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TITLE: Randomized Controlled Trial to Evaluate the Efficacy of PuraSinus versus Bioresorbable Nasal Dressings in Improving Patient Comfort During Postoperative Debridements

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Synposis

Study Title	Randomized Controlled Trial to Evaluate the Efficacy of PuraSinus versus Bioresorbable Nasal Dressings in Improving Patient Comfort During Postoperative Debridements
Problem statement	Postoperative care of patients undergoing endoscopic sinus surgery (ESS) is important both to minimize discomfort for the patients and to obtain the optimal long-term outcomes. Postoperative sinonasal cavity debridement has been advocated to prevent potential synechiae and sinus ostial stenosis, as well as to improve patient symptoms. Removal of old blood, nasal secretions, crusting, and unabsorbed packing are thought to reduce the inflammatory load, minimize potential for scarring, and allow for improved access of topical medications. However, the debridement procedure can cause bleeding, pain, and discomfort which may interfere with the effective execution of postoperative care. Postoperative formation of adhesions, scarring, synechiae, middle turbinate lateralization, ostial stenosis and edema are major concerns often addressed by the placement of bioresorbable packing intraoperatively. Bioresorbable packing has been demonstrated to decrease the incidence of adhesions and bleeding while improving patient comfort compared to no packing at all. However, bioresorbable nasal dressings, such as PosiSep X, oftentimes have not dissolved by the time of the first postoperative debridement 1-2 weeks after the surgery and therefore need to be removed. The removal of bioresorbable packing during postoperative debridements is usually an uncomfortable experience for the patient. An ideal nasal dressing would optimize both patient comfort as well as wound healing. PuraSinus is a novel topical haemostatic agent based on nanotechnologies in the form of a transparent hydrogel suitable for endoscopic use and for which the use in sinonasal surgery could achieve these various goals. The potential of PuraSinus to enhance endoscopic mucosal wound healing may play a role in optimizing patient comfort during postoperative debridements after ESS. However, clinical evidence on its effectiveness in ESS is limited. We aim to perform a randomized controlled trial to evaluate the efficacy of PuraSinus in improving patient comfort during postoperative debridements among patients who underwent ESS.
Type of Study	prospective, randomized, controlled, single-blinded study.
Study Participants	Patients with chronic rhinosinusitis undergoing bilateral endoscopic total ethmoidectomy receiving standard of care and PosiSep X on one side and PuraSinus in addition to standard of care on the other side. The patients are their own control.
Planned Sample Size	30 patients (over a maximum 12 month recruitment period).
Follow-up duration	All patients will be followed up as per standard clinical care with repeat examination 1 week, 4 weeks, and 12 weeks after surgery.
Planned Study Period	18 months
Primary Objective	• To investigate the efficacy of PuraSinus in reducing patient pain during postoperative debridement after ESS compared to PosiSep X.
Secondary Objectives	• To assess the time needed to perform postoperative debridements in patients with PuraSinus in their ethmoid cavity after endoscopic sinus surgery • To assess the efficacy of PuraSinus in preventing postoperative complications from endoscopic sinus surgery (adhesions, bleeding, crusting, edema) • To assess the amount of PuraSinus retained in the ethmoid cavity postoperatively • To assess the need for further intervention postoperatively in patients

Primary Endpoint	• Patient-reported pain (1-10) during postoperative debridement of ethmoid cavity 1 week after surgery
Secondary Endpoints	• Time required to perform sinonasal cavity debridement for ethmoid cavity 1 week after surgery • Postoperative healing assessment of mucosal edema, crusting, secretions, and polyps 1 week, 4 weeks, and 12 weeks using validated Lund-Kennedy scoring rubric. • Presence of adhesions at 1 week, 4 weeks and 12 weeks. • Severity of bleeding during week 1 debridement • Amount of residual PuraSinus or bioresorbable dressing in ethmoid cavity 1 week after surgery • The need for further intervention postoperatively 4 weeks after surgery as evaluated by an independent blinded reviewer of the video-endoscopy
Intervention (s)	PuraSinus randomized to one ethmoid cavity after bilateral endscopic sinus surgery and bioabsorable nasal dressing to the contralateral ethmoid cavity
Inclusion criteria	• Patient is 18 years of age or older • Patient has a clinical indication for and has consented for primary or revision bilateral ESS and had evidence of ethmoid disease bilaterally (Lund-Mackay score at least 1 on each side). • Diagnosed with CRS based on American Academy of Otolaryngology – Head and Neck Surgery guidelines
Exclusion criteria	• Patient has a known history of immune deficiency such as immunoglobulin G or A subclass deficiency, or Human Immunodeficiency Virus (HIV). • Patient has concurrent condition requiring active chemotherapy and/or immunotherapy management for the disease (e.g. cancer, HIV, etc.) • Patient has clinical evidence of disease or condition expected to compromise survival or ability to complete follow-up assessments during the 90 day followup period. • Patient is currently participating in another clinical trial. • Patients with known coagulation disorders. • Patients with allergies to shellfish.
Study management	The study is an Investigator Initiated Trial sponsored by the University of Southern California. A grant will be provided by 3-D Matrix in the framework of an agreement with the University of Southern California.
Study timelines	Planned start date: By late 2021 End of recruitment latest: By end of 2022 End of follow-up period latest: By early 2023 End of study latest: By early 2023 Study results latest: By mid-late 2023

1.0 BACKGROUND AND HYPOTHESES

Chronic rhinosinusitis (CRS) is one of the most common health problems in the United States and there is evidence that it is increasing in its prevalence and incidence. An estimated 16% of the adult population (>30 million people) is affected annually.[1] Chronic sinusitis causes significant physical symptoms, negatively affects quality of life, and can substantially impair daily functioning. A conservative estimate is that chronic sinusitis results in 18 to 22 million U.S. physician office visits annually, and all forms of sinusitis result in significant health care expenditures.[2]

The inflammatory response to CRS manifests itself in patient-reported symptoms such as facial pain and pressure, nasal congestion, edema of various local tissues, headache and a variety of other symptoms. Addressing the underlying causes of sinusitis and controlling the symptoms caused by the inflammatory process is the focus of medical therapy. Patients who are recalcitrant to medical therapy may be referred for functional endoscopic sinus surgery (ESS) to improve ventilation and drainage and to remove polyps.

Several hundred thousand ESS procedures are performed in the U.S. annually and this number appears to be increasing. Primary ESS typically involves uncinectomy, ethmoidectomy, maxillary antrostomy, and frontal sinus surgery (sinusotomy). Typical anterior ethmoidectomy involves dissection and removal of the bulla ethmoidalis (the first and most constant ethmoid cell in a highly variable anatomy), anterior ethmoidal cells and agger nasi cells. Complete ethmoidectomy is accomplished by extending the dissection through the basal lamella to reach and remove septations of the posterior ethmoid cells and to reach the sphenoid sinus.

Postoperative care of patients undergoing ESS is important both to minimize discomfort for the patients and to optimize long-term outcomes. Postoperative sinonasal cavity debridement has been advocated to prevent potential synechiae and sinus ostial stenosis, as well as to improve patient symptoms.[3] Removal of old blood, nasal secretions, crusting, and unabsorbed packing are thought to reduce the inflammatory load, remove potential for scarring, and allow for improved access of topical medications. However, extensive debridement can cause bleeding, pain, and discomfort which may interefere with the effective execution of postoperative care. Furthermore, debridement is time consuming and may cause mucosal damage and thus delay the postoperative healing process.

Formation of adhesions, scarring, synechiae, middle turbinate lateralization, ostial stenosis and edema are major concerns often addressed by the use of bioresorbable packing postoperatively. Bioresorbable packing has been demonstrated to decrease the incidence of adhesions and bleeding while improving patient comfort compared to no packing at all.[4] Commonly used bioresorbable packing placed in the middle meatus include chitosan-based nasal dressings such as PosiSep X. Bioresorbable nasal dressings have favorable wound healing characteristics and slowly degrade over time. However, bioresorbable nasal dressings oftentimes have not dissolved by the time of the first postoperative debridement 1-2 weeks after the surgery and therefore need to be manually removed. The removal of bioresorbable packing during postoperative debridements has similar levels of discomfort as the removal of tradiational nonresorbable packing.[5] While bioresorbable packing has advantages in preventing postoperative complications such as adhesions and bleeding, the packing is noticeably uncomfortable to remove for patients during postoperative debridements. An ideal nasal dressing would optimize both patient comfort as well as wound healing.

PuraSinus is a novel topical hemostatic agent based on a self-assembling peptide nanotechnology in the form of a transparent hydrogel suitable for endoscopic use. In otolaryngology, a case series was published by Ananda in 2017 where PuraSinus was applied to the inferior turbinates in 60 patients who underwent endonasal powered turbinoplasty where results were observed for post-operative re-bleeding and adhesion formation. In all 60 patients, no post-operative re-bleeding was observed and there was no adhesion formation.[6]

The hydrogel form of PuraSinus allows the surgeon to only have to apply a thin layer of the product to the surgical site to achieve its desired hemostatic and wound healing effect. This minimizes the amount of the hydrogel needed to be placed into the ethmoid cavity, which in theory would limit the amount of debridement necessary after surgery leading to minimal patient discomfort.

Therefore, we hypothesize that PuraSinus will have less patient discomfort during postoperative debridement compared to traditional bioresorbable packing. We also hypothesize that PuraSinus will have the same incidence of adhesions, bleeding, crusting, edema as PosiSep X.

2.0 OBJECTIVES AND PURPOSE

The objective of this study is to assess the efficacy of PuraSinus in improving postoperative outcomes in patients who undergo endoscopic sinus surgery for chronic rhinosinusitis compared to standard postoperative absorbable packing.

2.1 Primary objective

- To investigate the efficacy of PuraSinus in reducing patient pain during postoperative debridement after endoscopic sinus surgery compared to bioresorbable packing.

2.2 Secondary objectives:

- To assess the time needed to perform postoperative debridements in patients with PuraSinus in their ethmoid cavity after endoscopic sinus surgery
- To assess the efficacy of PuraSinus in preventing postoperative complications from endoscopic sinus surgery (adhesions, bleeding, crusting, edema)
- To assess the amount of PuraSinus retained in the ethmoid cavity postoperatively
- To assess the need for further intervention postoperatively in patients

3.0 STUDY DESIGN

3.1 Type of Study

This is a prospective randomized controlled multicenter study at the University of Southern California that will enroll at least 30 participants who satisfy criteria to compare the efficacy of PuraSinus versus standard of care in patients undergoing endoscopic sinus surgery. The study will utilize an intra-patient control design to assess the safety and efficacy of PuraSinus compared to PosiSep X on the contralateral side. The study patients will undergo PuraSinus placement in one nasal cavity following traditional endoscopic sinus surgery. The study is blinded, meaning that patients will be blinded throughout the study duration to which side received PuraSinus placement. The independent surgeon performing review of the video-endoscopies will also be blinded to which side received PuraSinus.

3.2 Randomization

The patient will undergo a bilateral operation. At the end of the surgery, hemostasis will be performed with bioresorbable nasal packing placed in the ethmoid cavity on one side and PuraSinus in the other ethmoid cavity. The randomization will occur using the concealed envelope method to determine which nostril will receive PuraSinus and which nostril will receive a bioresorbable nasal dressing. The envelope will be opened at the conclusion of the surgery just prior to when hemostasis is about to be performed with PuraSinus and PosiSep X.

3.3 Study outcome measures

3.3.1 Primary outcome

- Patient reported pain (1-10) during postoperative debridement of ethmoid cavity 1 week after surgery

3.3.2 Secondary outcomes

- Time required to perform sinonasal cavity debridement for ethmoid cavity 1 week after surgery
- Postoperative healing assessment of mucosal edema, crusting, bleeding, adhesions and polyps 1 week, 4 weeks, and 12 weeks after surgery
- Amount of residual PuraSinus or bioresorbable dressing in ethmoid cavity 1 week after surgery
- The need for further intervention postoperatively 4 weeks after surgery

4.0 DRUG/DEVICE INFORMATION

PuraSinus belongs to a group called self-assembling peptides. The peptide is a fully synthetic 16-unit oligopeptide termed RADA16 with four repeating amino acid sequences of four amino acids, Arginine (R) – Alanine (A) – Aspartic acid (D) – Alanine (A). The synthetic origin of the material can eliminate the potential risk of infections observed with the existing haemostatic agents that contain animal-derived products. The PuraSinus

peptide is in the form of a 2.5% aqueous acidic solution that is safe, non-biogenic, biocompatible, resorbable, sterile filtered and aseptically filled. The product may be used within a sterile field during surgical procedures.

Under physiological conditions (pH approximately 7, in the presence of Na+ and K+ ions) PuraSinus forms a gel similar to collagen fiber structure when it comes into contact with blood or bodily fluid. The gel forms a transparent scaffold which plugs the open micro-vessels leading to hemostasis. The transparent nature of the gel allows the practictioner to visualize the state of hemostasis and allows for easy application of additional therapy if required (figure 1).

Figure 1: PuraSinus® hydrogel

PuraSinus is currently available in 3ml and 5ml syringes (Figure 2). The syringe is connected to an appropriately sized nozzle for direct application to the targeted tissue.

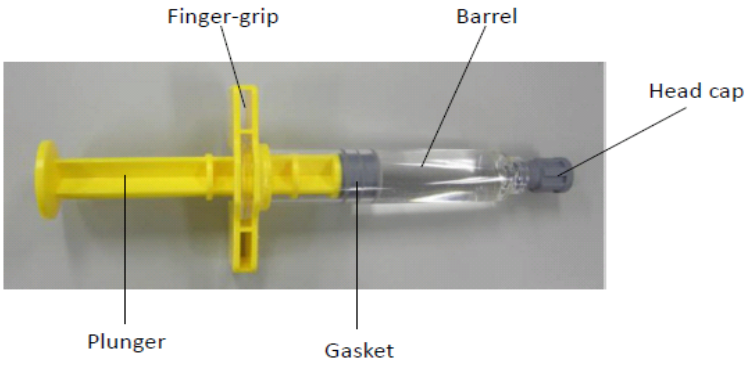

Figure 2: PuraSinus® syringe

The gel is applied to the bleeding site in liquid form and is colorless and completely clear enabling continuous monitoring of the bleeding site. It is thus a product well designed for use during surgical and endonasal endoscopic procedures.

5.0 SELECTION AND WITHDRAWAL OF SUBJECTS

The study population will comprise of adult patients with chronic rhinosinusitis scheduled to undergo bilateral total ethmoidectomy in whom placement of PuraSinus is both feasible and medically appropriate.

5.1 Inclusion Criteria:

a. Patient has provided written informed consent using a form approved by the reviewing IRB.
b. Patient is 18 years of age or older
c. Patient is willing and able to comply with protocol requirements.
d. Patient has a clinical indication for and has consented for primary or revision bilateral ESS and had evidence of ethmoid disease bilaterally (Lund-Mackay score at least 1 on each side).
e. Patient can tolerate general anesthesia.
f. Diagnosed with CRS based on American Academy of Otolaryngology – Head and Neck Surgery guidelines

Sugical Inclusion Criteria:
g. Patient underwent an endoscopic total ethmoidectomy bilaterally that is performed with the same surgical technique.

5.2 Exclusion Criteria

a. Patient has a known history of immune deficiency such as immunoglobulin G or A subclass deficiency, or Human Immunodeficiency Virus (HIV).
b. Patient has concurrent condition requiring active chemotherapy and/or immunotherapy management for the disease (e.g. cancer, HIV, etc.)
c. Patient has clinical evidence of disease or condition expected to compromise survival or ability to complete follow-up assessments during the 90 day followup period.
d. Patient is currently participating in another clinical trial.
e. Patient has a known coagulation disorder.
f. Patient is allergic to shellfish (contraindiction for chitosan-based products).

5.3 Withdrawal Criteria

a. Patient death
b. Voluntary withdrawal – patient voluntarily chooses not to further participate in the study
c. Lost to follow-up: Patient is more than 7 days late to a study visit and 3 documented attempts to contact the patient are unsucessful. A patient who misses the week 1 or week 4 follow-up visit will be considered lost to follow-up.
d. In the investigator's opinion, it is not in the best interest of the patient to continue study participation.
e. Any study patient who does not attend a scheduled follow-up visit should be contacted by site personnel to determine the reason for the missed appointment(s).

6.0 STRATIFICATION/DESCRIPTIVE FACTORS/RANDOMIZATION SCHEME

6.1 The patient will undergo a bilateral operation. At the end of the surgery, hemostasis will be performed with PosiSep X placed in the ethmoid cavity on one side and PuraSinus in the other ethmoid cavity. The randomization will occur using the envelope method to determine which ethmoid cavity will receive PuraSinus and which ethmoid cavity will receive PosiSep X.

Prior to the start of this trial, a randomization list will be generated and sealed opaque envelopes will be created for each participant in the study. Each envelope will instruct which ethmoid cavity (RIGHT or LEFT) will receive PuraSinus. During the surgery, after a total ethmoidectomy has been performed bilaterally by the surgeon, the research coordinator or research staff will open the assigned envelope and have the surgeon read which side the PuraSinus should be applied to. The contralateral ethmoid cavity will receive PosiSep X. The research staff or research coordinator will verify that the intervention (PuraSinus) was applied to the assigned ethmoid cavity.

7.0 STUDY AGENT ADMINISTRATION OR INTERVENTION AND TOXICITY MANAGEMENT PLAN

7.1 Treatment Strategy – The treatment phase begins upon introduction of PuraSinus and bioresorbable nasal dressing into the study patient at the time of surgery

a. Patient Preparation – The patient should be prepared for the planned surgical procedure according to standard surgery center procedures
b. Surgical Extent and PuraSinus Placement

- The technique of total ethmoidectomy should be the same on both sides
- Randomization of the ethmoid cavity to treatment assignment using the envelope method will occur after successful completion of total ethmoidectomy.
- PuraSinus must be used according to the Instructions for Use (IFU).
- Bioresorbable hemostatic packing materials (PosiSep X) will be placed in the opposite ethmoid cavity. Bioresorbable packing will be used according to the IFU.

c. Follow-Up Schedule

The follow-up period begins immediately post-treatment (once the patient exits the operating room). The patient will undergo follow-up assessments including endoscopic examination at three (3) post-operative visits at week 1, week 4, and week 12. A postoperative endoscopic debridement of the ethmoid cavities

will be performed bilaterally at week 1. A second debridement during week 4 is performed if clinically necessary as determined by the surgeon. Risks associated with debridement and nasal endoscopy include possible pain, bleeding, discomfort, irritation, headache, and sneezing.

An overview of the assessments to be performed at baseline and each follow-up interval along with required timing is provided in Table 1. Protocol-required visits occurring outside of the specified date range will be considered and reported as protocol deviations.

7.3 Criteria for removal from treatment (such as undue toxicity, progression of disease, etc.)

7.31 A patient may always be removed from treatment whenever he/she wishes.

7.4 Ancillary treatments.

7.41 Any ancillary treatment of the ethmoid cavity with steroid-eluting stents will not be allowed. If steroid-eluting stents are placed in the ethmoid cavity due to clinical indication, that participant will be excluded from the study.

7.42 Ancillary treatment with oral antibiotics, oral steroids, nasal saline irrigations, or topical steroids as part of standard postoperative care is allowed.

8.0 ASSESSMENT OF SAFETY

8.1 Side effects/Toxicities to be monitored.

8.1.1 Risks or side effects associated with PuraSinus:

- Nasal irritation
- Hypersensitivity reaction
- Intranasal bleeding
- Localized infection (bacterial, fungal colonization or viral) in the nose
- Nasal burning
- Nasal dryness

8.1.2 No long-term toxicities will be monitored as PuraSinus will be removed from the ethmoid cavity 1 week after surgery.

8.3 Adverse Event Reporting: Adverse events may occur during the investigational procedure or during the follow-up phase. Adverse events occurring during the baseline assessment and/or other pre-investigational proceudres will be documented in the patient's medical record.

8.3.1 Each adverse event will be reported in a timely fashion to the principal investigator. The principal investigator is responsible for ensuring that all adverse events are appropriately captured and when applicable, reported to the government, ethics committee, and the sponsor. Each adverse event will be recorded in the corresponding patient's file. Participating investigators will make a determination as to the relationship of each adverse event to the surgical or endoscopic procedure, comorbitidy, or the investigational device. Adverse event reports will identify the date of onset, severity, and duration. All adverse events will be monitored until they are adequately resolved or explained.

8.3.2 Places for submitting reports: The principal investigator will report the above to the University of Southern California IRB.

8.4 Study site monitoring will be performed by an otolaryngology faculty member at the University of Southern California who is independent of the study. The study monitor will be tasked with assessing the study's overall progress, including but not limited to the trial's ability to keep accurate records and to report study related data, including adverse events, to the study sponsor in a timely fashion. In order to appropriately monitor the progress of the study, the study monitor will have access to the source documents and other information necessary to ensure investigator compliance with the protocol and applicable rules and regulations and to assess the progress of the clinical investigation.

The study monitor will mainain contact with investigators and study coordinators by phone, email, or on-site visits. Monitoring will be performed concurrently during the period of patient enrollment to completion of the final patient follow-up visit. The frequency of monitoring may occur as often as a biweekly basis. Monitoring will ensure continued protocol compliance and accurate reporting of data, adverse events, protocol deviations and product accountability.

9.0 CLINICAL AND LABORATORY EVALUATIONS AND STUDY CALENDAR

All visits will occur during typical standard of care appointments for patients undergoing endoscopic sinus surgery.

Parameter	Pre-Surgery	Surgery	Week 1	Week 4	Week 12
Sociodemographic Questionnaire, informed consent	X				
Randomization: placement of PuraSinus		X			
Nasal endoscopy video recording			X	X	X
Patient-reported pain during debridement			X		
Endoscopic debridement procedure			X	X[1]	
Time required to perform debridement			X	X[2]	
Bleeding			X	X[2]	
Review of video-endoscopies by independent blinded surgeon for: 1. Lund-Kennedy score (mucosal edema, crusting, secretions, adhesions, polyps) 2. Residual packing amount 3. Adhesions			X	X	X
Review of video-endoscopy by independent blinded surgeon for: Need for further intervention				X	
Ascertainment of side effects and adverse events		X	X	X	X

Table 1. Study Calendar

[1]if clinically indicated.
[2]if debridement performed

10.0 CRITERIA FOR EVALUATION AND ENDPOINT DEFINITIONS

The outcome status of all eligible patients will be reported. All eligible patients who begin treatment and attend the week 1 postoperative visit will be included in the analysis.

ENDPOINT DEFINITIONS

10.1 Patient-reported pain during debridement

During postoperative debridements in week 1, the surgeon will topically anesthetize both nasal cavities. The surgeon will then begin debridement of the left ethmoid cavity, removing any residual packing, blood, secretions, obstructive crusting from that ethmoid cavity. The surgeon will then perform the same debridement in the right ethmoid cavity. Afterwards, the patient will be asked to rate their pain on a scale from 1-10 with 1 being the least pain and 10 being the most extreme pain during the procedure for each ethmoid cavity (left and right), which will be recorded by the research staff.

10.2 Time required to perform sinonasal cavity debridement for ethmoid cavity

During postoperative debridements in week 1, the research staff will record the time in minutes for each ethmoid cavity based on a video recording of the debridement. The debridement timing will start when the surgeon places the endoscope with a debriding instrument (suction or forceps) into the nasal cavity and ends when the surgeon stops removing any further packing, secretions, crusting, or blood from that ethmoid cavity. Two times will be recorded for each patient, one for each ethmoid cavity.

10.3 Bleeding During Debridement

The patient will be evaluated during the postoperative week 1 for bleeding during debridement via a recorded nasal endoscopy that will be evaluated by a blinded reviewer. Bleeding will also be assessed at week 4 if a second debridement is performed. The reviewer will grade bleeding during after debridement with the following scale:

Criteria	0	1	2	3
Bleeding	No bleeding	Minimal (confined to the nasal cavity)	Moderate (out of nasal cavity)	Severe (needs repacking or cauterization)

10.4 Postoperative healing assessment of mucosal edema, crusting, secretions, adhesions, and polyps

Nasal endoscopies will be recorded of each participant's ethmoid cavity at 1 week, 4 weeks, and 12 weeks and will be reviewed by a blinded reviewer to evaluate the healing of the ethmoid cavity. The reviewer will assess mucosal edema, crusting, secretions, and polyps using the validated Lund-Kennedy Endoscopy score. Adhesions will be evaluated as either present or absent in the middle meatus.

Criteria	0	1	2
Polyps in middle meatus	Absent	Restricted to middle meatus	Beyond the middle meatus
Discharge in middle meatus	Absent	Thin and clear discharge	Thick and purulent
Edema of the middle meatus	Absent	Mild-moderate	Moderate-severe
Crusting in middle meatus	Absent	Mild-moderate	Moderate-severe

Lund-Kennedy Endoscopy score

Criteria	0	1
Adhesions	No adhesion	Present in middle meatus

Adhesions Criteria

10.5 Amount of residual PuraSinus or bioresorbable dressing in ethmoid cavity

At 1 week after surgery, the amount of residual PuraSinus or PosiSep X in the ethmoid cavity will be measured as none, less than 50% of ethmoid cavity, or 50% or greater of ethmoid cavity.

10.6 The need for further intervention postoperatively at week 4

At 4 weeks after surgery, a recorded nasal endoscopy will be performed of each participant's ethmoid cavity and reviewed by an independent, blinded rhinologist to evaluate whether the participant required a postoperative intervention.

A post-operative intervention is a composite endpoint that includes:

- Surgical intervention required to debride obstructive adhesions or scar tissue formation
- Oral steroid intervention is warranted to resolve recurrent inflammation or polypoid edema

11.0 SPECIAL INSTRUCTIONS:

Participant remuneration: Participants in the clinical trial will receive remuneration in the form of $90 in gift cards. Participants will receive a $30 VISA gift card after each postoperative visit (week 1, week 4, and week 12) for a total of $90. The remuneration is to compensate the patient for parking fees and time associated with participating in all aspects of this trial.

12.0 DATA COLLECTION AND MONITORING

12.1 Data collection forms

Data will be recorded onto a dedicated data collection form following the initial surgical procedure where PuraSinus and bioresorbable packing were used. The data on these anonymized forms will then be entered onto a secure password protected electronic database (REDCap) with appropriate back up systems and security protocols in place. No patient identifiable data will be stored on the database.

Endoscopic video data will be coded by the patient's research ID and laterality (right vs. left). No patient identifiable data will be used to label the video files, which will be stored on a secure unviersity online database (Microsoft OneDrive).

12.2 Data management

Data collection forms will be transcribed into a dedicated encrypted electronic database and stored until 3 years after the study is completed with participant study charts. All electronic data will be stored on a password protected electronic database on computers with appropriate back up systems, anti-virus software and security protocols in place. The database will be backed up to an appropriate secure platform and no patient identifiable data will be stored on the database. Access to the database is restricted to participating investigators or a designated member of their research team.

13.0 STATISTICAL CONSIDERATIONS

13.1 Sample size

There are no published data available regarding trial outcomes for the PuraSinus hydrogel product. A study from Canada, reported pain during removal of a comparable bioresorbable packing (Nasopore) as 4.03/10 (SD 2.80) among 30 subjects.[5] In our clinical practice, PosiSep X bioresorbable packing removal is usually rated approximately 5-6/10 (it is uncomfortable) and PuraSinus removal around a 2/10. Using a mean difference of 2 (4.03 with bioresorbable packing versus 2 with hydrogel), a more conservative SD of 3.5 and testing at a 2-sided alpha=0.05, a sample of 30 subjects will provide 83% power to detect this difference in paired measures using a Wilcoxon signed rank test.

13.2 Statistical analysis

The sample will be described by demographic and clinical characteristics, summarizing continuous variables by mean (SD) and categorical variable by frequency (percent). All trial outcome comparisons will be tested at a two-sided p-value of 0.05.

Primary objective: To investigate the efficacy of PuraSinus in reducing patient pain during postoperative debridement after endoscopic sinus surgery compared to PosiSep X.

The primary outcome of pain at 1-week debridement, evaluated on a 1-10 scale, will be compared between interventions using a Wilcoxon signed rank test (paired test). The median and interquartile range of the pain score will be summarized for each intervention. To consider side (right/left), a generalized linear mixed effects model will analyze the pain score as a dependent variable, with a random intercept for participant; independent variables will include randomized intervention, side, and an interaction of intervention-by-side (testing if the intervention effect may differ by side).

Secondary objectives:

- To assess the time needed to perform postoperative debridements in patients with PuraSinus in their ethmoid cavity after endoscopic sinus surgery
- To assess the efficacy of PuraSinus in preventing postoperative complications from endoscopic sinus surgery (adhesions, bleeding, crusting, edema)
- To assess the amount of PuraSinus retained in the ethmoid cavity postoperatively
- To assess the need for further intervention postoperatively in patients

Continuously measured secondary trial outcomes (time required for debridement; Lund-Kennedy Endoscopy score) will be compared between interventions using Wilcoxon signed rank and generalize mixed effects model as described above. Amount of bioresorbable dressing retained will be presented as proportions, with 95% confidence intervals (in the categories of none, <50%, ≥50%). Bleeding during debridement and adhesions will be presented as proportions. The need for further intervention will also be presented as proportion (with 95% confidence interval) of participants required further surgical or oral steroid intervention.

14.0 REGISTRATION GUIDELINE

14.1 Participants in this study will be registered at the preoperative visit prior to their surgery or the day of their surgery in the preoperative area. All participants will receive the intervention (PuraSinus) in one

ethmoid cavity at the end of the ESS procedure which will be randomized in the operating room with the envelope method.

14.2 All registered participants will complete the following forms prior to participation in the study:

- Informed Consent
- Registration/Eligibility Worksheet
- Demographic questionnaire

Note: At the time of registration, two copies of a signed and dated patient Informed Consent form must be available (one copy for the patient; and the other for the PI's file).

15.0 BIOHAZARD CONTAINMENT

No biohazard materials will be handled at any time during this study.

16.0 ETHICAL AND REGULATORY CONSIDERATIONS

All institutional and Federal regulations concerning the Informed Consent form will be fulfilled. The study will be conducted in adherence to ICH Good Clinical Practice. The sponsor and investigator(s) shall avoid improper influence or inducement of the study patient, study coordinator, the clinical investigator(s) or other parties participating in or contributing to the clinical investigation.

17.0 REFERENCES

1. Slavin RG, Spector SL, Bernstein ILet al. The diagnosis and management of sinusitis: a practice parameter update. J Allergy Clin Immunol 2005; 116:S13-47.
2. Benninger MS, Ferguson BJ, Hadley JAet al. Adult chronic rhinosinusitis: definitions, diagnosis, epidemiology, and pathophysiology. Otolaryngol Head Neck Surg 2003; 129:S1-32.
3. Eloy P, Andrews P, Poirrier AL. Postoperative care in endoscopic sinus surgery: a critical review. Curr Opin Otolaryngol Head Neck Surg 2017; 25:35-42.
4. Vlastarakos PV, Iacovou E, Fetta M, Tapis M, Nikolopoulos TP. How effective is postoperative packing in FESS patients? A critical analysis of published interventional studies. Eur Arch Otorhinolaryngol 2016; 273:4061-4071.
5. Shoman N, Gheriani H, Flamer D, Javer A. Prospective, double-blind, randomized trial evaluating patient satisfaction, bleeding, and wound healing using biodegradable synthetic polyurethane foam (NasoPore) as a middle meatal spacer in functional endoscopic sinus surgery. J Otolaryngol Head Neck Surg 2009; 38:112-118.
6. Lee MF, Ma Z, Ananda A. A novel haemostatic agent based on self-assembling peptides in the setting of nasal endoscopic surgery, a case series. Int J Surg Case Rep 2017; 41:461-464.