Assessment of postsurgical outcomes between different implants in patients with empty nose syndrome: A meta-analysis

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Abstract
Objectives: The aim of this study was to evaluate the impact of surgery and different implant materials on subjective outcomes in patients with empty nose syndrome (ENS).
Methods: Postsurgical outcomes were assessed in a meta-analysis of patients with ENS who underwent treatment with different implants.
Results: We identified 122 relevant studies, and 6 were included in the meta-analysis (4 prospective trials and 2 randomized controlled trials). A significant difference was found between the preoperative and postoperative Sino-Nasal Outcome Test (SNOT) scores for different implants. With respect to implant materials, significant differences were observed between autografts/allografts (AG) and foreign material grafts (FGs). A subgroup analysis of different countries showed that more patients from China underwent surgical implant therapy than patients from other countries.
Conclusions: This meta-analysis suggests that surgery can improve the symptoms and SNOT scores of patients with ENS, AGs are more effective than FGs in patients with ENS, and that more patients from China undergo surgical implant therapy than patients from other countries.

Keywords
Empty nose syndrome, implants, meta-analysis, postsurgical outcomes, Sino-Nasal Outcome Test, turbinectomy

Date received: 3 April 2017; accepted: 23 May 2017

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Introduction

Empty nose syndrome (ENS) is clinically defined as an iatrogenic disorder that develops after turbinate surgery. Symptoms of ENS include paradoxical obstruction, dryness, suffocation, and dizziness. ENS, a term first coined by Kern and Stenkvist in 1994, is a rare yet potentially debilitating complication of inferior turbinate resection. There are three subtypes of ENS: ENS-inferior turbinate, ENS-middle turbinate, and ENS-both based on the pathological changes in the inferior, middle, and both turbinates, respectively. Although ENS is not a mental illness, it greatly influences patients’ quality of life, and psychological factors often cause patients to experience more pain. The inability to diagnose ENS objectively has fuelled further speculation that it could be either a form of nasal neuropathy or rhinitis hystericus. In fact, ENS has not been given enough attention. It is described as an iatrogenic disease that can make affected patients feel a paradoxical obstruction, and some patients subjectively believe that the operation was unsuccessful. In recent years, some such patients have retaliated against the surgeon, and others have even committed suicide as a result of their disabling sinonasal symptoms. However, the common etiologies, optimal management, and various treatment options for ENS remain controversial. Thus, investigation of ENS treatment is necessary. Surgical therapy is a safe and effective treatment modality for patients with ENS, especially those with poor outcomes of conservative treatment.

The Sino-Nasal Outcome Test (SNOT) is a validated survey that examines general nasal symptoms and can be used to compare preintervention and postintervention outcomes. We used the SNOT to compare preoperative and postoperative symptoms excluding olfactory disturbances after placement of various ENS implants. The purpose of nasal surgery is to reduce the nasal cavity volume, increase the nasal airway resistance, and reconstruct the nasal anatomical structure.

Recent studies have revealed that surgery may result in clinical improvement in patients with ENS but that it does not guarantee improvement in all patients, and insufficient evidence is available to favor any particular implant material. Radical turbinate surgery is strongly opposed because it results in ENS, while the safety and low invasiveness partial turbinectomy are guaranteed. Surgical treatment of ENS is technically difficult, and the outcome is poor. Some studies have indicated that different materials have different treatment effects. The nasal airway resistance must be increased by narrowing the nasal valve region or reconstructing a pseudoturbinate in patients with ENS. Some researchers have found that acellular dermis grafts are reliable, predictable, and readily shaped. Placement of Medpor implants (Stryker, Kalamazoo, MI) in patients with ENS is associated with statistically significant improvements in disease-specific quality-of-life measures. Some studies have revealed that costal cartilage may be more useful than conchal cartilage in endonasal microplasty implants and in the treatment of patients with ENS. Bastier et al. found that use of a β-tricalcium phosphate implant to repair the head of the inferior turbinate is safe and efficient for restoration of nasal comfort. Different materials are used in ENS implants to alleviate ENS symptoms. Thus, whether and how ENS can be cured is an important clinical question. Various materials are used, but there is currently no evidence that demonstrates the superiority of any one material or technique. Therefore, the present meta-analysis was performed to evaluate the efficacy of implantation of foreign material grafts (FGs) versus autografts/allografts (AGs) in patients with ENS. Additionally, because the efficacy of nasal air conditioning differs among various
countries, the curative effects of surgical methods for ENS were compared to identify any differences between China and other countries. The results are expected to provide patients and clinicians with a realistic viewpoint on surgical outcomes.

**Methods**

**Search strategy**

We consulted the Preferred Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. A literature search was conducted in MEDLINE (OVID and PubMed), EMBASE (OVID), and the Cochrane Library (Wiley) from 1 January 1990 to 1 June 2016 using the following key words: “empty nose syndrome,” “atrophic rhinitis,” “implants,” and “transplanting.” The literature search was limited to the English language. The abstracts were appraised for relevance, and full-text articles were obtained as appropriate. The bibliography of each article was reviewed to identify any other potentially relevant study. The search covered the literature published from the year the database was established to 1 June 2016. We used the SNOT to compare preoperative and postoperative symptoms after placement of ENS implants and attainment of objective surgical outcomes by radiologic examination, nasal air flow evaluation, and endoscopic scoring.

**Ethical considerations**

All analyses were based on previously published studies; thus, no ethical approval or patient consent was required.

**Inclusion criteria**

The inclusion criteria for this meta-analysis were as follows: (i) All patients had a clinical diagnosis of ENS, had failed conservative nasal hydration therapy, and had undergone ENS implantation; (ii) the intervention involved the implantation of AGs or FGs; (iii) preoperative and postoperative parameters were compared; (iv) surgical outcomes were assessed by the SNOT scores after implantation; and (v) the study was a randomized controlled trial (RCT) or observational study.

**Exclusion criteria**

The exclusion criteria were as follows: (i) Duplicate publications, case reports, animal studies, reviews, and systematic reviews and (ii) lack of a control group.

**Data extraction**

Data were extracted in duplicate by two independent investigators (Drs. Yang and Ke). Any disagreement was settled by discussion with a third reviewer (Dr. Hu). A third researcher was consulted when there were discrepancies in the data, and agreement was reached after discussion. The following data were extracted from the original studies: first author, year of publication, country, sample size, age, sex, surgery allocation, study design, follow-up, surgery technique, and SNOT scores.

**Quality assessment**

Quality assessment of the included RCTs was performed using the Cochrane quality assessment criteria. The prospective studies were evaluated using the Newcastle–Ottawa quality assessment scale. Two researchers conducted a blinded quality assessment of the included studies. When the researchers’ assessments were discrepant, a third researcher was consulted for the final grading.

**Statistical analyses**

All analyses of outcomes were performed with Review Manager software (ver. 5.2; Cochrane Collaboration, Oxford, UK).
A Mantel–Haenszel fixed-effects model or random-effects model was used to calculate summary effect measures (risk ratio) with the corresponding 95% confidence interval (CI), and forest plots were created. Homogeneity was measured by the Cochrane $\chi^2$ test. Subgroup meta-analyses were performed according to the implant material and sources of different countries. The pooled parameters were the 95% CI and relative risk (RR). Publication bias was examined using Begg’s test and Egger’s test. A sensitivity analysis was completed by converting the pooled results into a fixed-effects model.

**Results**

In total, 1612 publications were retrieved from the electronic and manual searches. No conference materials were retrieved. After inputting the search limits (Title/Abstract, non-English, and Date: 1 January 1990 to 1 June 2016), 265 publications remained. After excluding articles on primary atrophic rhinitis, 29 publications remained. Finally, after excluding reviews and case reports, six articles on ENS implantation remained. We analyzed these studies and used the SNOT to compare the preoperative versus postoperative outcomes of patients with ENS.

Six publications involving 122 patients were included in our meta-analysis $^{2,4,7,13–15}$ (Figure 1). Of these, two studies were RCTs and four were non-RCTs (Table 1). We found that the overall kappa statistic between AGs and FGs was 0.53 (95% CI, 0.85–0.21), while that between the China group and other countries group was 0.47 (95% CI, 0.11–0.82).

In the forest plot of the SNOT scores, the standardized mean difference for AGs was 23.18 and that for FGs was 28.07 (Figure 3b), indicating that the treatment effects of AGs were superior to those of

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**Figure 1.** Flow diagram of the literature search strategy.

MeSH = Medical Subject Heading, ENS = empty nose syndrome, SNOT = Sino-Nasal Outcome Test.
FGs. The standardized mean difference in the China group was 27.50 while that in the other countries group was 25.09 (Figure 3c), indicating that more patients in China than in other countries underwent surgical implant therapy; this difference was statistically significant \((P < 0.05)\). As shown in Figure 3a, Figure 3b, and Figure 3c, the preoperative and postoperative SNOT scores were obtained in all six clinical studies involving implantation of AGs and FGs in patients with ENS. Our meta-analysis was carried out according to the sample sizes of the patients, and the results showed statistical significance with an interval variance of 26.13 (95% CI, 21.06–31.21). A significant difference was observed in the preoperative and postoperative SNOT scores between the different implant groups \((P < 0.05)\). There was also a significant difference between the preoperative and postoperative SNOT scores for the different implants. In the subgroup analysis of the implant materials, there was a significant difference between AG and FG \((P < 0.05)\). With respect to the country subgroups, there was a significant difference in the effects of the China group versus the other countries group \((P < 0.05)\). These results indicate that AGs are superior to FGs based on SNOT outcomes.

Begg's test and Egger's test\(^{16,17}\) were employed to examine the pooled values from five or more studies. The results indicated no publication bias in any of the analyzed data. A sensitivity analysis (Figure 2a and Figure 2b) was conducted for the pooled results by converting the pooled model (fixed-effects model). The implant materials and country subgroups exhibited large differences in the RRs and 95% CIs before and after surgery, indicating instability in the pooled values for these two subgroups (Table 2).

**Discussion**

In this meta-analysis, all patients reported that their subjective symptoms were
improved, and a statistically significant improvement in the SNOT scores was achieved. We found a significant difference between the preoperative and postoperative SNOT scores in the different implants (\(P < 0.05\)). In the subgroup analyses based on implant materials, there was a significant difference in AG and FG (\(P < 0.05\)); we also found a significant difference between the China group and the other countries group (\(P < 0.05\)). The results of these subgroup analyses indicate that AGs are superior to FGs. We found that a greater number of patients with ENS in China than in other countries were treated by surgical implant therapy.

ENS is a rare rhinologic disorder that typically develops many years after sinonasal surgery, most notably turbinate surgery.\(^\text{18}\) Effective treatment is necessary for patients with ENS. All patients with ENS in the present meta-analysis had undergone a previous inferior turbinectomy. This meta-analysis included six trials reporting the postsurgical outcomes in patients with ENS who were treated with different implants. Besides the preoperative and postoperative SNOT scores, the following factors were also considered: implant material, country of origin, and follow-up duration. The results of these subanalyses provide evidence-based practices for such surgeries and were statistically significant with an interval variance of 26.13 in the forest plot (95% CI, 21.06–31.21, \(P < 0.00001, I^2 = 0\%\)) (Figure 3a). Patients with ENS experienced significant
Figure 3. (a) Forest plot of preoperative and postoperative Sino-Nasal Outcome Test (SNOT) scores for studies using different implants. \( P < 0.05 \) indicates a statistically significant difference. (b) Forest plot of preoperative and postoperative SNOT scores for studies comparing autografts/allografts versus foreign material grafts as a solo procedure. \( P < 0.05 \) indicates a statistically significant difference. (c) Forest plot of preoperative and postoperative SNOT scores for studies comparing China versus other countries as a solo procedure. \( P < 0.05 \) indicates a statistically significant difference.

SD = standard deviation, CI = confidence interval, IV = interval variance.
improvement in their symptoms after implantation surgery. The results of the subgroup analysis indicated that there was a significant difference between AGs and FGs after surgery ($P < 0.05$) (Figure 3b). We also found a significant difference between China and other countries ($P < 0.05$) (Figure 3c). In one previous study, patients with silastic implants and acellular dermis grafts showed marked subjective and objective improvements.1 In the comparison of the SNOT outcomes between AGs and FGs, the summary effect measures were estimated by a fixed-effects model. The $I^2$ measure of heterogeneity for AGs was $0\%$, while that for FGs was $34\%$, suggesting little heterogeneity between the preoperative and postoperative SNOT scores among the studies. The present meta-analysis demonstrated that the SNOT can be used as a comprehensive assessment tool to aid in the evaluation of the effects of turbinate reconstruction surgery in patients with ENS, and the SNOT score can serve as a comparative parameter before and after surgery. Clinical diagnosis of ENS is difficult because no reliable objective tests are available; hence, the otolaryngologist must rely on the patient’s subjective symptoms.3 Some studies have indicated that submucosal implantation of Medpor (Stryker) is a feasible surgical treatment for ENS.12 Other studies have shown that endonasal microplasty by submucosal implantation of cartilage may be a useful treatment option in the management of ENS.19

Our results have potential implications for clinical practice and health policies regarding ENS. The SNOT scores were significantly different from the preoperative scores as shown by an interval variance of $26.13$ (95% CI, 21.06–31.21) ($P < 0.05$). Although based on only six clinical trials, the current findings indicate that the symptoms of ENS were alleviated after the implantation surgery; furthermore, there was difference between AGs and FGs. We consider that ENS should not be overlooked, especially because it can severely affect certain patients whose only presenting complaint is nasal obstruction.20 The aim of treatment is to increase the nasal airway resistance by narrowing the nasal valve region or

### Table 2. Comparison of preoperative and postoperative outcomes of patients with ENS by SNOT.

| First author (year of publication) | Number of patients | Preoperative SNOT score (mean ± SD) | Postoperative SNOT score (mean ± SD) |
|------------------------------------|--------------------|------------------------------------|-------------------------------------|
| House (2007)                       | 8                  | 58.3 ± 16.6                        | 38.3 ± 17.4                         |
| Saafan (2012) – AG study           | 12                 | 61.4 ± 16.3                        | 33.6 ± 17.1                         |
| Saafan (2012) – FG study           | 12                 | 63.7 ± 15.4                        | 34.2 ± 15.2                         |
| Jiang (2013)                       | 19                 | 50.1 ± 18.7                        | 22.6 ± 15.8                         |
| Tam (2013)                         | 16                 | 39.3 ± 21.4                        | 19.8 ± 16.2                         |
| Jung (2013) – AG study, costal cartilage | 17          | 54.0 ± 45.0                        | 35.9 ± 24.0                         |
| Jung (2013) – AG study, conchal cartilage | 14         | 43.8 ± 27.0                        | 21.9 ± 09.0                         |
| Jiang (2014)                       | 24                 | 68.3 ± 43.5                        | 23.8 ± 19.6                         |

The preoperative and postoperative outcomes refer to the two subgroups. AG = autografts/allografts, FG = foreign material grafts, ENS = empty nose syndrome, SNOT = Sino-Nasal Outcome Test, SD = standard deviation.
reconstructing a pseudoturbinate by surgical intervention. Modrzynski\textsuperscript{21} reported that hyaluronic acid injections appear to be worth considering in less severe forms of ENS. Graft material implanted below the mucosa is a practical choice to reconstruct the deficient anatomy in patients with ENS.\textsuperscript{22} Computational fluid dynamic studies of nasal aerodynamics may have a role in planning the placement and quantity of implants for prediction of neonasal airflow in patients with ENS.\textsuperscript{23} Nevertheless, surgeons must employ a realistic but empathetic approach that takes the current evidence regarding surgical intervention into consideration. Future studies are needed to establish the efficacy and safety of the implant approach.

In this meta-analysis of randomized observational studies, the heterogeneity of the studies was estimated using the I\textsuperscript{2} test as shown in Figure 2a and Figure 2b. We found a low degree of heterogeneity among the studies, indicating reliability of our results. One limitation of our study is the fact that the SNOT 20, SNOT 22, and SNOT 25 comprise slightly different evaluation items; however, these differences did not affect the assessment of ENS symptoms by the meta-analysis. A second potential limitation involves the fact that only six studies were included and that the sample size was small after application of the rigorous inclusion criteria and review procedures. This limitation is associated with a high risk of false-positive results. Third, the meta-analyses was performed to compare subjective symptoms, not objective symptoms. Overall, evaluation of the efficacy of AGs versus FGs in patients with ENS by a meta-analysis is clinically useful. The results are expected to be helpful for patients and doctors in the clinical setting. Because we demonstrated the superiority of AGs over FGs based on a meta-analysis, we speculate whether this justifies a change in the operative treatments of patients with ENS in the future.

**Conclusion**

The present meta-analysis suggests that surgery can improve the symptoms and SNOT scores of patients with ENS. The results also indicate that AGs are more effective than FGs in patients with ENS and that patients from China undergo surgical implant therapy more frequently than do patients from other countries.

**Declaration of conflicting interest**

The authors declare that there is no conflict of interest.

**Funding**

This work was supported by the National Nature Science Foundation of China (NSFC 81271061).

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