Availability of Preoperative Systemic Steroids on Endoscopic Sinus Surgery for Chronic Rhinosinusitis with Nasal Polyposis

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Purpose: To analyze the outcome of endoscopic sinus surgery (ESS) after preoperative systemic steroid (PSS) treatment for chronic rhinosinusitis (CRS) with nasal polyposis (NP) and to investigate and compare clinicopathological factors associated with the outcome.

Materials and Methods: We performed a retrospective chart review of 468 patients with CRS with NP who underwent primary ESS between January 2005 and October 2011. 124 patients who met the inclusion criteria were included. Beginning from 2008, our clinic administered steroid preoperatively in patients of CRS with NP, thus there were 84 patients with preoperative systemic steroid (PSS group) and another 40 patients without such regimen (no PSS group).

To evaluate the outcome after ESS, poor outcome and complication were analyzed according to the following parameters: age, sex, follow-up duration, eosinophilic infiltration, atopy, asthma, Lund-Mackay score, and polyp grade. Results: There was no significant difference in poor outcome rates between the PSS and no PSS group (35.0% vs. 47.6%, \(p=0.185\)). There was no significant difference in complication rates between the PSS and no PSS group (10% vs. 6%, \(p=0.468\)). As with the multivariate analysis of the clinopathological factors to the poor outcome rate, presence of asthma and eosinophilic infiltration were significantly related (odds ratio as 6.555 and 4.505, respectively), whereas PSS was confirmed as less likely related (odds ratio 0.611).

Conclusion: Low dose PSS administration does not seem to have an effect on the outcome after ESS in patients who have CRS with NP. Eosinophilic infiltration and presence of asthma are important predictors of surgical outcome.

Key Words: Steroid, chronic rhinosinusitis, nasal polyp, endoscopic sinus surgery

INTRODUCTION

Chronic rhinosinusitis (CRS) can be classified by phenotypical presentation as either CRS without nasal polyps (NP) or CRS with nasal polyps.1 CRS with NP is a distinct pathologic subtype of CRS, which has a greater burden of symptoms and a higher relapse rate after management.2,4 Despite the significant morbidity and the difficulty of treatment, the exact etiology of NP unfortunately has not been elucidated, and evidence to guide practitioners is also limited.
NP decreases the surgical success rates considerably to 50–70%, and the management of CRS with NP typically requires multimodal therapy.\(^2,^4\) Currently, steroid therapy (oral and topical) and surgery are the mainstays of therapy. Medical therapy using systemic corticosteroid bursts followed by long-term intranasal steroids is a primary treatment modality, and a short course of oral steroids is reported to improve subjective symptoms and objective findings in sinonasal polyposis.\(^5,^6\) However, persistently symptomatic patients and those with advanced diffuse polyposis often require surgical therapy. Meanwhile, several studies have reported that intranasal steroids are effective for preventing polyp recurrence after endoscopic sinus surgery (ESS).\(^7,^11\)

Systemic oral steroids are used and have been shown to be effective in the perioperative period to intraoperatively reduce the inflammatory burden.\(^12\) Many predict that the reduction of inflammation during ESS would lead to a better result after surgery.\(^2,^12,^13\) Nevertheless, most previous studies are based either on the perioperative period or short term outcome. As for the authors’ knowledge, up to date, no such study had dealt with the long-term data concerning the preoperative systemic steroid (PSS) in ESS.

Previously proposed predictors of ESS outcome include CT score, polyp score, asthma, allergy, aspirin sensitivity, adenontsillar hypertrophy, smoking, depression, and previous history of ESS.\(^14-19\) However, there is no clear consensus to predict the result of the operation due to variation in results caused by the heterogenic pathophysiologic characteristics of CRS, especially in NP. Therefore, we also analyzed the clinicopathological factors related to operation outcome, with inclusion of PSS as a clinical factor for comparison with the other factors.

The purpose of this study was to analyze the influence of PSS on the long-term outcome of ESS, along with investigation and comparison of the predictive clinicopathological factors associated with poor outcome of ESS.

### MATERIALS AND METHODS

#### Patients and treatments

During the beginning in August 2008, preoperative oral steroids were explained and offered to patients undergoing routine ESS in order to facilitate the surgery, regardless of severity. However, patients with HTN, DM, CVA history, chronic renal disease, gastric ulcer history, glaucoma, or immunologic disease were not considered for the preoperative steroid treatment. Patients were all informed about steroid use and possible complications before administration. This policy made it possible to conduct a comparative study of patients with and without PSS administration according to the period during which they were managed (no PSS group from January 2005 to July 2008 and PSS group from August 2008 to October 2011).

We performed a retrospective chart review of 468 patients who had been diagnosed with CRS with NP after primary ESS between January 2005 and October 2011. Factors that would influence the study outcomes were discussed, and exclusion criteria were set as follows: 1) patients who underwent ESS simultaneous with other nasal surgeries including septoplasty, turbinate surgery, and palatal surgery (n=179); 2) patients with systemic steroid that were not discontinued for at least one month prior to PSS (n=66); 3) patients with follow-up periods less than six months (n=28); 4) patients with mucocele, antrochoanal or unilateral polyp, fungal sinusitis, or inverted papilloma (n=53); and 5) patients with hypertension, diabetes mellitus, chronic renal disease, cardiovascular attack history, or immunologic disease history.

Exclusion criteria
- Simultaneous surgery of nose (septoplasty, turbinate surgery, palatal surgery) (n=179)
- Systemic steroid use in the past 1 month prior to ESS (n=66)
- Antrochoanal or unilateral polyp, fungus, mucocle, inverted papilloma related (n=53)
- Less than 6 months of follow-up (n=28)

Exclusion criteria
- HTN, DM, CVA, chronic renal disease, immunologic disease history (n=18)

Patients diagnosed as CRS with NP after primary ESS between January 2005 and October 2011 (n=468)
- January 2005 to July 2008 (n=102)
- No preo-steroid group (n=84)
- August 2008 to October 2011 Preo-steroid group (n=40)

Fig. 1. Detail of exclusion and classification of study patients. CRS, chronic rhinosinusitis; NP, nasal polyposis; ESS, endoscopic sinus surgery.
CRS was diagnosed using the diagnostic criteria of the American Academy of Otolaryngology-Head and Neck Surgery based on the presence of two or more of the following symptoms lasting longer than 12 weeks: 1) nasal obstruction; 2) mucopurulent drainage; 3) facial pain-pressure-fullness; and 4) a decreased sense of smell. Surgery was chosen after failure of medical therapy including antibiotics, oral decongestants, and topical nasal steroids and mucolytics. All patients underwent preoperative CT and were postoperatively classified as either having CRS without NP or CRS with NP. Postoperative CT was not acquired in routine manner, so comparison of pre and post CT was not available in the present study.

The 124 patients who met the criteria were categorized into two groups according to the usage of oral steroids. The PSS group was comprised of 40 patients who received preoperative oral steroids (prednisolone, 15 mg/day) for 10 days. The no PSS group was comprised of 84 patients who did not receive oral steroids. Both groups underwent ESS and received postoperative antibiotics, mucolytics, and a topical nasal steroid spray. ESS was performed by one senior surgeon using the standard anterior-to-posterior approach according to the disease extent revealed by the CT scan. Topical nasal steroid spray was prescribed postoperatively for six weeks. Each patient visited our office once a week for two weeks, then twice per month for one month, and finally once per month for up to six months. Meticulous endoscopic dressing was maintained until the cavity healed. During set points in the follow-up schedule, endoscopic photo documentation was collected and used for the assessment of outcome. This study was approved by the Institutional Review Board at the Kangbuk Samsung Hospital, Sungkyunkwan University School of Medicine (Seoul, Korea).

**Histological analysis**
Pathologic examination for eosinophilic infiltration was performed with samples obtained through ESS. All nasal polyp tissues were taken to be fixed in 4% formaldehyde, dehydrated, and then embedded in paraffin. Serial sections of each specimen were then cut to a 4 µm thickness, after which hematoxylin and eosin staining was performed. For each section, eosinophils in the subepithelial area were counted under a light microscope (Zeiss, Oberkochen, Germany) in 10 non overlapping consecutive high-power magnification fields (>400). The eosinophil infiltration count was blindly checked by two pathologists. The number of eosinophils divided by the total number of inflammatory cells counted provided the percentage of eosinophil content for each sample.

**Assessment of patient data**
Analysis was performed in a retrospective manner using a standardized list of patient characteristics, follow-up durations, poor outcomes and complications. Patient characteristics included age, sex, asthma, atopy, preoperative radiologic findings and endoscopic findings. The presence of atopy was determined by the multiple allegro sorbent test (MAST) or skin prick test (SPT). SPT/MAST was performed using 55 common aeroallergens. Atopy was defined as a positive response to one or more allergens on SPT and/or MAST. Eosinophilic infiltration was defined when eosinophils account for >20% of the total inflammatory cells. The radiologic findings of paranasal sinus (PNS) CT were scored using the Lund-Mackay scoring system. Polyp scores were categorized by a polyp grading system based on the endoscopic findings: 0, no visible NPs; 1, small amount of polypoid disease confined within the middle meatus; 2, multiple polyps occupying the middle meatus; 3, polyps extending beyond the middle meatus, within but not totally obstructing the sphenoethmoid recess, or both; 4, polyps completely obstructing the nasal cavity. Postoperative outcomes were evaluated objectively under Kennedy’s criteria; cases with evidence of purulent discharge, mucosal hypertrophy, inflammation, recurrent polyposis, or middle meatal adhesion based on endoscopic findings after the six-month follow-up were classified as the poor outcome group.

**Statistical analysis**
Quantitative data are expressed as mean±standard deviation, and qualitative data are expressed as proportion. Data were analyzed using the t-test, Pearson’s chi-square test, Fisher’s exact test, and the binary logistic regression test. All data were analyzed with IBM SPSS Software Version 20.0 for Windows (IBM, Armonk, NY, USA). p<0.05 was accepted as statistically significant.

## RESULTS

### Patient demographics and characteristics
A total of 124 patients, comprising 82 males and 42 females, were enrolled in this study. 40 patients were included in PSS group and 84 patients were included in no PSS group. The...
baseline characteristics (age, sex, mean follow-up duration, eosinophilic infiltration, atopy, asthma, preoperative CT score, and preoperative polyp grade) of patients in both groups are provided in Table 1. Statistical differences in the above-mentioned characteristics were not found between the two groups, as shown in Table 1. The mean number of eosinophil infiltration in the PSS group (130.33±3, n=6) was significantly lower than in the no PSS group (470.41±3, n=20, p=0.001) (Table 1).

**Poor outcome and complications according to the administration of preoperative steroid**

The overall poor outcome rate was 43.5%, with a rate of 35% in the PSS group and 47.6% in the no-PSS group. Complications included orbital complications (lamina papyracea dehiscence, orbital fat exposure) and major bleeding. The overall complication rate was 7.3%, with a rate of 10% in the PSS group and 6% in the no PSS group. Although the tendency of poor outcome rate was higher in the no-PSS group, the difference between the two groups was not found in the statistical analysis (p=0.185). And also for the complication rates, there was no statistically significant difference between PSS group (10%) and no PSS group (6%, p=0.468) (Table 2).

**Poor outcome and eosinophil infiltration according to the administration of preoperative steroid**

The poor outcome rate of eosinophil infiltration patients was 76.9%, with a rate of 33.3% in the PSS group and 90.0% in the no PSS group. Poor outcome rate in the PSS group was lower than in the no PSS group, and it showed statistically significant difference between two groups (p=0.028) (Table 3).

**Univariate analysis of clinicopathological factors and poor outcomes**

Since there was no difference in poor outcome or complication rate between the two groups defined according to PSS baseline characteristics (age, sex, mean follow-up duration, eosinophilic infiltration, atopy, asthma, preoperative CT score, and preoperative polyp grade) of patients in both groups are provided in Table 1. Statistical differences in the above-mentioned characteristics were not found between the two groups, as shown in Table 1. The mean number of eosinophil infiltration in the PSS group (130.33±3, n=6) was significantly lower than in the no PSS group (470.41±3, n=20, p=0.001) (Table 1).

**Table 1. Patient Demographics**

|                        | Overall (n=124) | PSS group (n=40) | No PSS group (n=84) | p value |
|------------------------|-----------------|------------------|---------------------|---------|
| Mean age (yrs)         | 47.97           | 45.70±13.29      | 49.05±13.21         | 0.190   |
| Sex (male:female)      | 82:42           | 27:13            | 55:29               | 0.824   |
| Mean duration of follow-up (months) | 12.73       | 14.88±12.48      | 11.71±10.86         | 0.152   |
| Eosinophilic infiltration | 26            | 6 (15%)          | 20 (23.81%)         | 0.260   |
| The mean number of eosinophil infiltration* (n=26) | 130.33±3 (n=6) | 470.41±3 (n=20) | <0.001 |
| Atopy                  | 78              | 30 (75%)         | 48 (57.14%)         | 0.054   |
| Asthma                 | 16              | 4 (10%)          | 12 (14.29%)         | 0.506   |
| Lund-Mackay score      | 16.02           | 16.43±4.13       | 15.82±4.53          | 0.477   |
| Polyp grade            | 4.08            | 4.15±1.87        | 4.05±2.33           | 0.794   |

PSS, preoperative systemic steroid.

t-test: mean age, mean duration of follow-up, Lund-Mackay score, polyp grade. Pearson chi-square: sex, atopy, eosinophilic infiltration, asthma.

*Statistically significant with p<0.05.

**Table 2. Poor Outcome and Complication**

|                        | Overall (n=124) | PSS group (n=40) | No PSS group (n=84) | p value |
|------------------------|-----------------|------------------|---------------------|---------|
| Poor outcome           | 54 (43.5%)      | 14 (35%)         | 40 (47.6%)          | 0.185   |
| Complication           | 9 (7.3%)        | 4 (10%)          | 5 (6%)              | 0.468   |
| Orbital complications  | 2 (5%)          | 2 (5%)           | 2 (2.4%)            |         |
| Major bleeding         | 2 (5%)          | 2 (5%)           | 3 (3.6%)            |         |

PSS, preoperative systemic steroid.

Pearson chi-square: poor outcome, complication. Statistically significant with p<0.05.

**Table 3. Poor Outcome Rate of Eosinophil Infiltration Patients**

| Eosinophil infiltration | Overall (n=26) | PSS group (n=6) | No PSS group (n=20) | p value |
|-------------------------|----------------|-----------------|---------------------|---------|
| Poor outcome*           | 20 (76.9%)     | 2 (33.3%)       | 18 (90.0%)          | 0.028   |

PSS, preoperative systemic steroid.

Fisher’s exact test was performed.

*Statistically significant with p<0.05.
DISCUSSION

Sinonasal polyps may develop from the inflammation of the lateral wall of the nose, and NP has a multifactorial etiology, such as allergy, viral or bacterial infection, fungal infection, and environmental pollution.23–24 These events disrupt the epithelial lining and initiate inflammation, and if the inflammation does not subside, stromal edema may consolidate and result in tissue hyperplasia and nasal polyposis.23 Even though the pathogenesis of nasal polyp is not yet well established, steroids are used to reduce mucosal inflammation and to prevent polyp recurrence after ESS. Intranasal steroids have been investigated extensively, and topical nasal steroids are reported as the first therapeutic choice for polyps.23,25 In a national survey from the American Rhinologic Society, 88.82% of the study population of physicians used PSS in their practice.26 There are few recent reports with randomized and blinded trials, and most of the evidence to support PSS use in ESS is anecdotal and based on expert opinion.

Table 4. Univariate Analysis for the Effect of Clinicopathological Factors on Poor Outcome

| Factor                        | Poor outcome | p value |
|-------------------------------|-------------|---------|
| Age                           | Yes (n=54)  | No (n=70) | 0.168   |
| Sex (male:female)             |             |         |         |
| Length of follow-up (months)  | 13.30       | 12.30    | 0.633   |
| Atopy                         | 34 (63%)    | 44 (62.9%) | 0.990   |
| Asthma*                       | 13 (24.1%)  | 3 (4.3%) | 0.017*  |
| Eosinophilic infiltration*    | 20 (37.0%)  | 6 (8.6%) | 0.000*  |
| Lund-Mackay score*            | 17.26       | 15.06    | 0.005*  |
| Polyp grade*                  | 4.61        | 3.67     |         |
| Preoperative systemic steroid | 14 (25.9%)  | 26 (37.1%) | 0.185   |
| Complications                 | 4 (7.4%)    | 5 (7.1%) | 1.000   |

Table 5. Multivariate Analysis for the Effects of Clinicopathological Factors on Poor Outcome

| Factor                        | Coefficient | Odds ratio (95% CI) | p value |
|-------------------------------|-------------|---------------------|---------|
| Age                           | -0.023      | 0.978 (0.947–1.009) | 0.160   |
| Sex                           | 0.033       | 1.034 (0.425–2.511) | 0.942   |
| Atopy                         | -0.451      | 0.637 (0.259–1.565) | 0.326   |
| Asthma*                       | 1.880       | 6.555 (1.511–28.442) | 0.012*  |
| Eosinophilic infiltration*    | 1.505       | 4.505 (1.560–13.011) | 0.005*  |
| Lund-Mackay score*            | 0.101       | 1.106 (0.976–1.254) | 0.115   |
| Polyp grade                   | 0.066       | 1.068 (0.835–1.366) | 0.599   |
| Preoperative systemic steroid | -0.493      | 0.611 (0.245–1.524) | 0.291   |

CI, confidence interval.
*Statistically significant with p<0.05.

administration, we tried to determine the degree of influence related to the PSS as a factor affecting poor outcome compared to other clinicopathological factors. Results of the univariate analysis are shown in Table 4. A significant correlation with poor outcome was found with presence of asthma, eosinophilic infiltration, Lund-Mackay score, and polyp grade (p=0.001, 0.000, 0.005, and 0.017, respectively). Meanwhile, as for the PSS, statistically significant correlation with poor outcome was not found (p=0.185), with a p-value comparable to that of an age (p=0.168).

Multivariate analysis of clinicopathological factors and poor outcomes

Table 5 shows the results for the multivariate analysis of factors related to poor outcome. According to the analysis, the presence of asthma and eosinophilic infiltration were related to poor outcome, with odds ratio of 6.555 and 4.505, respectively, whereas other factors seemed to have less of an effect on the result of the operation. PSS being revealed as not related to the poor outcome also in the multivariate analysis.
Recently, there have been several studies regarding oral systemic steroids; however, the reported studies have focused on medical management of systemic steroid or the effect of systemic steroid on bleeding and visualization during surgery. There have been few studies about the effect of PSS on the long term outcome after ESS. As such, the aim of this study was to analyze the efficacy of preoperative oral steroids for surgical outcomes after ESS in CRS with NP in long term and to investigate clinicopathological factors associated with poor outcome.

In this present study, there was no significant difference in surgical outcomes, including recurrence and poor outcome between the steroid (35%) and non-steroid groups (47.6%). Our results are unique and somewhat shows discrepancy with other previously reported studies, in which, the PSS less likely related to the outcome of the ESS. This result must be considered with two main different conditions from other studies: low dose steroid and long term effect. Most previous studies have adopted using high dose steroid (30 mg or more) whereas our study was conducted with retrospective data based on the low dose steroid (prednisolone, 15 mg/day). It is well known that the dose of administered steroid is an important factor in regards to manipulating the disease status. Therefore, some discrepancy might have resulted from the dose difference. If available, a high dose PSS data comparison study in the future can be useful to elucidate this matter. As for the long term effect, no previous has ever dealt with long term results (present study overall mean follow-up period=12.73 months). Although our study is retrospective, as a preliminary study, long term results according the factors with poor outcome delivers some meaningful message and should not be overlooked. Future prospective studies are required and must be evaluated regarding the long term, since some discrepancy was found with the previous short term data.

Many studies have reported that systemic steroids produce subjective and objective improvement in short term. Preoperative steroids have been reported to help in stabilizing the inflammation of the disease state, resulting in easier surgery compared to the non-steroid administration group. Also, preoperative steroids have been shown to be associated with less bleeding during surgery and shorter operation time. Nevertheless, postoperative outcomes have not been clearly elucidated, and long-term results have not been analyzed. We focused on patients with long-term follow-up (mean duration of follow-up: 12.73 months), and analyzed long-term effects including surgical outcome. Furthermore, this study enrolled more patients with CRS with nasal polyposis than previous studies. From a surgical point of view, there are definitely many advantages since the size of the polyp decreases and the inflammation is stabilized. However, as shown in the present study, steroid does not seem to have a significant effect on the long-term consequences of surgery.

In the analyses of pathological factors, patients with eosinophilic infiltration (37.0%) and asthma (24.1%) had significantly more recurrence than those without eosinophilic infiltration (8.6%) and asthma (4.3%). Jankowski, et al. reported that eosinophil infiltration is a striking feature of nasal polyposis, and systemic steroids appear to be significantly more effective at reducing eosinophil infiltration than topical steroids in selected patients undergoing surgery. Won, et al. also reported that the eosinophil infiltration ratio in polyp tissues decreased after steroid administration. As previous studies have reported, eosinophil infiltration seems to be reduced by systemic steroid therapy. Thus, the mean number of eosinophil infiltration in the PSS group was significantly lower than in the no PSS group (p<0.001) (Table 1). In this present study, we found that PSS was not significantly related to the surgical outcome. However, among the eosinophil infiltration patients (n=26), the poor outcome rate in the PSS group was statistically significant lower than in the no PSS group (p=0.00) (Table 3).

CT score using the Lund-Mackay system is widely used in the assessment of chronic rhinosinusitis and is reported to be correlated with surgical outcome. However, some studies reported a discrepancy between CT score and outcome after surgery. Bhattacharyya also reported that the CT scan stage alone cannot predict outcome after ESS, and Basu, et al. reported that the Lund-Mackay CT scoring scheme does not predict symptomatic improvement after ESS. The variation in surgical outcome after ESS may be due to multifactorial causes. In this study, the Lund-Mackay score was not correlated with poor outcome in multivariate analysis.

Treatment with systemic steroids is thought to control symptoms such as improving the sense of smell and, for advanced nasal polyposis cases, decreasing the polyp size. Steroids are known to be effective at reducing eosinophil infiltration in polyp tissues decreased after steroid administration. As previous studies have reported, eosinophil infiltration seems to be reduced by systemic steroid therapy. Thus, the mean number of eosinophil infiltration in the PSS group was significantly lower than in the no PSS group (p<0.001) (Table 1). In this present study, we found that PSS was not significantly related to the surgical outcome. However, among the eosinophil infiltration patients (n=26), the poor outcome rate in the PSS group was statistically significant lower than in the no PSS group (p=0.00) (Table 3).
Systemic steroid treatment should be administered carefully in patients with diabetes, glaucoma, uncontrolled hypertension, or congestive heart failure. Preoperatively predictive factors for recurrence should be assessed, and postoperatively, patients with eosinophilic infiltration should be more closely observed. In the experimental design of the present study, a low-dose steroid was administered, so additional prospective double-blind randomized controlled trials with higher dose of steroid would be helpful to retrieve more frank outcome of PSS in ESS.

In conclusion, low dose PSS does not seem to have an effect on the long term outcome after ESS in CRS with NP. Eosinophilic infiltration and presence of asthma are important predictors of surgical outcome in such cases.

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