The Use of Self-Assembling Peptides (PuraStat™) in Functional Endoscopic Sinus Surgery for Haemostasis and Reducing Adhesion Formation. A Case Series of 94 Patients

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ABSTRACT

Introduction: Functional endoscopic sinus surgery (FESS) is a treatment option for patients with chronic rhinosinusitis. Bleeding and adhesions are common complications postoperatively.

Objective: To assess the effectiveness of PuraStat™ (3-D Matrix Medical Technology Pty Ltd, Melbourne, Australia) for use in FESS to achieve haemostasis and reduce adhesion formation.

Materials and Methods: A retrospective chart review over four years was performed on 94 patients undergoing FESS by a single surgeon, using PuraStat™ in absence of nasal packing.

Results: Twenty-eight patients underwent complete FESS and 66 cases limited FESS most often combined with nasal surgery. Six patients had bleeding postoperatively, of which only four required additional treatment (4.25%). Twenty-three patients (24.47%) required debridement during the follow up, simply performed by suction for 13 or by scissors for 10. No patient required revision surgery for adhesion.

Conclusion: PuraStat™ used for the first time in context of FESS seems to be effective in achieving haemostasis, reducing adhesion formation, and avoiding nasal packing in most patients.

INTRODUCTION

Functional endoscopic sinus surgery (FESS), one of the most common surgeries performed in otolaryngology, has become the standard of care for patients suffering from chronic rhinosinusitis (CRS) and failing maximal medical therapies.[1] CRS is a prevalent condition affecting millions of individuals of all ages and genders and has a significant impact on quality of life.[2] In most cases, CRS can be managed conservatively; however, surgical intervention is warranted in patients with failed maximal medical therapy, complicated CRS, or suspected anatomical abnormalities.[3] FESS has seen a significant evolution in surgical advancements over the past few decades and is currently the treatment option for these patients.[4] The surgical approach aims to restore drainage and airflow throughout the affected sinuses and to provide access for topical therapies.[5]

Sinonasal surgery carries a moderate bleeding risk given the vascularity of nasal mucosa, particularly in inflammatory conditions such as CRS.[6] Haemostasis is imperative to prevent postoperative complications, such as bleeding and adhesions. Adhesions, also known as synechiae, form fibrous tissue from opposing moist surfaces intranasally and therefore can inhibit normal airflow and impair mucociliary clearance and access for topical therapies, counteracting the initial indication for surgery.[7]

Nasal packing is among the wide range of practices used to ensure haemostasis.[8] However, traditional nasal packing can contribute to patient discomfort, rhinorrhea, crusting, or excessive pressure leading to delayed healing, and is a potential source of infection.[9] To avoid the use of nasal packing, different topical haemostatic agents have been used.[9-12] The ideal haemostatic agent should prevent and manage epistaxis, allow healing of traumatised mucosa, and mould within the confines of the nasal cavity without further damage to epithelium.[10]

PuraStat™ (3-D Matrix Medical Technology Pty Ltd, Melbourne, Australia) is a haemostatic agent, CE marked and licensed in Australia, which fulfills these criteria. It is a transparent 2.5% aqueous acidic solution composed of three chemically synthetized amino acids (RADA: aRginine, Alanine, aspartic aciD, Alanine) in a sequence repeated four times, forming RADA16 peptides. On exposure to an ionic solution such as blood, the peptides self-assemble and form a three-dimensional hydrogel matrix that mechanically contributes to haemostasis within seconds.[13] The mode of action is independent of the patient's coagulation. It is indicated for haemostasis from small blood vessels and capillaries in situations encountered during surgery when haemostasis by ligation or standard means is insufficient or impractical.[13,14]

We have used this haemostatic agent in a series of consecutive patients undergoing FESS. The aim of this study is to assess the effectiveness of PuraStat™ in achieving haemostasis and reducing adhesions following FESS.

MATERIALS AND METHODS

Study design

This case series was a retrospective chart review of 94 consecutive patients undergoing FESS, using PuraStat™, and operated on by a single senior ear, nose, and throat (ENT) surgeon in a single centre in Perth, Western Australia, over a four-year period. Ethics approval was obtained from St John of God Health Care Human Research Ethics Committee (ref: 1619).

Patient population

The study population included adult patients failing medical therapies who underwent FESS procedures in combination with nasal surgery (septoplasty and/or turbinoplasty). Both primary and revision surgeries were included. Patients taking anticoagulants and/or antiplatelets at therapeutic doses were managed according to specialist recommendations. Patients were excluded if another haemostatic agent had been used (in addition to PuraStat™). Patients were discharged the day after surgery with a recommendation to perform frequent saline nasal irrigations (no less than four times a day). A follow-up visit was scheduled postoperatively. Patient characteristics, indication for surgery, extent of surgical intervention, bleeding, and adhesion details were recorded. A de-identified database on Excel® (Microsoft Corporation, Redmond, Washington) file was created based on patient's documentation.

Surgical categories

Procedures were performed according to the minimally invasive sinus technique (MIST), including a combination of maxillary antrostomy, ethmoidectomies, sphenoidotomies and frontal sinus (Draf IIa, or Draf III), and turbinate reduction and/or septoplasty. FESS procedures were categorised into two groups according to the extent of the surgery: complete FESS (including all sinuses—maxillary antrostomy, ethmoidectomy, sphenoidotomy, and frontal sinusotomy) or limited FESS (anything less than complete FESS, usually involving antrostomy and ethmoidectomy). The surgical extent was dictated by the patient's disease process and the surgeon's clinical judgement. No systemic postoperative antibiotic therapy or corticosteroids were used. Only topical steroids were used in cases with polyposis.

Material used—PuraStat™

PuraStat™ (3D-Matrix) is a colourless peptide hydrogel that comes packaged in a pre-filled sterile syringe (available in a 3mL and 5mL form) with a thin application nozzle. It does not require any preparation and is stored at refrigerated temperatures between 2°C and 8°C (Fig. 1). At completion of the FESS procedure, PuraStat™ was applied in a thin and even layer as close as possible to the bleeding point and haemostasis was rapidly achieved in absence of nasal packing. A similar application technique has been outlined previously.[9]

Figure 1. PuraStat™ RADA16 Self-Assembling Peptide Hydrogel © 3-D Matrix.

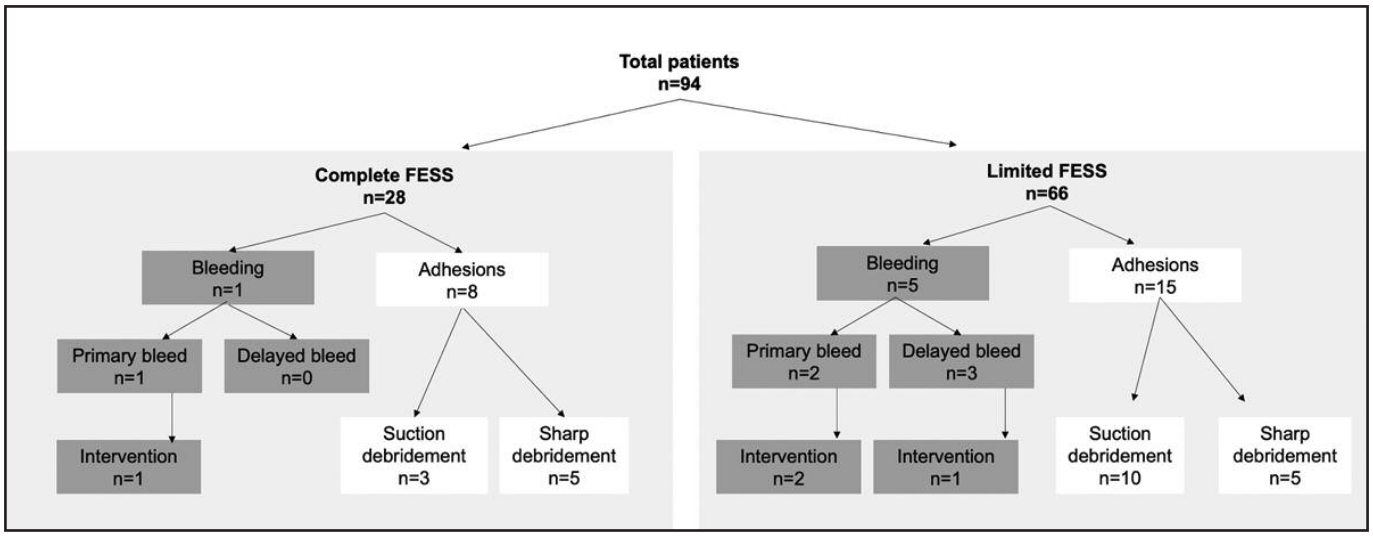

Figure 2. Flowchart of patients based on extent of surgery and outcomes.

Outcomes and objectives

The primary objective was to assess the effectiveness of PuraStat™ in reducing primary bleeding, with the secondary objectives to assess at follow-up visits the incidence of delayed bleeding and adhesion formation (performed via endoscopic observation of the nasal mucosa). Primary bleeding was defined as bleeding occurring within 24 hours of surgery and secondary or delayed bleeding defined as occurring ≥24 hours postoperatively.

Data analysis

Statistical analysis was performed using descriptive statistics for continuous variables, and categorical variables expressed as proportions. Patient demographics were reported. The rate of successful haemostasis, and rate of adhesions formation, were calculated as a proportion of total patients undergoing FESS.

This case series has been reported in line with the PROCESS criteria.[15]

RESULTS

Results were analysed from a total of 94 consecutive patients who underwent surgery over the study period from May 2017 to February 2021. There were 38 males and 56 females, with ages ranging from 18 to 83 years (median 48 years, mean ± SD 47.91 ± 15.79 years). Table I lists patient characteristics. The most common indication for undergoing surgery was CRS with or without nasal polyposis. Twenty-eight patients underwent a complete FESS procedure, of which the majority also underwent a septoplasty (25/28) and turbinate reduction surgery (27/28). Sixty-six patients had a limited FESS procedure, of which the majority also underwent a septoplasty (59/66) and turbinate reduction surgery (62/66). Of the total 94 patients, seven were considered revision surgery. One patient didn't show up for control. These results are illustrated in Figure 2.

Bleeding

A total of six patients (6.38%) experienced postoperative bleeding. These results are summarized in Table II. One patient had undergone a complete FESS and five had a limited FESS. There were three patients with primary bleeds (either in theatre or occurring as emerging from anaesthesia), one of which the patient was

Table I
Patient characteristics

CHARACTERISTICS	PATIENTS (n=94)
Age, mean years (range)	47.91 (18–83)
Sex, n (%)	
Female	56 (59.57%)
Male	38 (40.43%)
Surgical indication, n (%)	
ARS or recurrent ARS	13 (13.83%)
CRSsNP	37 (39.36%)
CRSwNP	41 (43.62%)
CSF rhinorrhea	1 (1.06%)
Sinonasal tumour	2 (2.13%)
Surgical extent, n (%)	
Complete FESS	28 (29.79%)
Limited FESS	66 (70.21%)
Primary or revision FESS, n (%)	
Primary FESS	87 (92.55%)
Revision FESS	7 (7.45%)
Adjuvant surgical procedures, n (%)	
Septoplasty	84 (89.36%)
Turbinate reduction	89 (94.68%)
Polypectomy	47 (50.00%)
First postoperative review, mean days (range)	13.89 (7–30)

ARS: Acute rhinosinusitis; CRSsNP: chronic rhinosinusitis without nasal polyps; CRSwNP: chronic rhinssinusitis with nasal polyps; CSF: cerebrospinal fluid

Table II
Patient characteristics

CHARACTERISTICS	PATIENTS (n=94)
Bleed	6 (6.38%)
Primary	3 (3.19%)
Secondary	3 (3.19%)
Gender	
Female	5
Male	1
Extent of surgery	
Complete FESS	1
Limited FESS	5
Intervention required	4 (4.26%)
Primary bleed	3 (3.19%)
Secondary bleed	1 (1.06%)
Type of intervention	
Cautery + Surgiflo	1
Cautery + additional PuraStat™	1
Cautery alone	1
Packing	1
Other factors	
Suspected or confirmed coagulopathy	2
On anticoagulation/antiplatelets post-op	1

Table III
Results of patients with adhesion formation

CHARACTERISTICS	PATIENTS (n=23/94)
Adhesion formation	
Total	23 (24.47%)
At first follow-up visit	18 (19.15%)
Gender	
Female	16
Male	7
Extent of surgery	8
Complete FESS	15
Limited FESS	
Intervention (debridement)	
Suction	13 (13.83%)
Scissors (sharp)	10 (10.64%)
Adhesion location	
Inferior turbinate / septum	12
Medial turbinate / lateral wall	7
Inferior turbinate/septum + medial turbinate/ lateral wall	4
Adhesion final outcome	18
Resolved adhesions	5
Persisting adhesions	

suspected to have a coagulopathy. These three patients required the use of cautery for haemostasis. In addition to cautery, SURGIFLO® (absorbable gel haemostat) (Ethicon, Somerville, New Jersey) was used in one patient, and a second application of PuraStat™ was successfully used in another. Three other patients experienced a secondary bleed, on days two, five, and nine, respectively. Only one of them required intervention; this patient had been restarted on his usual dual antiplatelet therapy the day after surgery and had bilateral packing (Rapid Rhino®, Smith & Nephew, Watford, United Kingdom) inserted on day five. The other two patients were managed conservatively, despite one of them having confirmed Von Willebrand's disease. In total, four patients (three primary bleeds and one secondary bleed) required intervention for bleeding (4/94: 4.25%). All four patients had also undergone a septoplasty and turbinate reduction surgery in combination with their limited FESS (3/4 patients) or complete FESS (1/4 patients). There were no re-bleeds recorded from any of the patients with primary or secondary bleeds.

Adhesions

A nasal endoscopy was performed at the first follow-up visit occurring between seven and 30 days after surgery (median 15 days, mean ± SD 13.95 ± 3.72 days). On average, the subsequent follow up was performed on day 42 and ranged from 28 to 79 days. No material residue was identified, and all patients expressed comfort without any pain reported regarding adhesion formation. A total of 23 patients (24.47%) were found to have adhesions formation during the full follow-up period, of which eight had undergone a complete FESS and 15 a limited FESS. Eighteen (19.15%) of these 23 patients were found to have adhesions at the first follow-up visit. The most common site found to have adhesion formation was the inferior turbinate/septum (n=11/23, 47.83%). Table III lists sites and characteristics of adhesions found in patients undergoing FESS. Debridement was performed in these cases in the outpatient setting by either suction (n=13) or scissors (n=10). As a result, 71 patients in total were found to have no adhesions and 13 had adhesions that were easily removed via suction division. None of the patients who had required intervention for haemostasis

presented with adhesion formation. Furthermore, no patients in this case series required revision surgery for adhesion.

DISCUSSION

Part of the success of FESS as a surgery depends on the degree of haemostasis and postoperative wound healing to prevent poor outcomes such as bleeding and adhesion formation.[16] Many types of nasal packing are available, and although they are often utilised as a safety measure postoperatively, there still remains much debate on the optimal use and type of nasal packing after FESS.[17] The most common disadvantage of nasal packing, particularly non-absorbable, is the discomfort experienced by the patient, as well as mucosal damage and possible impairment of muco-ciliary function associated with composition and removal of packing.[18] We demonstrated that the application of PuraStat™, a peptide hydrogel, is effective in limiting bleeding and adhesions, whilst avoiding nasal packing post-FESS in most patients in this study.

Up to 25% of postoperative haemorrhage in FESS may occur within 24 hours. Although a significant bleed can occur up to six weeks postoperatively, the most common timeframe is between one and two weeks after FESS.[6] Similarly, in our study, of the six patients who experienced a bleed, three had postoperative bleeds on days two, five, and nine. The other half of the patients had a recorded primary bleed (occurring within 24 hours). This discrepancy is likely due to smaller numbers in our cohort, and contributing to this, was the fact that one of the patients with a primary bleed had a suspected coagulopathy. Unfortunately, there are varied definitions in the literature when investigating bleeding during and after FESS. For example, some studies have identified bleeding postoperatively in FESS as severe haemorrhage, a patient requiring a blood transfusion or a return to surgery for haemostasis, or have recorded bleeding as a complication only when it necessitates a readmission.[19-22] Excessive perioperative bleeding has been reported to occur in approximately 5% of patients after FESS, with 0.76% of major bleeds needing a transfusion.[11,23] Comparably, in our study the rate of patients with any bleeding was 6.38% but the rate of those that required additional treatment was only 4.25% (n=4/94), with all having turbinate reduction. None of the patients in this study required a blood transfusion. In a large retrospective study of 3,402 patients over 25 years, Stankiewicz et al. only considered bleeding as a complication when it necessitated packing or surgery for control.[24] Thus, according to our definition of haemostatic effectiveness, like that of Stankiewicz et al., 95.74% of patients (n= 90/94) who underwent FESS in our study did not have any bleeding postoperatively or in those that did, did not require any intervention. One of the most common complications of FESS is the postoperative formation of adhesions, which is often a reason for revision surgery in up to 25% of these patients.[24-26] These may occur despite cautious surgical technique and postoperative care. The incidence of synechiae recorded in the literature, ranges widely from about 10-40%.[26-29] Again, the definitions differ, some include all adhesions found in the postoperative period; whereas, other studies include only patients with significant scarring. In a double-blinded prospective comparison of three haemostatic absorbable agents, Antisdel et al. found the overall adhesion rate was 19.4%, with 4.2% of patients having severe synechiae formation but the rate of revision surgery was not detailed.[11] In another prospective study looking at longer-term outcomes of synechiae following FESS, Henriquez et al. found that the overall incidence of adhesions at baseline for the entire cohort was 36.7%.[30] The rates in our study are similar and are at the lower range of incidences previously stated.[3,11,12] Twenty-three (24.47%) patients were found to have adhesions throughout their postoperative follow-up appointment. However, only 10 required sharp debridement, while the remaining 13 had adhesions easily debrided with suction. As a result, 71 patients had no adhesions found during the first follow-up period and 13 patients had adhesions easily removed. Most patients who had adhesions were found to be resolved after intervention. No patient required revision surgery.

Evidently, the incidence of adhesion formation and bleeding after sinus surgery differs considerably in the literature and is likely related to the heterogeneity of studies. Some confounding variables include the extent of surgery, septoplasty, or other adjuvant surgery involved, patient factors (smoking and comorbidities), and the type of nasal packing used. Wang et al. conducted a systematic review and meta-analysis to compare the efficacy of non-absorbable versus absorbable nasal packing in FESS.[31] Their study found there may be evidence that absorbable nasal packing can provide some improved outcomes even when, compared to non-absorbable packing after FESS, there was a lack of homogeneity between studies.[31] They were unable to make definitive conclusions from their review and suggested the need for more randomized clinical trials on the topic. Similar findings were established in another meta-analysis and systematic review on middle meatal packing after FESS. Authors concluded that it does not significantly decrease the risk of adhesion formation.[32]

PuraStat™, as a topical haemostat, has been used extensively in gastrointestinal endoscopic procedures[33-37] as well as in cardiovascular surgery[38-40] with successful haemostasis rates ranging from 72.6–100%.[14] However, clinical evidence within the field of ENT surgery is limited. Lee and Ananda (2017) published a case series of 60 patients undergoing turbinate reduction surgery (TRS).[9] Comparable to this current study, exclusion criteria included any concurrent haemostatic adjuncts and a similar technique of PuraStat™ application and standard postoperative instructions were used.[9] Lee and Ananda found that PuraStat™ was very effective, with none of their patients experiencing bleeding or adhesion formation postoperatively. Although this is an excellent outcome, it does differ from the total adhesion and bleeding rates in our study, 24.47% and 6.38%, respectively. This is likely due to several differences between the two studies. Lee and Ananda's case series includes patients with TRS surgery only[9]; whereas, our study examines a cohort of patients who have undergone FESS (complete or limited), including TRS, septoplasty, and polypectomies. As this involves a greater extent of diseases and surgical interventions, there may have been an increased risk of adhesions and bleeding.[24] Additionally, data was recorded only from the first follow up at four weeks in the case series of 60 patients, unlike our current study where a longer follow up extended up to several months, resulting in identification of a further five patients with adhesions (whereas, only 18 of 23 patients were identified at the first follow-up appointment). It was noted that all patients were compliant with their postoperative care and nasal irrigation in the case series by Lee and Ananda. Nasal saline irrigation is almost universally recommended post-FESS and plays an

important role in wound healing and prevention of crusting and synechia formation.[7,41,42] Patient compliance with postoperative care was not formally recorded in our study and could impact patient outcomes. Despite these differences, we found a promising overall effectiveness of PuraStat™ for haemostasis and adhesion reduction.

This study has several limitations. There was no control group, resulting in difficulty making comparisons to other types of haemostatic agents or packing. Although all surgeries were performed by a single surgeon in a single centre, the patient population is heterogenous, including the extent of disease and surgery, surgical indications, and adjuvant operations performed. Also, certain variables that may influence outcomes were not recorded, such as associated comorbidities, smoking history, and patient compliance. Furthermore, it would be valuable to identify the site of postoperative bleeds, as was done with postoperative adhesions. Additionally, it would be valuable to record other quantifiable information to assess these outcomes, for example, grading of severity using the scarring component of the Lund-Kennedy endoscopic score.[30] The total adhesion rate in this study using PuraStat™, although within the range found in literature, does not compare as greatly as some other non-absorbable dressings, and it may be worthwhile considering its use in conjunction with another method to prevent synechiae formation postoperatively.[31] Despite the patient population being close to 100 patients, a larger study would be useful to allow analyses with power.

PuraStat™ is suitable for endoscopic endonasal use and its transparent nature allows clear visualization of the treated surfaces. To our knowledge, this is the first study to report on the use and outcomes of PuraStat™ in endoscopic sinus surgery.

CONCLUSION

The demonstrated simple technique of PuraStat™ application in patients undergoing sinus surgery was effective in achieving haemostasis, reducing adhesion formation, and avoiding nasal packing in most patients. Further prospective trials are warranted to validate these findings and to assess the safety and effectiveness of PuraStat™ comparable to the current standard care. **STI**

AUTHORS' DISCLOSURES

Dr. Bagot d'Arc and Ms. Delin are consultants for 3-D Matrix. All other authors have no conflicts of interest to disclose.

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