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STUDY PROTOCOL

The NoSeal Trial – Nasal Outcome Study Evaluating Artificial Leak-Sealing: A Prospective, Randomized, Controlled, Single-Blinded, Single-Center Clinical Trial Comparing Fibrin Glue (Tisseel®) and a Two-Component Synthetic Polymer Sealant (PEI/PEG, Adherus®) Versus No Sealant for the Prevention of Cerebrospinal Fluid Leak and Promotion of Wound Healing Following Endonasal Skull Base Surgery, Designed in Accordance with the SPIRIT 2025 Guidelines

Protocol ID: NIO-NS2025

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ABSTRACT

Introduction

Postoperative cerebrospinal fluid (CSF) leak is a significant complication of endoscopic endonasal approaches (EEA) to the skull base. The use of tissue sealants such as fibrin glue (Tisseel) or synthetic agents (PEI/PEG) is widespread in surgical practice, however, recent high-quality evidence challenges their clinical benefit and cost-effectiveness. This study aims to investigate whether the routine use of sealants in patient with peri-operatively assessed low CSF leak risk, significantly improves outcomes over no sealant use, to guide more cost-effective, evidence-based closure strategies. To the best of our knowledge, the present study is the first randomized clinical trial to evaluate the necessity and comparative effectiveness of fibrin and synthetic sealants versus no sealant in preventing postoperative CSF leaks following endoscopic endonasal surgery in low-post operative CSF leak risk patients.

Materials and Methods

This is a prospective, randomized, controlled, single-center clinical trial conducted at the Maria Skłodowska-Curie National Research Institute of Oncology in Warsaw, Poland. Adult patients scheduled for endoscopic endonasal surgery (EES) will first undergo screening based on medical history and detailed radiological evaluation. Those who meet all predefined inclusion and exclusion criteria will be enrolled and randomized preoperatively using a computer-generated allocation sequence into one of three treatment arms: (1) no sealant (standard multilayer closure), (2) fibrin glue application (Tisseel®), or (3) synthetic polyethylene glycol-based sealant (Adherus®). Following randomization, surgery will be performed in accordance with the assigned intervention. The primary endpoint is the incidence of postoperative cerebrospinal fluid (CSF) leak within 3 months. Secondary outcomes include endoscopic evaluation of mucosal healing at 6 weeks and 3 months, postoperative complication rates (e.g., meningitis, pneumocephalus), reoperation rate, patient-reported quality of life, and a cost-effectiveness analysis comparing sealant use to standard closure.

The study is designed and will be reported in accordance with the SPIRIT 2025 (Standard Protocol Items: Recommendations for Interventional Trials) guidelines to ensure methodological transparency and reproducibility.

Results

Initial enrollment includes a target of 225 patients (75 per arm). Interim data analysis focuses on early healing parameters, safety profiles, and cost metrics. Hypothesis testing will determine if either sealant significantly reduces CSF leak rates compared to no sealant and whether the marginal benefit justifies routine use in all patients. Exploratory endpoints include biomaterial handling characteristics and surgeon-reported usability.

Conclusion

The NoSeal Trial addresses a critical gap in evidence regarding the necessity and comparative performance of sealants in skull base reconstruction. By evaluating both clinical outcomes and economic impact, the study seeks to optimize surgical protocols and improve the safety and efficiency of endonasal neurosurgical procedures.

Keywords

Endoscopic endonasal surgery – pituitary surgery- CSF leak - Skull base repair - Fibrin glue - Synthetic polymer sealant - PEI/PEG - Mucosal healing ·

1. INTRODUCTION

Postoperative cerebrospinal fluid (CSF) leaks remain a notable complication of endoscopic endonasal surgery (EES), contributing to increased risks of meningitis, reoperation, and extended hospital stay[1]. Although tissue sealants such as fibrin glue (Tisseel®) and synthetic polyethylene glycol-based polymers (e.g., Adherus®) are frequently employed to reduce leak rates, evidence suggests that in experienced, high-volume centers, their use may be unnecessary. Moreover, comparative data on the effectiveness and clinical utility of these sealants remain limited. The NoSeal Trial aims to determine whether adjunctive sealants provide measurable benefit over standard multilayer closure without sealants, and to assess their overall clinical value and cost-effectiveness.

2. MATERIALS AND METHODS

Primary Objective

To compare the incidence of postoperative CSF leaks within 3 months among patients receiving:

1. No sealant (standard multilayer closure- GROUP A)
2. Fibrin glue (Tisseel® – GROUP B)
3. Two-component synthetic polymer sealant (PEI/PEG – Adherus® – GROUP C)

Secondary Objectives

a) Assess mucosal healing at 4 weeks and 3 months postoperatively (endoscopic grading)
b) Evaluate rates of postoperative complications (e.g., meningitis, pneumocephalus, CSF leak)
c) Analyze cost-effectiveness of each closure strategy
d) Record revision surgery rate

e) Assess patient-reported quality of life (VAS, SNOT-22)

Exploratory Analysis:

a) Post hoc stratification by CSF leak occurrence to create subgroups: A1 (leak), A2 (no leak), B1, B2, C1, C2

b) Correlation between laboratory results, imaging (pre-op MR and post-op CT), intraoperative findings, and outcome

Study Design and Setting
Prospective, randomized, controlled single-center clinical trial conducted at the National Institute of Oncology Maria Skłodowska-Curie, Warsaw, Poland.

Inclusion Criteria

a) Age ≥ 18 years
b) Undergoing endoscopic endonasal surgery for skull base pathology
c) Informed written consent obtained
d) Hemodynamic and electrolyte stability prior to surgery
e) Surgery expected to be completed without high-flow intraoperative CSF diversion techniques

Exclusion Criteria

a) Re-do surgery or complex reconstruction techniques (e.g., extended EEA with cribriform or clival defects)
b) Pathology that initially requires extended approach and complexed sella reconstruction
c) Preoperative hydrocephalus
d) Allergy to fibrin or polymer sealant components
e) Active sinus infection or systemic inflammatory condition
f) Prior radiotherapy to the sellar/parasellar region
g) Uncontrolled diabetes mellitus (HbA1c > 7.0%)
h) Participation in another interventional trial interfering with wound healing or CSF assessment
i) Radiologic signs of chronic intracranial hypo/hypertension

Participant timeline: Schedule of enrollment, interventions, and assessments according to SPIRIT 2025 Guidelines.

TRIAL PERIOD	Enrollment	Post-randomization				
TIME POINT	-48h to 0	0 (surgery)	t_1 = Day 2	t_2 = Day 5-7	t_3 = Day 30	t_4 = Day 90
ENROLLMENT:						
Eligibility screen	X					
Informed consent	X					
Baseline data collection	X					
Randomization	X					
INTERVENTIONS:						
Tisseel (Group A)		X				
Adherus (Group B)		X				
No sealant (Group C)		X				
ASSESSMENTS:						
Demographics, medical history	X					
Laboratory checklist	X		X			X
Imaging checklist	X		X			
Intraoperative findings		X				
Surgical procedure checklist		X				
CSF leak observation		X	X	X	X	X
Endoscopic healing assesment			X		X	X
SNOT-22			X	X	X	X
VAS	X		X	X	X	X
Adverse events/infection			X	X	X	X
Reoperation						

Randomization and Groups

Eligible patients will be initially enrolled in the trial preoperatively based on medical history and radiological imaging assessment. Final allocation to treatment arms will be performed intraoperatively using a computer-generated randomization sequence via the free academic software Randomizer for Clinical Trials (https://www.randomizer.at/).

Group A: No sealant (standard closure)
Group B: Fibrin glue (Tisseel)
Group C: Synthetic PEI/PEG sealant (Adherus)

Secondary analyses will stratify patients in each arm (A–C) according to the presence or absence of postoperative cerebrospinal fluid (CSF) leak, resulting in analytical subgroups

A1–A2, B1–B2, C1–C2. These subgroups will be used for post hoc analysis of outcomes, including mucosal healing, quality of life (SNOT-22), and cost-effectiveness

PERIOPERATIVE ASSESSMENT

A) Demographics, medical history

B) Preoperative Imaging Checklist (MRI-based) of features that predispose to CSF leak

MRI Finding	Clinical Significance
Tumor size with suprasellar extension	Increased risk of herniation into subarachnoid space
Diaphragm penetration ('mushroom sign')	High risk of breaching the CSF compartment
Absent or atrophic diaphragma sellae	No anatomical barrier to prevent leakage
No visible suprasellar cistern (absent arachnoid cap)	Tumor adheres to chiasm or brainstem
Depressed or absent chiasmatic cistern	Risk of opening cisternal space during resection
Acute, tapered angle between tumor and cistern	Suggests tension and arachnoid membrane vulnerability
Heterogeneous enhancement, cysts, necrosis	Tumor collapse after resection → secondary leak
Displaced or obscured pituitary stalk	Risk of superior structure injury and hormonal complications
Extensive sphenoid sinus pneumatization (sellar type)	Difficult reconstruction due to lack of bony support
Thinned or absent sellar bony floor	Potential leakage into sphenoid sinus
Visible CSF cap or persistent fluid spaces above tumor	Evidence of prior or chronic microleaks
Presence of arachnoid cyst above tumor or near chiasm	Additional risk of CSF compartment violation

C) Postoperative Imaging (CT checklist)

Assessment Area	Signs	Clinical Significance
Pneumocephalus	Presence of intracranial air, especially in the chiasmatic cistern, lateral ventricles, or above the tentorium	Indicates communication with CSF space, i.e., an open leak
Fluid levels in sphenoid or ethmoid sinus	Air-fluid levels or isolated fluid in the sphenoid sinus	May indicate leakage into the sinus
Thickened mucosa of the sphenoid sinus	Edema, exudate, opacification	Could be secondary to chronic leak or infection
Presence of reconstructive materials	Fat, sponge, flap – presence and position	Absence or displacement may suggest reconstruction failure
Fluid in the sella	Hypodense content in the sella turcica	May represent persistent CSF leak into the cavity
Additional CSF collections	Hypodense areas near the tentorium or Sylvian fissure	Accumulation of CSF due to leakage
Displacement of pituitary, stalk, or chiasm	Downward shift or deformation	May reflect collapsed cistern due to CSF leak
Connection between sphenoid sinus and nasal cavity	Evaluation of possible fluid pathway	May indicate anterior skull base leak

D) Laboratory Assessment:

Test	Preoperative (Day -1)	Postoperative (Day 1–2)	Follow-up (Day 90)
CRP	X	X	
ESR	X		
Leukocytes (WBC)	X	X	X
NLR (Neutrophil/Leukocyte Ratio)	X	X	X
Platelets (PLT)	X		
INR	X		
APTT	X		
Fasting glucose	X	X	
HbA1c	X		
Sodium (Na)	X	X	X
Potassium (K)	X	X	X
Chloride (Cl)	X	X	
Serum osmolality	X	X	
Urine osmolality		X	
Daily diuresis		X	
Total protein	X		X
Albumin	X		X
Procalcitonin (PCT)	X	X	
Cortisol (8:00)	X	X	X
ACTH	X	X	X
FT4	X	X	X
TSH	X	X	X
Prolactin	X	X	X
IGF-1	X	X	X
LH	X	X	X
FSH	X	X	X
Estradiol/Testosterone	X	X	X

E) Intraoperative findings
   a) Intraoperative CSF leak observed (Keller, Esposito scale)
   b) Large or irregular sellar floor defect
   c) Tumor adherence to arachnoid/chiasm
   d) Arachnoid herniation into the sella
   e) Invasion of the cavernous sinus
   f) Difficult hemostasis at skull base
   g) Extended surgical time (>3 hours)

F) CSF leak observation
   a) Clinical signs of CSF leak through the whole trial
   b) Endoscopic evaluation (day 2, 30 and 90 post-op)

G) Endoscopic healing assessment
   a) Endoscopic evaluation (day 2, 30 and 90 post-op) – Lund-Kennedy Scale

H) Assessment of patient symptoms and quality of life with Sino-Nasal Outcome Test (SNOT-22) (day 2, 7, 30 and 90 post-op)

I) Pain assessment - Visual Analogue Scale (VAS) (day 0, 2, 7, 30 and 90 post-op)
J) Observation for adverse effects
K) Need for revision surgery

Interventions

All patients will undergo a standard multilayer closure using mucosal flap, and haemostatics (Surgicel, Tachosil). Sealants (Tisseel or Adherus) will be applied only in intervention arms. Lumbar drainage will not be routinely used.

Outcomes

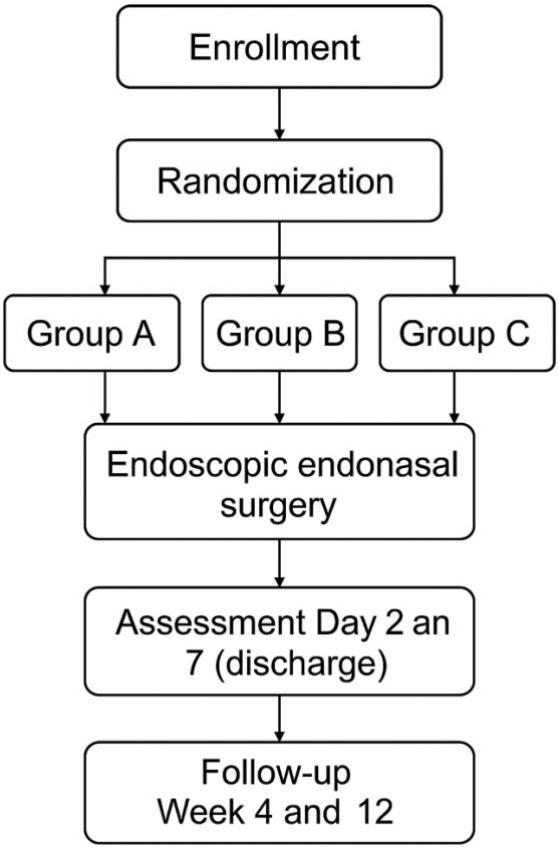
Primary Endpoint

Incidence of postoperative CSF leak within 90 days

Secondary Endpoints

a) Endoscopic mucosal healing score at 4 weeks and 3 months
b) Occurrence of infectious/inflammatory complications
c) Hospital length of stay
d) Need for reoperation
e) Cost analysis of sealant use
f) Patient quality of life (VAS and SNOT-22 scores)

Study Procedures



Statistical analysis

All statistical analyses will be conducted using the Statistica software (ver. 13.3, TIBCO Software Inc., Palo Alto, CA, USA). Baseline characteristics will be summarized using descriptive statistics. Continuous variables will be presented as means ± standard deviations (SD) or medians with interquartile ranges (IQR), depending on distribution assessed by the Shapiro–Wilk test. Categorical variables will be expressed as counts and percentages.

Primary Outcome:

The incidence of postoperative cerebrospinal fluid (CSF) leak within 90 days will be compared among the three groups (no sealant, fibrin glue, synthetic sealant) using the Chi-square test or Fisher's exact test, as appropriate. A log-binomial regression with robust error variance will be used to calculate relative risk (RR) and 95% confidence intervals (CI), adjusting for key baseline covariates (e.g., tumor size, suprasellar extension).

Secondary Outcomes:

Mucosal healing (graded endoscopically at weeks 4 and 12) will be analyzed using the Kruskal–Wallis test or ordinal logistic regression.

Complication rates (e.g., meningitis, pneumocephalus) will be compared using Chi-square tests.

Patient-reported outcomes (VAS, SNOT-22) will be analyzed using repeated-measures ANOVA or linear mixed-effects models.

Subgroup Analysis:

A post hoc stratified analysis will be conducted within each treatment group to compare outcomes in patients with versus without postoperative CSF leak (e.g., A1 vs A2, B1 vs B2, C1 vs C2). Interaction effects will be tested using likelihood ratio tests.

Missing Data:

Missing data will be handled using multiple imputation by chained equations (MICE) under the assumption of missing at random (MAR), with sensitivity analyses to assess the impact of missingness.

Statistical Significance:

A two-sided p-value <0.05 will be considered statistically significant. No correction for multiple comparisons will be applied to exploratory outcomes.

Sample Size and Statistical Analysis

Based on published data, the incidence of postoperative cerebrospinal fluid (CSF) leaks has been reported to range between 3% and 10%, depending on surgical technique, patient selection, and use of adjunctive sealants.

Assuming the following parameters:

Significance level $\alpha = 0.05$ (two-tailed),
Statistical power $1–\beta = 0.80$,

An expected absolute difference in CSF leak rate of 7 percentage points (e.g., 10% vs. 3%), the calculated sample size required to compare two groups using a test for proportions is approximately 190 patients per group.

For a comparison across three parallel groups, while accounting for multiple testing and maintaining sufficient statistical power, the recommended sample size is approximately 70–80 patients per group, resulting in a total of 210–240 patients. Thus, the planned sample size will include a minimum of 75 patients in each group (225 patients in total). If full recruitment proves unattainable, the study may be concluded earlier, and post hoc statistical methods with power correction may be applied to ensure valid interpretation of the results.

Quality assurance

This clinical trial will be conducted at the Department of Neurosurgery, Maria Skłodowska-Curie National Research Institute of Oncology in Warsaw— a tertiary reference neurosurgical center in Poland with extensive experience in endoscopic skull base surgery. The department is nationally recognized for its excellence in pituitary and anterior skull base procedures. All procedures will be carried out by neurosurgeons with high expertise in minimally invasive techniques, ensuring consistency, adherence to protocol standards, and optimal patient safety. The institution's well-established infrastructure for clinical research and postoperative follow-up supports rigorous data collection and quality control throughout the trial.

Data collection and management

All clinical, radiological, intraoperative, and laboratory data will be collected prospectively using standardized electronic case report forms (eCRFs) designed specifically for this study. Data will be entered into a secure, password-protected electronic database hosted on institutional servers, compliant with GDPR and local data protection regulations. Each participant will be assigned a unique study identification number to ensure pseudonymization and confidentiality. Source documents, including operative reports, imaging, and laboratory results, will be retained for verification and monitoring purposes.

Data entry will be performed by trained study personnel and independently verified by a second investigator for accuracy. Quality control procedures will include periodic audits, range checks, and logic checks to detect inconsistencies or missing values. Access to the dataset will be restricted to authorized study investigators. Any changes to data entries will be tracked and documented with audit trails. The final locked dataset will be used for statistical analysis.

Ethics and Registration

This trial was approved by the Bioethics Committee of the National Institute of Oncology (33/2025).

It will be conducted in accordance with the Declaration of Helsinki and is planned for registration at ClinicalTrials.gov.

3.**Discussion**

Cerebrospinal fluid (CSF) leakage is one of the most critical and surgeon-dependent complications following endoscopic transnasal skull base surgery[2]. Despite advances in multilayer reconstruction techniques and vascularized flap design, the occurrence of postoperative CSF leak significantly increases the risk of meningitis, prolongs hospitalization, and often necessitates reoperation[1]. Various biological and synthetic sealants—such as fibrin glue and polymer-based adhesives—are routinely employed in clinical practice to reinforce skull base reconstruction[3]. However, their clinical effectiveness in patients with low preoperative risk of CSF leak, as compared to standard multilayer closure without sealants, remains uncertain and is not well supported by high-quality evidence.

Experimental studies, including animal models, have suggested a potential benefit of fibrin sealants in enhancing mucosal graft adhesion strength[4]. Nevertheless, clinical trials have yielded conflicting results. Some studies have confirmed the safety profile of synthetic sealants like Adherus [5]yet failed to demonstrate a significant reduction in CSF leak rates or superiority over conventional techniques. Others, including Mohindra et al. [6] and Ganesh et al. [7], reported no statistically significant difference in leak frequency between patients treated with and without sealants. Notably, a large prospective cohort study from the University of Pittsburgh observed a paradoxically higher CSF leak rate in the sealant group (14%) compared to the non-sealant group (6%), further questioning the clinical value of routine sealant use[8]. However, they investigated only patients operated diagnosed with CSF leak pre-operatively.

Recent systematic reviews and meta-analyses have reinforced these concerns. Pang et al. [3]and Khan et al. [9]independently concluded that the use of sealants does not significantly lower CSF leak incidence, while also highlighting the methodological heterogeneity and low quality of available evidence. As a result, current surgical practice often relies on institutional preferences and individual surgeon experience, rather than on standardized, evidence-based guidelines.

The NoSeal Trial addresses a pivotal gap in skull base surgery: whether adjunctive sealants provide clinical and economic benefits in patients deemed low-risk for CSF leak.

Unlike prior studies focused on confirmed intraoperative leaks, our protocol excludes high-risk profiles at baseline, aligning with real-world practice in many centers.

Sealants may lead to unintended complications, including foreign body reactions, delayed mucosal healing, and tissue necrosis, while also imposing significant additional costs [10], [11], [12]. Also, given the lack of clear benefit and the variability in clinical outcomes, a cost-effectiveness analysis is warranted. Given the lack of clear benefit and variability in reported outcomes, a comprehensive cost-effectiveness analysis is warranted. Consequently, the widespread use of sealants in skull base reconstruction requires validation through rigorous, high-quality trials.

The absence of demonstrable benefit—and even potential harm—associated with sealant use in the Pittsburgh cohort underscores the need for more nuanced, risk-stratified trials[8]. By pre-selecting patients without preoperative leaks, we reduce heterogeneity and target the true effect of sealants. The randomized comparison between fibrin and synthetic sealants, as well as a no-sealant control, addresses limitations in previous head-to-head studies, and directly tests whether either sealant offers superior outcomes or is cost-effective compared to standard multilayer closure alone. Should our results demonstrate non-inferiority-or superiority-of the no-sealant approach, the implications could be practice-changing: promoting resource-efficient, evidence-based protocols without undue reliance on adjunct sealants.

Nevertheless, this study has several limitations. As a single-center trial conducted in a high-volume, experienced neurosurgical department, the findings may not be generalizable to centers with lower surgical caseloads or different levels of expertise. Due to the nature of surgical interventions, blinding of the operating surgeons is not feasible, which may introduce performance bias. Although patients are randomized preoperatively, actual CSF leak severity is determined intra- and postoperatively, potentially resulting in imbalanced distribution of high- and low-flow leaks across study arms. Additionally, heterogeneity in tumor pathology, size, and invasiveness may influence outcomes despite uniform surgical protocols.

Conclusion

The NoSeal Trial addresses a critical evidence gap in the management of cerebrospinal fluid (CSF) leaks following endoscopic endonasal skull base surgery. While tissue sealants are widely adopted in clinical practice, their routine use has not been supported by high-quality comparative data, particularly in low-risk patients undergoing standard multilayer reconstruction. By directly comparing fibrin-based and synthetic polymer sealants against no sealant, this randomized controlled trial aims to determine whether these adjunctive materials confer a meaningful clinical benefit in preventing postoperative CSF leaks and enhancing wound healing.

In addition to clinical endpoints, the study evaluates safety, usability, and cost-effectiveness—key dimensions for guiding evidence-based practice. The revised sample size ensures sufficient statistical power to detect clinically significant differences, while the standardized surgical protocol enhances the internal validity of findings. Results from the NoSeal Trial are expected to establish clinical guidelines, reduce unnecessary healthcare expenditures, and contribute to the safe and judicious use of biomaterials in neurosurgical reconstruction.

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