Nasal nitric oxide in relation to quality-of-life improvements after endoscopic sinus surgery

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ABSTRACT

Background: The level of nasal nitric oxide (nNO) in patients with chronic rhinosinusitis (CRS) has been proven to increase after surgical treatment. The relationship between nNO and treatment outcome has not been documented to date.

Objective: To evaluate the levels of and changes in nNO after sinus surgery and its effects on quality-of-life improvements for patients with CRS after surgical treatment.

Methods: By using a clinical cohort study design, we identified patients who were receiving bilateral endoscopic sinus surgery for CRS with nasal polyps (CRSwNP) and CRS without nasal polyps (CRSsNP) with a 1-year follow-up. We assessed the demographics, preoperative prognostic predictors, pre- and postoperative nNO levels, and disease-related quality of life via a questionnaire.

Results: Sixty-nine patients were enrolled, including 53 with CRSwNP and 16 with CRSsNP. The CRSwNP group had lower initial nNO levels, and higher endoscopic and image scores but similar demographics and questionnaire scores. In the patients with CRSsNP, nNO levels recovered and reached a plateau at the third month after surgery. However, nNO levels in the CRSwNP group continued to increase until 6 months after surgery before reaching a steady level. Higher preoperative nNO levels were significantly related to better quality-of-life improvements at 3 months after surgery in both groups.

Conclusion: The nNO levels in patients with CRS increased and reached a plateau after sinus surgery for both groups. Under similar subjective disease severity, the CRSsNP group had higher preoperative nNO levels and maintained a continuously longer rise before reaching a steady level after surgery. For both CRS groups, a higher initial nNO level brought better quality-of-life improvements and could be provided as a preoperative prognostic indicator.

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Materials and Methods

Study Design and Patient Selection

This prospective study included patients who underwent bilateral endoscopic sinus surgery for CRS with nasal polyps (CRSwNP) or CRS without nasal polyps (CRSsNP), and were refractory to medication therapy for more than 12 weeks. Institutional review board approval (no. 100-0908B) was obtained from Chang Gung Memorial Hospital, Taoyuan, Taiwan. All the patients in this study were recruited from the Department of Otolaryngology–Head and Neck Surgery over a 12-month recruitment period and were followed-up for 1 year after surgery. All the patients met the criteria of the Rhinosinusitis Task Force Committee for CRS.¹⁴ Demographic information on patient age, sex, nasal allergies, asthma, or current smoking status of each individual was recorded as potential medical variables. Patients with the following characteristics and/or conditions were excluded from this study: <18 years of age, unilateral sinus diseases, dyskinesia, and as a potential postoperative biomarker after sinus surgery for chronic sinusitis because NO levels correlated well with radiographic staging,¹² and symptom severity as well.¹³ In comparison with image studies, such as CT or magnetic resonance imaging, nNO is relatively noninvasive, and nNO levels are feasible to determine the treatment outcomes for patients with sinusitis. To our knowledge, there has never been long-term postoperative changes in nNO levels or changes in nNO levels have been reported and surgical outcomes estimated by the evaluation of preoperative nNO levels or changes in nNO levels have never been documented. It is increasingly important to not only determine the effectiveness of therapeutic interventions but also to predict treatment outcomes in advance. Patients, regardless of their disease severity, are concerned about their prognosis given their individual current conditions and wish to know the likelihood of major symptom-specific improvement, which is usually most patients’ major concern before surgery. We conducted this investigation in which we examined the correlation between changes in nNO levels and the improvements in QOL. Our findings should be helpful for the development of predicting surgical outcomes in advance.
related previous sinonasal surgeries, sinonasal tumors, and current pregnancy.

**Subjective and Objective Measurements**

Subjective evaluation of specific symptoms for subjects was carried out via the Sino-nasal Outcome Test 22 (SNOT-22), with grades from 0 (no symptoms) to 5 (severe) for each symptom. A subjective questionnaire survey was conducted on the day before surgery and after surgery at 3, 6, and 12 months. This instrument was administered by an experienced research assistant blinded to the radiographic staging in this cohort.

Preoperative CTs were evaluated by a surgeon (C.-H.F.) in a blinded fashion to record the severity of sinusitis by using the Lund-Mackay scoring system. For each patient, we also recorded the Lund-Kennedy endoscopy score, total nasal resistance by rhinomanometry, olfaction function test by the Sniffin Stick test, (Burghart, Wedel, Germany) allergy test results, and routine peripheral blood tests (eosinophil count, total immunoglobulin E level) before endoscopic sinus surgery was performed.

**Treatment after Surgery**

Immediately after FESS, all the patients were prescribed oral antibiotics (Augmentin [GlaxoSmithKline, London, UK] 1 g twice daily) for 2 weeks. One week after surgery, daily sinus cavity irrigation with normal saline solution and an intranasal spray of mometasone furoate 100 µg (2 sprays) were applied over a 3-month period. In-clinic follow-ups with sinus cavity debridement were performed on a weekly basis during the first month after surgery, followed by visits every 2 weeks after 1 month, and extended to monthly visits after the second month and visits every 2 months after 6 months.

**Nasal Nitric Oxide Measurements**

Nasal nitric oxide (nNO) measurements were done with an electrochemical analyzer (NIOX MINO; Phadia AB/Aerocrine AB, Uppsala, Sweden) by following The American Thoracic Society/European Respiratory Society recommendations. An automatic measurement was set to 45 seconds, and the flow rate of aspiration was set to 5 mL/s. The first 15 seconds of sampling were for instrument dead space washout, and the air from the last 30 seconds of sampling was collected in the buffer chamber and run over the NIOX MINO sensor. The subject was asked to sit in a relaxed position, to exhale to tidal volume, and to insert a filtered mouthpiece in his or her mouth and a NIOX nasal olive into one nostril at a time. The subject then gently inhaled orally to total lung capacity through the mouthpiece (not holding the breath) while NO levels were continuously measured (Fig. 1). The olive was held tightly against the nostril during sampling to prevent leakage of air. After 45 seconds, the olive was removed from the subject’s nostril, and the nasal NO values were analyzed within 2 minutes. The other side was then analyzed in the same manner. Postoperative nNO levels were analyzed at 3, 6, and 12 months after surgery.

**Statistical Analyses**

With QOL improvement (SNOT-22) as the study end point, the minimum required sample size was calculated by using the statistical software PASS 2008 (NCSS, LLC, Kaysville, UT). A minimum of 22 subjects were required in each study group to have statistic power at 0.05. The smallest change in SNOT-22 score that can be detected by the Mann–Whitney U test was 1.0 (α = 0.05, two-tailed). Patients in the CRSwNP group had better willingness to receive surgical treatment and complied with a 1-year follow-up for the concept that nasal polyp is generally thought as a more complicated inflammatory disease compared with CRSsNP. Hence, the compliance to postoperative visits in the patients with CRSsNP was lower in comparison with that of the patients with CRSwNP.

The demographic data and clinical factors are shown in Table 1. There was no significant difference in the basic background between these two groups. Potential related medical variables were analyzed, and the results revealed that patients in the CRSwNP group had higher endoscopy scores (9.3 versus 5.8; p = 0.001) and CT scores (16.4...
bilateral endoscopic sinus surgery. There was no significant differ-
ence in preoperative nNO levels, endoscopy scores, CT scores, SNOT-22
scores, or other variables. Postoperative nNO levels elevated sig-
ificantly in both patients with allergy and patients without allergy
(Fig. 4), and the postoperative nNO levels tended to keep continu-
ously increasing at 12 months in the allergy group. The improvements
in postoperative QOL had no significant differences between the
allergic and nonallergic groups at 3, 6, and 12 months after surgery.

**DISCUSSION**

Most of the literature reports that patients with CRS have lower
nNO levels when compared with normal controls, and that these
nNO levels increase after medical or surgical treatment. Collection
of nNO has been provided as a fast, safe, and valuable objective
measurement to monitor the responses of CRS to therapeutic inter-
ventions. Several techniques for measuring nNO have been pro-
posed. We followed the standardized procedure for the measure-
ment of airway NO established by the American Thoracic Society/
European Respiratory Society. Velum closure is required to isolate
nNO, which prevents the contamination of NO from lower airway
gases. Slow oral exhalation against a mouthpiece not only reliably
closes the velum but also avoids contamination of ambient NO during
sampling. While air is aspirated continuously via one nasal olive at a
constant low rate of 5 mL/s, the subjects can orally breathe and inhale
to total lung capacity. Some confounding factors can be avoided by
this method, and those patients who cannot hold their breath for 45
seconds or perform a standard humming do not need to be excluded.
As generally thought, patients with CRS and with more advanced
disease severity had higher CT scores or subjective symptom scores,
although these two scores are not necessarily compatible. In this
investigation, patients with CRSwNP and patients with CRSsNP had
similar preoperative SNOT-22 scores. Most other demographic data
showed no differences between the two groups, except for higher
endoscopy and CT scores in the CRSwNP group. Hence, the
CRSwNP group had a lower mean preoperative nNO level in agree-
ment with previous literature reports. In this cohort study, postop-
erative nNO levels were elevated in both the CRSwNP and CRSsNP
groups, as previously reported. However, to our knowledge, follow-
up of nNO change after FESS has not been documented in the
medical literature. We found that the progress of nNO elevation was
not exactly the same for the two groups. The nNO level increased

| Table 1: Demographic data and clinical parameters of the two groups |
|----------------|----------------------------|
|                | CRSwNP (n = 53) | CRSsNP (n = 16) | p Value |
| Age, mean (SD), y | 44.5 ± 15.1 | 45.6 ± 15.6 | 0.727 |
| Sex, men: women  | 36:17 | 9:7 | 0.550 |
| AR, no. (%)      | 10 (18.9) | 4 (25.0) | 0.724 |
| Asthma, no. (%)  | 11 (20.8) | 2 (12.5) | 0.716 |
| Smoker, no. (%)  | 17.0 | 18.8 | 1.000 |
| CT score, mean (SD) | 16.4 ± 4.5 | 11.8 ± 5.9 | 0.004* |
| Endoscopy score, mean (SD) | 9.3 ± 2.4 | 5.8 ± 3.9 | 0.001* |
| Nasal resistance, mean (SD), Pa | 2.6 ± 1.8 | 1.6 ± 0.7 | 0.276 |
| Olfaction test score, mean (SD) | 15.3 ± 7.0 | 17.8 ± 7.9 | 0.421 |
| Total IgE, mean (SD), kU/L | 142.4 ± 198.8 | 178.3 ± 369.3 | 0.860 |
| Eosinophil count, mean (SD), % | 2.0 ± 1.7 | 4.4 ± 5.0 | 0.059 |
| Preoperative nNO, mean (SD), ppb | 165.2 ± 165.5 | 253.4 ± 175.0 | 0.032* |
| SNOT-22 score, mean (SD) | 42.7 ± 18.3 | 47.7 ± 16.4 | 0.296 |

CRSwNP = chronic rhinosinusitis with nasal polyps; CRSsNP = CRS without nasal polyps; SD = standard deviation; AR = allergic rhinitis; CT = computed tomography; IgE = immunoglobulin E; nNO = nasal nitric oxide; SNOT-22 = Sino-nasal Outcome Test 22. *Statistically significant.
significantly and reached a plateau at the third month after surgery for the CRSwNP group. It was generally acknowledged that the mucociliary function of the sinonasal tract tended to recover 3 months after surgery; however, in the CRSsNP group, the nNO level did not increase significantly until 6 months after surgery. It seemed that nNO levels recovered sooner in the CRSwNP group once the blockage of the sinonasal pathways by nasal polyps was eradicated and ventilation of sinuses was restored. Because iNOS in sinus mucosa has been reported to synthesize nNO, the results of this study indicated that the function of iNOS may not completely recover from an inflammatory state in patients with CRSsNP until 6 months after surgery, despite ventilation of the sinus passage and the mucociliary clearance function being restored. However, postoperative biopsy should be obtained, and a longer follow-up period would be necessary to prove this hypothesis and provide a more definitive conclusion on the postoperative nNO change.

Subjective measurements (QOL questionnaires) had a poor correlation with objective measurements (endoscopy scores, CT scores) in our patients with CRS as reported in the literature. The finding was similar when there was poor correlation between the subjective measurement (SNOT-22 scores) and the objective measurement (nNO level), both before and after surgery. There was a trend, however, for the SNOT-22 scores and nNO levels in both the CRSwNP and CRSsNP groups to reach a plateau at a certain period after surgery (at 3 and 6 months, respectively), and the initial nNO levels were found to significantly correlate with short-term surgical outcomes, which indicated that higher initial nNO levels produce more symptom score improvements at the third postoperative month for both groups.
Although no statistically significant correlation was found between the plateau of postoperative QOL and the nNO levels 6 months after surgery, we could still see a similar trend that indicated higher preoperative nNO levels in relation to better SNOT-22 score improvements for both the CRSwNP and CRSsNP groups. Because there are no other strong prognostic preoperative factors available, our study results indicated the potential role of the preoperative nNO levels in patients with CRS before endoscopic sinus surgery in predicting postoperative QOL improvement. In addition, the negative correlation between nNO and CT scores that was found before surgery may further indicate the potential role of using nNO level during follow-up in place of CT, which reduces patients’ exposure to radiation after surgery. Postoperative long-term QOL improvements for patients with CRS still remain complex. A multidisciplinary approach with more patients should be used to obtain a more definite conclusion for long-term outcomes.

Nasal allergies theoretically cause an elevation of nNO, which thus has an adverse effect on patients with CRS. The correlation between allergy-related eosinophilic inflammation and surgical outcomes of FESS remain uncertain. In this study cohort, the presence of nasal allergy did not play a critical role in preoperative nNO, SNOT-22 scores, or postoperative improvements in QOL. Nevertheless, in contrast to the steady postoperative nNO levels of patients without allergy since the third month, the allergy group in this investigation had continuously rising nNO levels until 12 months after surgery. The supposed role of allergy in elevating nNO levels was revealed only after the sinus surgery and became more obvious with time. Thus, we may presume that the function of iNOS in the sinus mucosa was restored after postoperative sinus function recovery and that this phenomenon was more apparent and lasting for patients with allergy.

CONCLUSION
We concluded that the noninvasive measurements for nNO could be an alternative prognostic factor for disease severity in patients with CRS in both groups. In the long term, after sinus surgery, nNO levels increased and then remained at a steady level in both groups. Nevertheless, under similar subjective disease severity, as observed in the CRSwNP group, the CRSsNP group had higher preoperative nNO levels. Postoperative nNO levels in the CRSsNP group took more time to reach a plateau. Initial nNO levels detected before endoscopic sinus surgery were related to postoperative improvements in the QOL for both groups. Further studies may clarify the correlation of nNO levels, other potential prognostic parameters, and multidimensional surgical outcomes.

REFERENCES