Rhinology, 41, 244-249, 2003

Hemostasis in endoscopic sinus surgery using a specific gelatin-thrombin based agent (FloSeal™)*

Ariane Baumann and Marco Caversaccio

Department of ENT, Head and Neck Surgery, University Hospital, Inselspital, Berne, Switzerland

SUMMARY

The safety and efficacy of a new hemostatic sealant, based on a gel with collagen derived particles and topical thrombin (FloSeal™, Fusion Medical Technologies, Inc. Fremont, CA) were assessed as an alternative to nasal packing for hemostasis in functional endoscopic sinus surgery. In a prospective clinical study of 50 patients undergoing bilateral endoscopic anterior ethmoidectomy, 2 ml FloSeal™ was used after surgery to stop bleeding. The results were compared to a control group of 50 patients with Merocel™ packing and showed that intraoperative hemostasis was rapid and equal in both groups. The main advantages of the new hemostatic sealant included a higher degree of comfort during postoperative nasal breathing and absence of complaints due to pressure or pain. There was only one case of postoperative bleeding on the 6th day, which required nasal packing. There were no more cases of stenoses or synechia in the ostiomeatal complex than were found in the Merocel™ group. No systemic side effects due to FloSeal™ were observed.

This specific hemostatic sealant was shown to be a safe and efficacious alternative method for hemostasis in endoscopic sinus surgery with high patient satisfaction and an easy and fast mode of application.

Key words: nose, hemostasis, bleeding, sinus, Floseal™

INTRODUCTION

The aim of endoscopic sinus surgery is to restore good ventilation and drainage to sinuses with thickened and inflamed mucosa. Unfortunately, this may be complicated by postoperative bleeding, infection and formation of synechiae due primarily to denuded large ethmoidal wound surfaces. To treat postoperative bleeding and to prevent synechia or restenosis, many surgeons use packing or stents with controversial benefits (Von Schoenenberg et al., 1993; Weber et al., 2000). As a result, nasal packing is still the method most widely used for hemostasis after endoscopic sinus surgery.

The main drawbacks of using packing are postoperative disturbance of nasal breathing, especially during sleep with reduced nocturnal oxygen pressure, discomfort on facial swelling, sensation of intranasal and periorbital pressure, as well as pain and risk of hemorrhage on removal of the packing (Von Schoenenber et al., 1993). Often, patients complain of Eustachian tube obstruction. Furthermore, with packing, there is an increased risk of infection and of its dislocation with possible aspiration. Spillman (1981) described two deaths due to postoperative aspiration of fingerstall packs. Paraffin granulomas and spherulocytosis after paraffin or antibiotic-containing ointments on nasal packings as well as allergies against Merocel™ packs (*Medtronic, Jacksonville*) have been described (Weber et al., 1995; Weber et al., 2000; Dowel and Strachan, 2001). Mucosal damage and septal perforations after using balloon or ribbon gauze packs have been reported (Cox and Barker, 1988; Watson at al., 1989; Illum et al., 1992).

Because of these limitations, we searched for an alternative method of postoperative dressing in endoscopic sinus surgery that would provide more patient comfort, easier and faster modes of application and fewer negative effects on wound healing. Thus, a comparative study with FloSeal™ (*Fusion Medical Technologies, Inc. Fremont, CA*), a specific hemostatic product, was performed. FloSeal™ has been available in Europe and the USA since 1999 but has been used preferentially in vascular surgery and neurosurgery (Reuthebuch et al., 2000; Oz et al., 2000; Weaver et al., 2002; Ellengala et al., 2002).

MATERIAL AND METHODS

FloSeal™ is a hemostatic product in which thrombin (bovine) in a 1 ml syringe and specially engineered dry collagen parti-

This paper was presented at the 19th Congress of the European Rhinologic Society combined with the 21st International Symposium on Infection and Allergy of the Nose, Ulm, Germany, June 19, 2002.

*Received for publication: May 19, 2003; accepted: September 25, 2003

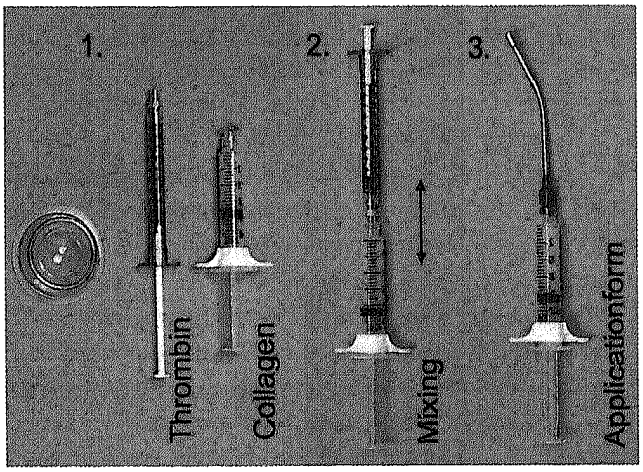

Figure 1. FloSeal™- mixing in 2 steps: 1) 5000 units of lyophilised bovine thrombin were hydrated by 0.8 ml saline water in a 1 ml syringe. 2) The thrombin syringe becomes directly adapted on a second syringe with the gelatin matrix; the two components are easily mixed. 3) FloSeal™ is ready for application.

cles (bovine) in a 5 ml syringe are easily and quickly mixed to a gel just before use (Figure 1). This gel is of high viscosity and is directly applied to the surgical wound. In contact with blood, the FloSeal™ particles swell and, by the action of the thrombin, they are covered by fibrin polymers from the hemorrhage, without platelet activation. Being a highly viscous gel, FloSeal™ attaches well to the surface of the irregular ethmoid wound, even if the wound is wet and bleeding (Figures 2 and 3), and there is no risk of aspiration. Since this hemostatic sealant is reabsorbed within 4 weeks, consistent with the body's normal healing process, it does not need to be removed postoperatively. Furthermore, surplus material can be rinsed away easily.

Between May 2001 and July 2002, 50 patients with nasal polyps in chronic rhinosinusitis (31 male and 19 female, age ranging from 14 to 76 years, average of 46 years) were treated with FloSeal™ for hemostasis after anterior ethmoidectomy. Fifteen patients of the FloSeal™ and 18 patients of the Merocel™ group had previously undergone endoscopic sinus surgery. All patients were asked for their informed consent, but the study was classified as exempt by the local institutional review board. Patients were examined 24 hours preoperatively with blood analysis: blood count, blood cell differential, prothrombin time, quick, hepatic and renal parameters. Perioperative antibiotic treatment was performed with 1.2 g amoxicillin/clavulan acid.

At the end of the operation, 2 ml FloSeal™ was applied directly to the ethmoid wound on each side without any other hemostatic product. The results were compared to a group of 50 patients with 4 cm Merocel™ packing in the middle meatus. These patients had been followed in 2000 in a study on nasal comfort.

Both methods were performed independent of the degree of hemorrhage. The interventions, 48% of which were second operations of recurrent nasal polyps, were performed without hypotension. If the bleeding was not under control after 5 minutes, then the surgeon could use any other packing of choice. Excluded from the study were patients with known hemostatic disorders or allergies to bovine protein or patients pretreated with FloSeal™.

The following factors were examined: intraoperative bleeding time after FloSeal™ application, postoperative bleeding within the first 10 days, cost of application and duration of hospitalisation. The degree of postoperative breathing comfort was also measured by means of a subjective symptom score scale rang-

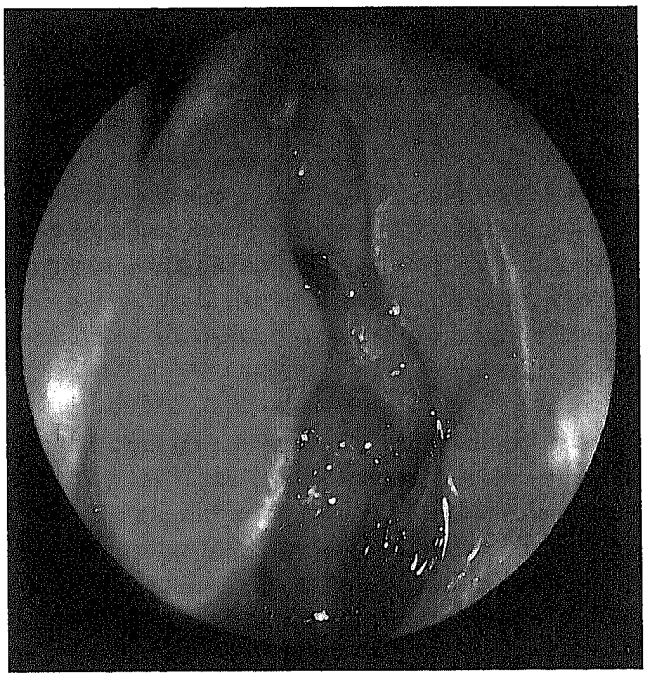

Figure 2. Picture of a typical status during anterior ethmoidectomy on the left side.

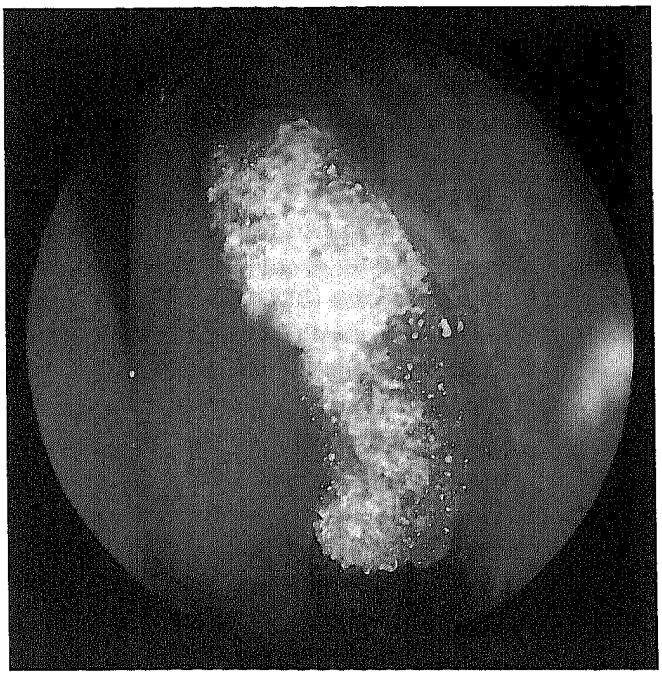

Figure 3. Middle meatus on the left side with 2 ml FloSeal™ in the anterior ethmoid.

ing from good to moderate to poor, and patients' complaints such as congestion, facial pressure and pain on removal of the Merocel™ packing were assessed using a visual analogue scale (VAS) of pain severity ranging from 0 to 10. Furthermore, the occurrence of stenoses and synechiae in the ostiomeatal complex were evaluated during the postoperative follow-up.
For postoperative nasal care, Dexpanthenol ointment, saline water and topical steroid spray were used. Patient examinations with nasal cleaning were performed on the 2nd, 5th, 10th, 20th and 30th postoperative days and follow-up thereafter was monthly for 6 to 14 months.

RESULTS

Intraoperative hemostasis was rapid, within at least 3 minutes, and equal in both groups. In the FloSeal™ group, the results were excellent in 98% of the cases. Secondary additional packing due to prolonged bleeding was needed only in one patient. In the Merocel™ group, further packing was needed in two patients (Table 1). Bleeding within the first postoperative week occurred once in the FloSeal™ and twice in the Merocel™ group and required nasal packing management. Duration of hospitalisation was 36% shorter for the FloSeal™ group: the average of 2 days in the FloSeal™ and 3 days in the Merocel™ group was prolonged in some cases by additional systemic illnesses. The cost of FloSeal™ application (Euro 198) was much higher than Merocel™ (Euro 19), but this was largely compensated for by the lower hospitalisation costs.
The main advantage of the application of this new gelatin-thrombin based sealant was high patient satisfaction with high postoperative comfort during nasal breathing and no complaints of pressure such as facial pressure, pain or swelling, as was found in the patients in the Merocel™ group (Table 2). Forty-eight of the patients in the FloSeal™ group had very good nasal breathing comfort and only two had a moderate degree because of blood crusting. In the group with 4 cm Merocel™, 35 patients had moderate comfort for nasal breathing and only 15 were satisfied with their postoperative breathing. Thirty-nine patients complained of periorbital pressure and 41 patients complained about pain on removal of the packing, with a VAS score of greater than 4.
The results of treatment were followed by anterior rhinoscopy and endoscopy of the nasal cavity. On the 2nd day, surplus FloSeal™ was removed. During the follow up, the gelatin-thrombin based sealant was reabsorbed continuously and disappeared after 7 days. Stenoses in the ostiomeatal complex or synechiae in the middle meatus were not found more frequently than in the Merocel™ group. No side effects were observed.

Table 1. General results of the application of FloSeal™ and 4 cm. Merocel™- packing in 100 patients.

General results	FloSeal™ n=50	Merocel™ n=50
Bleeding in postop week 1	1 patient	2 patiens
Duration of hospitalisation	2.1 days	3.3 days
Cost per application	198 Euro	19 Euro
Infections & side effects	none	none

Table 2. Patient-specific results with FloSeal™ and 4 cm Merocel™-packing in 100 patients.

Patient-specific results	FloSeal™ n=50	Merocel™ n=50
Nasal breathing comfort:		
- good	n=48	n=10
- moderate	n= 2	n=35
- poor	n= 0	n= 5
Complaints:		
- facial pressure	n=0	n=39
- pain on removal: VAS 0-3		n= 9
VAS 4-6		n=32
VAS 7-10		n= 9
Follow-up: (6 to 18 months)		
- ostiomeatal stenosis	n=1	n=1
- synechia (middle meatus)	n=2	n=1

(Visual analogue scale (VAS): 0=no pain, 10=severe pain)

DISCUSSION

The dilemma of postoperative scar formation and restenosis in the ostiomeatal complex after endoscopic sinus surgery still remains a problem for many rhinologists. As a result, a variety of stents and special packings have been created and used for improving surgical healing without scar retraction and thus reducing the recurrence of sinusitis. However, there are still many controversial considerations, as reported in the literature (Hosemann et al., 1991; Von Schoenenberg et al., 1993). Many surgeons use nasal packing routinely following nasal surgery, even if there is no bleeding and with the knowledge that removal of the packing is often traumatic for the patient. The more widely used packing is Merocel™, believed to be instrumental in improving breathing comfort with ventilation tubes (Doyle and Stoller, 1983). Illum et al. (1992) showed that these tubes are blocked quickly and do not fit well. They even reported three cases of septal perforations due to traumatic insertion and compression.

At the present time, apart from nasal packing, there are many different hemostatic products with or without fibrin available on the market (Table 3). Systemic hemostatic medications are also used for reducing surgery-related bleeding, but with limited or contradictory evidence of efficacy (Erstad, 2001).
Fibrin, the oldest hemostatic agent, was first used during surgery by Bergel in 1909 to establish hemostasis (Bergel, 1909). More recently, fibrin glue has become increasingly popular. Unfortunately, the ideal characteristics of a hemostatic

Table 3. Treatment after anterior ethmoidectomy.

Treatment	Authors	Patients (n)	Advantages	Disadvantages
Gauze packing	Illum P et al. *(Clin Otolaryngol 1992)*	23 patients	Inexpensive	Pain + bleeding on removal due to adherence to nasal mucosa
Iodiform paraffin paste pack	Von Schönberg M et al. *(J Laryngol Otol 1993)*	71 patients	Inexpensive	Pain + haemorrhage on removal, infections, septal perforations
Fingerstall packing	Illum P et al. *(Clin Otolaryngol 1992)*	32 patients	Easy to remove	Fever, breathing problems, dislocation
Hemostatic balloon in ethmoid cavity	Cox CW et al. *(Laryngoscope 1988)*		Atraumatic removal	Facial pressure + swelling
Pneumatic balloon	Watson MG et al. *(Rhinology 1989)*	37 patients	Atraumatic removal	Frequent adhesion formation, mucosal damage, septal perforation
Merocel™-with ventilation tube	Illum P et al. *(Clin Otolaryngol 1992)*	27 patients	No	Pain + bleeding on removal Blocked ventilation tubes
Fibringlue	Gleich LL et al. *(Otolaryngol Head Neck 95)*	12 patients	high patient satisfaction	
Surgicel	Shinkwin C et al. *(Rhinology 1996)*	60 patients	Less painful removal than Merocel / gauze	Pain on removal, fragmentation on removal in 12%
MeroGel	Jacob A et al. *(Laryngoscope 2002)*	10 mices	Easy to handle	Osteogenetic potential
Gelfoam	Fanous N *(J Otolaryngol 1980)*	8 patients	Nasal breathing	Often used in combination with other resorbable materials

agent differ from an adhesive one. Fibrin glue (Tissucol®, *Baxter, US*) does not adhere strongly to wet tissue; it often flows down before acting and has little impact on the activity of bleeding wounds, which is a problem with many hemostatic products (Davis and Sandor, 1998). Surgicel®, an oxidated cellulose (*Bristol-Myers Squibb, NY*) often does not sufficiently control the hemorrhage resulting from sinus surgery. It is difficult to remove and frequent fragmentation occurs, as reported in a study by Shinkwin et al. (1996). Another product often used in endoscopic sinus surgery is MeroGel®. It is easy to handle; however, Jacob et al. (2002) reported that it has osteogenetic potential. Their study involved placing MeroGel® on traumatised bone in the sinus cavities and the calvarias in mice. These results must also be considered in the use of this product in human surgery. Further studies are necessary to evaluate this potential problem.

FloSeal™ is neither a fibrin glue nor a sponge, but a high-viscosity gel that is effective and attaches well, even if the bleeding is severe and the surface in the ethmoid wound is very irregular and wet. Thus, the success of FloSeal™ may also be due to the special granular nature of the collagen particles, which swell by up to 20% when hydrated by blood and attach well to the irregular wound by the thrombin. The swollen FloSeal™ itself may offer a small tamponade effect.

Another advantage of FloSeal™ is that it can be used also in coagulopathic patients or patients with compromised platelet count and function. Conventional hemostatic agents, such as oxidized cellulose matrices (Surgicel®) or gelatine sponges (Gelfoam®), are unable to enhance this process in coagulopathic patients, even if these products are combined with thrombin, as shown by Weaver et al. (Huggins, 1969; Weaver et al., 2002).

An unresolved problem is the effect on wound healing. Weber et al. (1996) described that an occlusive dressing would have an improved healing effect on the wound, supporting the epithelialisation and reducing the inflammatory reaction and occurrence of necrosis in the earlier stages as well as the development of scar tissue in the later stages. However, it must be noted that wound healing is a very individualized process, especially where intensity and duration of soft tissue reaction are concerned. An intense and frequently local nasal treatment with moisturizing ointment, saline water and, in certain cases, the use of topical steroid spray can optimise postoperative healing. With our small sample of 50 patients, it is difficult to determine if there would even be an improvement in wound healing. Chandra et al. (2003) described increased degrees of granulation tissue and adhesion formation after using FloSeal™. We think that repetitive cleaning of the nose just after surgery is mandatory to impede adhesion formation. In our study, there were no differences between the FloSeal™ and the Merocel™ group concerning the formation of synechiae and ostiomeatal stenoses.

A primary advantage of using FloSeal™ for postoperative hemostasis in comparison to Merocel™ packing is the high patient satisfaction, which is shown in Table 2: patients have an increased sensation of nasal airway patency with mostly good nasal breathing comfort and are spared the painful experience of packing removal, an unnecessary process due to the

reabsorption of the material by the body. Many patients undergoing a second operation remembered only the unpleasant removal of the packing and the breathing disorders, and were happy about the improvements.

FloSeal™ is bovine-derived thrombin and collagen, raising anxiety about "bovine spongiform encephalopathy" (BSE). However, the risk is minimal and to date, no cases of prion-associated Creutzfeldt-Jakob disease have been described (Fusion Medical Tec, Inc., 2001). In Europe, all registered medical products of animal origin, such as FloSeal™, must pass the Guidelines of "BSE and Scrapie-Safety measurements for remedies" of the European federal ministry and must prove a maximal-minimal risk of virus contamination (Winterbottom and Shargill, 2000; internal report of Fusion Medical Technologies).

Nevertheless, there is awareness of the potential for development of inhibitors of bovine thrombin and human factor V (Banniger et al., 1993; Nichols et al., 1993). Since 1985, at least 180 million vials of topical thrombin have been sold. Worldwide, 80 cases have been reported in which immune-mediated coagulopathy has been found postoperatively associated with surgical use of bovine topical thrombin due to factor V antibodies, which cross-react frequently with the patient's factor V (Nichols et al., 1997). However, no patients have exhibited excessive perioperative bleeding or postoperative thrombosis, even when they were re-explored (Bänniger et al., 1993). Weaver et al. (2002) studied this human thrombin and/or factor V antibody problem in 89 patients who were treated with FloSeal™. There were no evident delayed or significant bleeding complications. The development of inhibitors of bovine thrombin as well as co-immunization to factor V occurs frequently in thrombin-associated surgery, but it depends on the amount of applied fibrin, and primarily on the type of application. This was shown in a study by Bänniger et al. (1993), in which all patients in whom vascular or cardiac valve graft material was pretreated directly with fibrin glue showed development of thrombin inhibitors; in contrast, none of the patients with only topically applied fibrin glue showed such changes. In addition, in the present production of thrombin products, attempts are being made to purify the thrombin in order to reduce the factor V levels. Human source thrombin would eliminate many of these problems, but it has limitations as well, considering the risk of human viral diseases transmission.

CONCLUSIONS

FloSeal™ is an expensive, but safe and efficacious method for hemostasis in endoscopic sinus surgery with high patient satisfaction and a quick and easy mode of application. Undesired effects on wound healing or the formation of restenoses or synechiae in the ostiomeatal complex were not observed. No systemic side effects like allergic or anaphylactic reactions occurred.

Acknowledgement

This work was supported by Fumedica, Switzerland. Many thanks to Dr. F. Harris, PhD, Tucson, Arizona, USA, for her editorial assistance.

REFERENCES

1. Banninger H, Hardegger T, Tobler A, Barth A, Schupbach P, Reinhart W, Lammle B, Furlan M. (1993) Fibrin glue in surgery: frequent development of inhibitors of bovine thrombin and human factor V. Br J Haematol 85: 528-532.
2. Bergel S (1909) Ueber Wirkungen des Fibrins. Dtsch Med Wochenschr. 35: 633.
3. Chandra RK, Conley DB, Kern RC (2003) The effect of FloSeal™ on mucosal healing after endoscopic sinus surgery: A comparison with thrombin-soaked gelatin foam. Am J Rhinol 17: 51-55.
4. Cox CW, Barker JH (1988) A hemostatic device for endoscopic surgery. Laryngoscope 98: 579.
5. Davis B, Sandor GK (1998) Use of fibrin glue in maxillo-facial surgery. J Otolaryngol 27: 107-112.
6. Dowley AC, Strachan DR (2001) Allergy to Merocel™ nasal packs causing septal perforation and inferior turbinate necrosis. J Laryngol Otol 115: 735.
7. Doyle DE, Stoller KP (1983) Intranasal airway-pack: Description of a new device. Laryngoscope 93: 808-809.
8. Ellengala DB, Maartens NF, Laws ER Jr (2002) Use of FloSeal™ hemostatic sealant in transsphenoidal pituary surgery: technical note. Neurosurgery 52: 513-516.
9. Erstad BL (2001) Systemic hemostatic medications for reducing surgical blood loss. Ann Pharmacother 35: 925-934.
10. Hosemann W, Dunker I, Göde U, Wiegand ME (1991) Experimentelle Untersuchungen zu Wundheilung in den Nasennebenhöhlen. HNO 39: 111-115.
11. Huggins S (1969) Control of hemorrhage in Otorhinolaryngologic surgery with oxidized cellulose. Eye Ear Nose Throut Mon 48: 420-423.
12. Illum P, Grymer L, Hilberg O (1992) Nasal packing after septoplasty. Clin Otolaryngol 17: 158-162.
13. IQS Immuno Quality Assurance System Booklet (2001) Vienna, Baxter AG
14. Jacob A, Faddis BT, Chole RA (2002) MeroGel hyaluronic acid sinonasal implants: osteogenic implications. Laryngoscope 112: 37-42.
15. Nichols WL, Daniels PK, Fisher PK, Owen WG, Pineda AA, Mann KG (1993) Antibodies to bovine thrombin and coagulation factor V associated with surgical use of topical bovine thrombin or fibrin glue: a frequent finding. Blood 82: 39 (suppl 1).
16. Nichols WL, O'Marcaigh AS, Daniels PK, Fisher PK, Gilchrist GS (1997) Incidence of immune- mediated coagulopathies associated with surgical use of fibrin sealant ("glue") or bovine topical thrombin. Thrombos Hämostasis 78: 177 (suppl 1).
17. Oz MC, Cosgrove DM, Badduke BR, Hill JD, Flannery MR, Palumbo R, Topic N (2000) Fusion Matrix Study Group: Controlled clinical trial of a novel hemostatic agent in cardiac surgery. Ann Thorac Surg 69: 1376-1382.
18. Reuthebuch O, Lachat ML, Vogt P, Schurr U, Turina M (2000) FloSeal™: A new hemostyptic agent in peripheral vascular surgery. Vasa 29: 204-206.
19. Shinkwin CA, Beasley N, Simo R, Rushton L, Jones NS (1996) Evaluation of Surgicel Nu-knit, Merocel™ and Vasolene gauze nasal packs: A randomised trial. Rhinology 34: 41-43.
20. Spillman D (1981) Aspiration von Nasentamponaden mit Todesfolge. Laryngo-Rhino-Otol 60: 56.
21. Von Schoenenberg M, Robinson Ph, Ryan R (1993) Nasal packing after routine nasal surgery - is it justified? J Laryngol Otol 107: 90.
22. Watson MG, Campell JB, Shenoi PM (1989) Nasal surgery: does the type of nasal pack influence the results? Rhinology 27: 105-111.
23. Weaver FA, Hood DB, Zatina M, Messina L, Badduke B (2002) Gelatin-thrombin-based hemostatic sealant for intraoperative

bleeding in vascular surgery. Ann Vasc Surg 16: 286-293.
24. Weber R, Keerl R, Draf W, Wienke A et al (1995) Periorbitales Parafingranulom nach Nasennebenhöhlenop-eration. Otorhinolaryngologia Nova 5: 87-90.
25. Weber R, Keerl R, Huppmann B, Schick B, Draf W (1996) Der Einfluss der Nachbehandlung auf die Wundbehanlung nach endonasaler Nasennebenhöhlenoperation. Laryngorhinootol 75: 208-214.
26. Weber R, Hochapfel F, Draf W (2000) Packing and stents in endonasal surgery. Rhinology 38: 49-62.
27. Weber R, Kratsch B (2001) Endonasale Mediandrainage, Indikationen und chirurgische Technik. HNO 49: 1047-1059.
28. Winterbottom N, Shargill NS (2000) Safety considerations of bovine gelatine and bovine thrombin Components of FloSeal™ Matrix Hemostatic Sealant. Fusion Medical Technologies GmbH (Internal report of Fusion Medical Technologies).

Marco Caversaccio
University Clinic of ENT
Head and Neck Surgery
Inselspital
3010 Berne
Switzerland

Tel: +4131-632-4174
Fax: +4131-632-4900
E-mail: marco.caversaccio@insel.ch

ANNOUNCEMENT