucosa at 1, 2, 3, and 4 months postoperatively. Results showed no significant difference in adhesion formation or histologic features of reepithelialization, cilial height, and reciliation between the arms.[31]

The sheep model has also been used to examine the effects of drug delivery associated with nasal packing. Robinson and colleagues[32] studied the effects of prednisolone-impregnated MeroGel and MeroGel alone and found no difference. Finally, growth factors have also been shown to be important in epithelialization and collagen deposition, including insulin-like growth factor. Insulin-like growth factor–impregnated MeroGel was analyzed in the same sheep model after ESS and found to have a positive effect on mucosal regrowth and maturity in healthy sheep. However, when introduced in a model of chronic sinusitis, this effect was negated.[33]

Mice Models

Only one study used a murine model to examine the effects of biomaterials. Jacob and colleagues[34] conducted a randomized controlled trial involving 20 mice to evaluate the

histologic effects of MeroGel. Results showed induced bone formation within the sinonasal cavity, indicating that MeroGel may have osteogenic potential.

Rabbit Models

Maccabee and colleagues[35] studied the effects of MeroGel in six self-controlled rabbits through denuding the maxillary sinuses and performing histologic analysis of the regenerating mucosa. At 2 weeks postoperatively, the MeroGel sinuses showed extensive fibrosis compared with control sinuses, with minimal reabsorption of the biomaterial along with incorporation of the biomaterial within the regenerating mucosa. Proctor and colleagues[36] confirmed these findings, analyzing the effects of MeroGel in a rabbit model. Results showed that MeroGel caused significant stenosis of the ostia over a 2- to 3-week follow-up. Mitomycin C has also been investigated in the rabbit model, with one pilot study showing that increasing concentrations of Mitomycin C can delay healing of an intranasal antrostomy (0.4 mg/mL, 1.0 mg/mL).[37]

Rahal and colleagues[38] confirmed these results. However, these trials were conducted in healthy rabbits without chronic rhinosinusitis, which may explain the discrepancies between these findings and those seen in human studies. Two published studies have investigated the effect of mucosa treated with retinoic acid (DPT Laboratories, San Antonio, Texas) in rabbits. Maccabee and colleagues[39] conducted a randomized controlled trial involving rabbits treated with retinoic acid, finding improved mucosal regeneration with less ciliary loss and fibrosis. These findings were also supported by Hwang and Chan,[40] again involving the healthy rabbit model.

Human Studies

Table 1 summarizes the data on adhesions and wound healing. MeroGel is a hyaluronic acid, which is the major constituent of the extracellular matrix, and therefore acts as a scaffold for wound healing.[41] It has been shown to be the key factor in eliminating scarring in fetal wounds.[42] Franklin and Wright[43] also conducted a single-blind, randomized controlled trial to compare the effects of MeroGel and a nonabsorbable nasal packing (2–3 days), showing a trend toward improved postoperative endoscopic scores; however, this failed to reach significance at all time points. Additionally, Wormald and colleagues[44] investigated whether MeroGel had any effect on wound healing after ESS, showing no significant difference between the sides at 2, 4, and 8 weeks in the endoscopic features of adhesions, edema, or infection. Vaiman and colleagues[16] compared Quixil and Merocel, showing comparable results in the incidence of adhesion formation between the arms.

Miller and colleagues[22] compared Merocel pack (5–7 days) and hyaluronic acid (MeroGel). Patients underwent follow-up to 8 weeks postoperatively. Results showed both packing agents were associated with an 8% adhesion rate.[22] This finding contrasts with those of Vaiman and colleagues[16] and Pomerantz and Dutton,[7] which showed no evidence of adhesion formation with Merocel packing. Discrepancies between these studies maybe related to the timing of pack removal. Bugten and colleagues[45] investigated the effects of Merocel versus no nasal packing to determine whether removable nasal packing had any role after ESS. Video recordings taken 10 to 14 weeks after surgery showed 7 of 62 adhesions in the Merocel arm versus 29 of 54 adhesions in the no packing arm, a finding that was highly significant ($P = .001$).

Only one published article investigated the effects on wound healing of a combination of Surgiflo (Ferrosan, Soeborg, Denmark) and thrombin. This uncontrolled prospective trial involving 30 patients after ESS showed no incidence of reported adhesion

formation. However, as indicated by the authors, further randomized controlled trials are indicated.[14]

Denatured porcine collagen (Gelfilm, Pharmacia and Upjohn Company, Kalamazoo, Michigan) has also been developed to reduce adhesion formation. It is an absorbable biomaterial manufactured from denatured porcine collagen. Results of two trials have shown adverse effects on wound healing, with one trial showing a significant increased in adhesions in patients implanted with Gelfilm compared with those implanted with MeroGel ($P<.05$),[24] and the second showing no significant difference in adhesion formation but a significant increase in granulation tissue formation in patients implanted with Gelfilm ($P<.05$).[46]

Mitomycin C is a topically applied agent that has been shown to reduce scar formation.[47] Additionally, it has been shown to inhibit nasal fibroblast proliferation and increase apoptosis.[48] It is isolated from the *Streptomyces caespitosus* strain of actinomyces, and used to crosslink DNA and inhibit cellular mitosis. Three human trials investigating the effects of mitomycin C against a saline control failed to show any significant findings regarding adhesion formation.[23,49,50]

Conclusions on Antiadhesion Effects of Biomaterials

No studies show that absorbable packing has any antiadhesion advantage over removable nasal packing or no packing at all. However, the same cannot be said for removable nasal packing, one single-blind randomized controlled trial showing a highly significant reduction in adhesion formation when Merocel is used. Three double-blind randomized controlled trials in the sheep model of chronic rhinosinusitis (CRS) confirm that MeroGel alone and with prednisolone or insulin-like growth factor has no effect on adhesion formation or cilial recovery. Two prospective, controlled rabbit trials suggested that MeroGel increases fibrosis and is incorporated within regenerating mucosa, and another showed that MeroGel displayed osteogenic potential.

Mitomycin C has shown promising results on healing ostia in two randomized controlled trials in the healthy rabbit model. However, these effects were not translated to patients who had post-ESS CRS, a conclusion also supported by Tabaee and colleagues.[51] Gelfilm stents have been shown to adversely affect the wound-healing process. One double-blind, randomized controlled trial shows that fibrin glue has no effect on adhesion formation, and one prospective trial suggests the same.

Finally, only one uncontrolled prospective trial has investigated the effects of the Surgiflo/thrombin combination, with no adhesions observed by the authors. Although the positive effects of vitamin A have been shown in healthy rabbit sinuses, further human trials are needed in patients who have CRS. Furthermore, although products containing oxidized regenerated cellulose (Surgicel) are widely known to have hemostatic properties,[6] and advocated as an absorbable nasal dressing after ESS,[18] no published literature has investigated their wound-healing properties after ESS.

20TH CENTURY BIOMATERIALS

An array of biomaterials are available. Several studies suggest that postoperative epistaxis is a rare event. In terms of immediate hemostasis, tranexamic acid and Surgiflo/thrombin combination have shown promising results. However, their wound-healing effects remain unknown. Although the effects of MeroGel on immediate hemostasis are unknown, human and animal trials show that it has no apparent positive effect on wound healing, and may worsen healing outcomes.

Sepragel sinus seems to have no objective effect on immediate hemostasis, and its effects on wound-healing are unknown. Mitomycin C has no effect on wound healing after ESS in patients. Finally, Gelfilm seems to potentially worsen healing outcomes and vitamin A shows promise in animal models only. The turn of the century clearly showed that a great need existed for the ideal biomaterial after ESS. Important characteristics of this product included the need to be effective in producing immediate and prolonged hemostasis, have no detrimental effect on wound healing, be absorbable and comfortable for patients, and, finally, have no risk for disease transmission.[7]

RECENT ADVANCES

Several recent advances and additions have been made to the biomaterial literature in recent years. Numerous additions to the already available biomaterials have been developed to meet the objectives of hemostatic properties and positive wound healing. FloSeal (Baxter International Inc, Deerfield, Illinois), carboxy-methyl-cellulose (AthroCare, Glenfield, United Kingdom), Platelet gel (PPAI Medical, Fort Myers, Florida), polyethylene glycol, microporous polysaccharide hemispheres (MPH, Medafor Inc, Minneapolis, Minnesota), and chitosan gel (Department of Chemistry, University of Otago, Dunedin, New Zealand) are all recent advances, developed with the hope of offering what no other product had previously offered.

FloSeal is a topical hemostatic agent consisting of gelatin matrix (bovine-derived) combined with human derived thrombin, and first became available to the market in 2000. Carboxymethylcellulose (CMC) nasal packing was developed in 2001, with its postulated ability to promote hemostasis by platelet aggregation.

Platelet gel is a fibrin tissue adhesive product manufactured from centrifugation of autologous whole blood, producing a platelet-rich plasma. It has the advantages of eliminating the risk for potential virus transmission and antibody formation to coagulation factors. Use in the rhinology community commenced in 2001, after a presentation to the American Rhinologic Society.

Microporous polysaccharide hemispheres (MPH) is a novel absorbable agent that is produced from purified potato starch, and acts to quickly extract fluids from blood, thereby concentrating serum proteins and platelets at the site of injury, and was approved for human use in 2006. A novel chitosan gel has also been recently developed from chitin, a natural biopolymer, and is postulated to achieve hemostasis through aggregation of erythrocytes. It also has been shown to have an inhibitory effect on fibroblast proliferation.[52,53]

No published literature has investigated the hemostatic or wound-healing properties of polyethylene glycol (NasoPore, Polyganics B.V., Groningen, The Netherlands) after ESS. All other products have recently been investigated in both human and animal trials, importantly in the area of hemostasis and wound healing. **Table 2** summarizes the data regarding human trials on these 21st century biomaterials.

EFFECT OF 21ST CENTURY BIOMATERIALS ON HEMOSTASIS

Intraoperative Hemostasis

Gall and colleagues[54] found that FloSeal was effective in producing hemostasis in 17 of 18 patients, and also found that the average time to hemostasis was 2 minutes. Additionally, Jameson and colleagues[19] showed that the FloSeal group had a significantly faster time to hemostasis (16.4 minutes) than the control group (30.8 minutes). Baumann and colleagues[55] compared FloSeal with Merocel in a nonrandomized trial, and found that intraoperative hemostasis occurred within 3 minutes in both arms. Significant variability is shown between these studies on the time to hemostasis.

Table 2
Human studies on 21st century biomaterials

Biomaterial	Study	Study Design	Intraoperative Hemostasis	Postoperative Hemostasis	Adhesions/Wound Healing
FloSeal[13,19,21,54,55]	18 pts[54]	Prospective (uncontrolled)[54]	Rapid hemostasis 17/18 pts[54] (P = .028[19])	17/18 pts (1 req packing)[54] FloSeal same as Merocel[55]	↑ adhesions and granulations (P = .006)[13] ↑ adhesions (P = .009)[21] No effect (same as removable pack)[19]
	45 pts[19]	DB RCT[19]			
	50 pts[55]	DB RCT[55]			
	20 pts[13]	DB RCT[13]			
	172 pts[21]	Retrospective[21]			
MPH[56,60]	65 pts[56]	Prospective (uncontrolled)[56]	Rapid hemostasis (30–45 s)[56]	65/65 pts,[56] less bleeding on POD#1 versus untreated side[60]	8/65 adhesions[56]
	40 pts[60]	SB RCT[60]			
Platelet gel[7]	16 pts	Prospective		16/16 pts (same as Merocel)	No adhesions (same as Merocel)
CMC mesh[58,59,62] CMC gel[59,62]	15 pts[58]	Prospective (uncontrolled)[58]	20% persistent bleeding[58]	15/15 pts[58] 41/41 pts (same as no pack)[59]	No adhesions[58] No effect (same as no pack)[62]
	41 pts[59]	SB RCT[59]			

Abbreviations: DB, double–blind; pts, patients; RCT, randomized controlled trial; req, required; SB, single-blind; ↑, increased; ↓, decreased.

One recent study investigating the effects of MPH on hemostasis showed that hemostasis occurred between 30 and 45 seconds after application.[56] Finally, Valentine and colleagues[57] conducted a randomized controlled trial into the efficacy of chitosan gel in producing hemostasis in the sheep model of CRS. This study involved a standardized wound injury, followed by application of chitosan gel to one nasal cavity, with the opposite acting as a control. The Boezaart bleeding scale was taken at 2-minute intervals to objectively evaluate hemostatic efficacy. Results showed that the chitosan gel side was significantly more hemostatic at 2, 4, and 6 minutes after injury ($P<.05$). Complete hemostasis occurred by 6 minutes for all chitosan gel sides; however, control side bleeding was noted on three sides at 8 minutes and one at 10 minutes.[57]

Postoperative Hemostasis

When comparing FloSeal and Merocel after ESS, the incidence of postoperative epistaxis was similar (ie, 1 among 50 versus 2 among 50), indicating that these were equally as effective.[55] However, removable nasal packing causes bleeding on removal, and when this was taken into consideration, a significantly greater number of bleeds was noted in the Merocel group (21.87%; $P<.001$).[16] Gall and colleagues[54] noted that 1 of 18 patients required nasal packing 6 hours after FloSeal application for persistent epistaxis postoperatively. Pomerantz and Dutton[7] reported no incidence of postoperative epistaxis in either the Platelet gel or Merocel arm.

Two studies reported on CMC's efficacy on hemostasis postoperatively. In an uncontrolled pilot study by Karkos and colleagues,[58] nursing staff reported persistent oozing in 20% of patients treated with CMC mesh; however, no patient required intervention. Kastl and colleagues[59] showed that CMC mesh had no significant effect on postoperative bleeding. No episodes of postoperative epistaxis were reported in 65 patients treated with MPH after ESS.[56]

In a randomized controlled trial evaluating MPH, 40 patients who had CRS underwent ESS and had only one side treated with MPH (with the opposite side serving as a control) at the conclusion of surgery. Patients were blinded to side of treatment, and the results showed that MPH significantly reduced bleeding (compared with the untreated side; $P = .001$) during the early recovery period after ESS.[60]

Conclusions on Hemostatics

FloSeal produces rapid hemostasis compared with control. Both studies investigating CMC seem to suggest that CMC mesh has no significant effect on postoperative bleeding. The effects of MPH after ESS have been reported in an observational study and in one prospective, randomized, controlled trial, and have shown efficacy in reducing postoperative bleeding. One randomized controlled trial investigates the efficacy of Chitosan gel, and shows rapid hemostasis in the sheep model of ESS.

EFFECT OF 21ST CENTURY BIOMATERIALS ON ADHESION FORMATION

Human Studies

Chandra and colleagues[61] investigated the wound-healing effects of FloSeal by comparing FloSeal versus thrombin-soaked Gelfoam (Pharmacia and Upjohn Company, Kalamazoo, Michigan). Patients were followed up at 1 and 6 weeks postoperatively. Results showed that the mean adhesion score was increased in the FloSeal side, a highly significant finding ($P = .006$). Adhesions developed on 11 sides treated with FloSeal, compared with only 2 of the sides treated with Gelfoam.

Similar findings were noted for granulation tissue formation ($P = .007$). Follow-up of these patients occurred for an average of 21 months after surgery and showed that 56% of FloSeal sides had an adhesion, compared with 11% of the thrombin-soaked Gelfoam sides ($P = .013$). Of the sides treated with Gelfoam, 28% required lysis versus none of the thrombin-soaked Gelfoam sides ($P = .046$). Histologic examination of an adhesion on the FloSeal side showed incorporation of the foreign material.[61]

Shrime and colleagues[21] attempted to determine the incidence, outcomes, and risk factors for adhesion formation after ESS with middle turbinate medialization with and without FloSeal. A statistically significant higher incidence of adhesion formation was noted in patients who underwent treatment with FloSeal (18.9%) versus those who received no packing (6.7%; $P = .009$).[21]

Statistical multivariate analysis comparing adhesion formation and surgical and demographic variables showed a statistically significant correlation only with the FloSeal ($P = .0063$; odds ratio, 5.3330; 95% CI, 1.61–17.71).[21] Explanation for this effect maybe the bidirectional relationship between coagulation and inflammation, wherein strong initiation of the coagulation cascade results in strong activation of inflammation and fibrosis.[26]

These results contrast with the findings of Jameson and colleagues,[19] who showed no significant difference between sides in 45 patients enrolled, which are similar results to those of a retrospective analysis by Pomerantz and Dutton,[7] who compared platelet gel and Merocel and found no incidence of adhesion formation in either arm, or evidence of exuberant granulation tissue.

Postoperative adhesion formation was not observed in a pilot study with the use of CMC mesh.[58] Kastl and colleagues[62] conducted a randomized controlled trial comparing the effects of CMC mesh, CMC gel, and no nasal packing in 26 patients after ESS. All patients acted as their own control. Results showed no significant clinical effect on wound healing. Sindwani[56] continued his observation of 65 patients who underwent treatment with MPH after ESS, and found a 12.3% incidence of adhesion formation; however, no control group was used for comparison.

Sheep Models

One study has investigated the efficacy of chitosan gel on mucosal wound healing after ESS in the sheep model of CRS. Athanasiadis and colleagues[63] conducted a double-blind randomized controlled trial involving 20 sheep infested with nasal bot fly (causing an eosinophilic sinusitis). Standardized mucosal injuries were created, followed by the application of either chitosan gel, polyethylene glycol (SprayGel, Confluent Surgical, Waltham, Massachusetts), recombinant tissue factor (rTF, Dade Innovin, Marburg, Germany), or no treatment. Histologic analysis of mucosal biopsies was then performed, with results showing that chitosan gel significantly decreased adhesion formation compared with rTF, with a noticeable trend when compared with SprayGel and control (14% versus 0% and 40% versus 0%, respectively). Chitosan gel significantly improved reepithelialization, reciliation, and cilial grade ($P<.05$).[63]

Rabbit Models

Maccabee and colleagues[35] studied the effects of FloSeal in six self-controlled rabbits by denuding the maxillary sinuses and performing histologic analysis of the regenerating mucosa. At 2 weeks postoperatively, FloSeal sinuses showed extensive fibrosis when compared with control sinuses, with minimal reabsorption of the biomaterial along with incorporation of the biomaterial within the regenerating mucosa.

Antisdel and colleagues[64] conducted a single-blind randomized controlled trial investigating the effects of microporous polysaccharide hemispheres versus FloSeal

in 14 self-controlled rabbits. Ten rabbits underwent bilateral maxillary sinus stripping, with five receiving unilateral FloSeal placement and five receiving unilateral MPH placement (opposite side acting as control). An additional two animals underwent unilateral FloSeal placement in an unstripped maxillary sinus, and two animals underwent unilateral MPH placement (opposite side acting as control).

Results showed no significant changes in MPH-treated sinuses compared with respective controls; however, FloSeal sides showed extensive loss of cilia, inflammation, and fibrosis, both in the denuded and mucosa intact sinuses,[64] a finding consistent with that of Maccabee and colleagues.[35]

Conclusions on Antiadhesion Effects of Biomaterials

To conclude on the effects of FloSeal on regenerating mucosa, one double-blind randomized controlled trial shows increased adhesion formation and granulations,[13] with this finding confirmed by a large retrospective case series.[21] Again, the rabbit model has shown that FloSeal increases fibrosis and is incorporated within the healing mucosa, a finding supported by a second independent study.[35,64]

CMC mesh and gel seem to have no appreciable effect on postoperative wound healing compared with no treatment.[62] MPH seems to have an adhesion incidence comparable to that reported by most endoscopic sinus surgeons.[56] Additionally, MPH has no appreciable detrimental effect on mucosal healing in the rabbit model.[64] Finally, chitosan gel, in the sheep model of chronic rhinosinusitis, significantly improves microscopic features of wound healing and reduces adhesion formation after ESS.[63]

CONCERNS AND CONCLUSIONS

Recent advances in the biomaterial literature has seen the addition of several agents, including those containing bovine or human blood products to exploit the intrinsic and extrinsic coagulation cascades for producing hemostasis. FloSeal, although an effective hemostatic agent, seems to have detrimental effects on wound healing in patients post-ESS and in animal models. Fibrin glue also seems to be effective against immediate bleeding after ESS.

Platelet gel seems to be equally effective as Merocel in its abilities to maintain hemostasis, and the only published trial after ESS shows no incidence of adhesion formation with either product. However, ongoing concern exists regarding antibody formation and disease transmission of thrombin, fibrin, and collagen products, limiting their usefulness in ESS.[16,65–67]

Dorion and colleagues[66] reviewed the use of topical bovine thrombin preparation in 120 surgical patients. They found that between 5% and 15% of exposed patients developed antibodies to coagulations factors, and those exposed more than once were eight times more likely to develop antibodies. They also noted a 1.7% risk for developing serious bleeding complications from exposure to bovine thrombin.[66] In addition, the theoretical risk exists for infectious disease transmission of HIV, hepatitis, and Creutzfeldt-Jakob disease, all possible with blood products.[68]

MPH and chitosan gel have recently entered the literature, both having the advantage of conferring no risk for disease transmission. Findings suggest that MPH has an attractive role in producing immediate intraoperative hemostasis, with one prospective randomized study showing efficacy in reducing postoperative bleeding during the early recovery period after surgery. A study using the rabbit model suggests that this substance does not interfere with normal mucosal regeneration and wound healing.

Only one product in the rhinology literature has shown positive effects in both wound healing and immediate hemostasis. Chitosan gel has been shown in the CRS sheep model of ESS to have produced rapid hemostasis after application and has been shown to significantly improve the microscopic features of wound healing and reduce adhesion formation after ESS in an animal model. Newer 21st century agents offer distinct advantages because of their unique composition and rapid clearance profiles. The selection of packing material for any given sinus procedure should be based on surgeon preference and the details of the specific case.

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