ORIGINAL ARTICLE

Early Endoscopic Sinus Surgery after Medical Failure Improves Postoperative Inflammation Control in Chronic Rhinosinusitis without Nasal Polyps

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Objective: To determine the association between time to elective endoscopic sinus surgery (ESS) and postoperative medication consumption and cost during a two-year follow up in patients with chronic rhinosinusitis without nasal polyps (CRSsNP).

Materials and Methods: The authors reviewed medical records of patients treated with ESS after medical failure between 2009 and 2020 at the Songklanagarind Hospital. The patients were divided into three groups, early surgery at less than one year, mid-surgery at one to five years, and late surgery at more than five years. The number of postoperative visits, CRS-related medications, and costs were compared among the groups. Multivariate analysis was performed to estimate the relationships between the independent factors.

Results: Sixty-nine patients were enrolled in the present study with 30.4% who underwent early surgery, 52.2% who were treated with mid-surgery, and 17.4% who underwent late surgery. The number of 2-year postoperative intranasal corticosteroids (INCS) used, and CRS-related medication costs compared with the time to surgery were significantly different. The higher frequency of prescriptions for INCS use and CRS-related medication costs were significantly different between the groups.

Conclusion: Time to sinus surgery was associated with the 2-year postoperative INCS use and CRS-related medication costs. Early surgery, after the appropriate medical treatment failed, was a better prognostic predictor for reduced INCS use and medication costs after surgery and could be an effective option for improving postoperative inflammation control and managing CRS.

Keywords: Chronic sinusitis; Sinus surgery; Outcome; Time to surgery; Predictive factor

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Chronic rhinosinusitis without nasal polyps (CRSsNP) is defined as a persistent symptomatic inflammation of the nasal and sinus mucosa. It is an important health problem that impacts the quality of life (QoL) of patients[1]. It is the second most common chronic disease in the United States with an estimated prevalence of 14% to 16% in the general population[2]. Appropriate medications are the mainstay of treatment, with endoscopic sinus surgery (ESS) recommended for patients with medical failure[3,4]. However, not all patients who underwent surgery benefit from the procedure and some patients continue to have persistent mucosal disease[5]. Furthermore, other patients have recurrent acute infectious exacerbations with purulent discharge despite adequately performed ESS. Intranasal corticosteroids (INCS) are typically used for long-term maintenance therapy to address underlying inflammatory disorder[6-8]. Antibiotics (ATB) are used to control bacterial infection after acute exacerbation. An overall long-term surgical revision rate of 9.7% was identified in CRSsNP patients[9], which was influenced by different factors.

Surgical outcomes were thoroughly investigated. For example, in the previous studies on CRSsNP, numerous factors were found to be associated with surgical outcomes, including gender[10], age[10-12], allergy[13], asthma[14], Samter's triad[15], smoking[14,16], severe symptoms or extent of disease[17], preoperative computed tomography (CT) staging[17-19], eosinophilic infiltrations in the sinus mucosa[20], and previous sinus surgery[14,19,21]. Other studies found that not all factors alter the postoperative improvement or still lacked conclusive evidence. Furthermore, one

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study compared the clinical outcomes of chronic rhinosinusitis (CRS) with time to surgery, within one year, one to five years, or more than five years after medical failure, and found that patients in the more than five years group had a greater symptom burden and more extensive preoperative radiographic disease[22]. Two other studies found that patients in the less than one year groups had significantly fewer postoperative healthcare visits and visit-related prescriptions than patients in the more than five years group[5,23]. However, the number of postoperative visits and drug prescriptions in the previous studies were dependent on individual practice and might not be related to inflammation control after surgery.

The goals of CRS treatment are to minimize and control mucosal inflammation, promote sinus drainage, and eradicate infections that may present. Therefore, to further investigate disease control postoperatively, the present study examined the association between the time to sinus surgery and postoperative CRS-related medications, and their costs during a two-year postoperative follow up, and related predictive factors.

Materials and Methods

Patient selection

The present study was a retrospective cohort study that obtained data of the patients diagnosed with CRSsNP between January 2009 and August 2020 using the Health Information System (HIS) database of Songklanagarind Hospital, a major tertiary care center in Southern Thailand. The inclusion criteria were CRSsNP, for at least three months of treatment with medications and medical failure was defined by an insufficient symptomatic response to appropriate medical therapy, characterized by the patient experiencing moderate to severe symptoms or a visual analog scale (VAS) score of more than 5, in conjunction with radiological or endoscopic evidence of CRS. Their treatment included a trial of INCS for more than eight weeks duration and a short course of ATB of two to three weeks duration or a prolonged course of systemic low-dose anti-inflammatory ATB of more than twelve weeks duration and nasal saline irrigation. Patients who previously underwent sinus surgery were excluded.

Data collection

All patients had confirmed diagnoses of CRSsNP based on the presence of clinical symptoms with radiological or endoscopic evidence. The medical codes identified in each patient's medical history were further reviewed to identify all codes associated with diagnoses, visits, and treatments for sinusitis and related diseases. The information collected included demographic characteristics, date of diagnosis, pre-treatment blood tests, endoscopic and Lund-Mackey scores, date of surgery, surgery details, the number of postoperative ATB for acute bacterial infection, INCS, and oral corticosteroid prescriptions, outpatient department (OPD) visits, CRS-related medication costs within two years following the surgery, date of last contact, and date of revision surgery if required. All the prescriptions were linked to medical visits. The prescription details were reviewed manually to ensure that all included prescriptions were targeted to treat CRS, analyzed on the basis of time to surgery as explained above, and categorized by main drug category such as ATBs, INCSs, and oral corticosteroids. Preoperative blood tests and sinus CT scans were routinely performed before the planned operation. The CT scan was performed by an experienced radiologist, while all patients underwent surgery performed by rhinologist staff using standard ESS. The authors calculated the time to surgery from the date of the first diagnosis of CRS to the date of surgery, while considering the onset of symptoms as the date of initial diagnosis and divided the patients into groups for comparison of early surgery for the patients waiting less than one year, mid-surgery for between one and five year, and late surgery for longer than five years. The study period for each patient was from the date of clinical diagnosis to the date of the last 2-year follow-up examination. All visits were analyzed based on the time of surgery. Patients with a postoperative period of less than two years were excluded from the study. All patients were followed up at a special rhinology clinic for several years according to their disease status.

Statistical analysis

Descriptive statistics were used to describe frequencies and percentages, means and standard deviations (SD), or medians and interquartile ranges (IQR), as appropriate. The chi-square test, Fisher's exact test, ANOVA or Kruskal-Wallis test were used to compare differences in patient characteristics and surgical outcomes by time to elective surgery. Regression analysis was used to estimate the relationships among independent factors, such as age group, gender, serum eosinophils, endoscopic scores, CT score, and surgical variables. Count outcome variables were tested for over-dispersion. Negative binomial regression was used for overdispersed

Table 1. Patient and surgical characteristics by time to sinus surgery (n=69)

Patient characteristics	Total (n=69)	Time to surgery			p-value
		Early surgery (n=21)	Mid surgery (n=36)	Late surgery (n=12)	
Sex; n (%)					0.498
Female	36 (52.2)	13 (61.9)	18 (50.0)	5 (41.7)	
Male	33 (47.8)	8 (38.1)	18 (50.0)	7 (58.3)	
Occupation; n (%)					0.724
Government officer/State enterprise	22 (31.9)	9 (42.8)	11 (30.6)	2 (16.7)	
Employee	14 (20.3)	5 (23.8)	8 (22.2)	1 (8.3)	
Farmer/gardener	5 (7.2)	1 (4.8)	2 (5.6)	2 (16.7)	
Student	15 (21.7)	4 (19.0)	6 (16.7)	5 (41.7)	
Other	13 (18.8)	2 (9.6)	9 (25.1)	2 (16.7)	
Age at diagnosis; mean [SD]	35.3 [17.08]	38.7 [19.8]	34.3 [15]	32.2 [18.4]	0.512
<18 years	12 (17.4)	4 (19.0)	6 (16.7)	2 (16.7)	0.924
18 to 60 years	54 (78.3)	16 (76.2)	29 (80.6)	9 (75.0)	
>60 years	3 (4.3)	1 (4.8)	1 (2.8)	1 (8.3)	
Allergic rhinitis; n (%)	13 (18.8)	3 (14.3)	7 (19.4)	3 (25.0)	1.000
Asthma; n (%)	3 (4.3)	1 (4.8)	1 (2.8)	1 (8.3)	0.768
Serum eosinophils (% of WBC), median (IQR)	2.0 (1.25 to 4.80)	2 (1.5 to 4.8)	2 (1 to 3.8)	3.8 (3.1 to 5.7)	0.14
Lund-Mackey CT score 0-24; median (IQR)	7 (4 to 12)	8 (6 to 13)	6.5 (4 to 10.8)	7 (5.8 to 9)	0.605
Endoscopic score 0-12; median (IQR)	6 (6 to 6)	6 (5 to 6)	6 (6 to 6)	6 (6 to 6.5)	0.529
Duration of operation (hour), mean [SD]	3.422 [0.8]	3.4 [1]	3.5 [0.7]	3.4 [0.8]	0.933
Estimated blood loss (mL), median (IQR)	100 (50 to 250)	100 (100 to 300)	100 (50 to 262.5)	65 (50 to 150)	0.265

SD=standard deviation; IQR=interquartile range; WBC=white blood cell; CT=computed tomography

count outcome variables. The medical cost variable had to be adjusted for normalized distribution using a logarithmic transformation. Variables with p-value less than 0.2 according to univariate analysis and those considered to be clinically relevant were included in the multivariate analysis to determine any independent predictors. A multivariate analysis was performed using stepwise backward elimination. A p-value of less than 0.05 was considered significant. All statistical analyses were performed using the R Statistical software, version 3.6.2 (Foundation for Statistical Computing, Vienna, Austria)[24].

Ethical approval

Ethical approval for the present study was provided by the Institutional Review Board of the Prince of Songkla University (IRB number: 60-244-13-1), and all data were anonymized in a secure database. The Ethics Committee of the Faculty of Medicine, Prince of Songkla University, approved the study protocol. All procedures involving human participants were performed in accordance with the ethical standards of the Institutional and/or National Research Committee and the 1964 Declaration of Helsinki and its later amendments or comparable ethical standards.

Results

Analysis of patient and surgical characteristics

The patients and surgical details are presented in Table 1. Sixty-nine CRSsNP patients were enrolled in the present study, 33 men (47.8%) and 36 women (52.2%) with a mean age of 35.3 (SD 17.08) years. Overall, 21 patients (30.4%) were treated with early surgery, 36 (52.2%) with mid-surgery, and 12 (17.4%) with late surgery. Patients and surgical characteristics were not significantly different among the three groups (p>0.05).

Analysis of surgical outcomes

Surgical outcomes are summarized in Table 2. The number of 2-year postoperative INCS bottle uses, and CRS-related medication costs compared with the time to surgery were significantly different (p=0.049 and 0.041, respectively). The higher frequency of prescriptions for INCS use and CRS-related medication costs were significantly different among the groups (p<0.001). Other surgical outcomes showed no significant differences among the groups. The overall revision surgery rate within two years was 2.9%.

Multivariate analysis of 2-year postoperative INCS uses, and CRS-related medication costs is

Table 2. Surgical outcomes by time to sinus surgery (n=69)

2-year-postoperative outcomes	Total (n=69)	Time to surgery			p-value
		Early surgery (n=21)	Mid surgery (n=36)	Late surgery (n=12)	
Bottles of INCS; mean [SD]	24.3 [13.095]	18.7 [13.4]*	25.9 [13]	29.0 [10.1]§	0.049
Courses of prednisolone; median (IQR)	1 (0 to 2)	1 (0 to 1)	1 (0 to 2)	0.5 (0 to 1)	0.591
Tabs of prednisolone; median (IQR)	30 (0 to 50)	30 (0 to 42)	30 (0 to 55.5)	10.5 (0 to 30)	0.469
Courses of ATB; median (IQR)	6 (4 to 8)	6 (4 to 10)	6 (3.8 to 8)	5.5 (3.8 to 7.2)	0.909
Days of ATB; median (IQR)	45 (32 to 82)	50 (37 to 91)	45 (31.8 to 81.2)	49.5 (33 to 85.5)	0.964
OPD visits; median (IQR)	12 (10 to 16)	12 (10 to 16)	12.5 (10 to 16.5)	11 (9.8 to 14)	0.389
Revision surgery; n (%)					0.118
Yes	2 (2.9)	2 (9.5)	0 (0.0)	0 (0.0)	
No	67 (97.1)	19 (90.5)	36 (100)	12 (100)	
CRS-related medication costs (Baht); median (IQR)	16,640 (10,722 to 20,852)	12,521 (8,139 to 16,970)*	17,072.5 (10,589.5 to 21227.2)†	18,860 (15,714.5 to 22,519)§	0.041

SD=standard deviation; IQR=interquartile range; INCS=intranasal corticosteroids; ATB=antibiotics; OPD=outpatient department; CRS=chronic rhinosinusitis

* Early vs. mid-surgery, p<0.001; § Early surgery vs. late surgery, p<0.001; † Mid surgery vs. late surgery, p<0.001

Table 3. Multivariate analysis of 2-year postoperative INCS use and CRS-related medication costs

Factors	2-year-postoperative outcomes							
	INCS (bottles)				CRS-related medication costs			
	Univariate IRR (95% CI)	p-value	Multivariate IRR (95% CI)	p-value	Univariate GMR (95% CI)	p-value	Multivariate GMR (95% CI)	p-value
Time to surgery		0.056		0.056		0.036		0.058
0 to 1 year	1 (reference)		1 (reference)		1 (reference)		1 (reference)	
>1 to 5 years	1.39 (1.02 to 1.88)	0.037	1.35 (1.01 to 1.80)	0.040	1.38 (1.04 to 1.83)	0.027	1.35 (1.02 to 1.7)	0.038
>5 years	1.55 (1.04 to 2.33)	0.032	1.53 (1.05 to 2.24)	0.028	1.53 (1.06 to 2.22)	0.025	1.48 (1.02 to 2.14)	0.041
Age group		0.133		0.034		0.926		ND
<18 years	1 (reference)		1 (reference)		1 (reference)			
18 to 60 years	1.45 (0.99 to 2.06)	0.047	1.62 (1.13 to 2.30)	0.008	1.05 (0.75 to 1.47)	0.789		
>60 years	1.58 (0.80 to 3.41)	0.210	1.67 (0.87 to 3.39)	0.144	0.95 (0.75 to 1.89)	0.878		
Sex		0.114		0.024		0.074		0.135
Female	1 (reference)		1 (reference)		1 (reference)		1 (reference)	
Male	1.25 (0.95 to 1.64)		1.36 (1.05 to 1.77)		1.26 (0.98 to 1.62)		1.21 (0.95 to 1.54)	
Eosinophil count	1.01 (0.97 to 1.06)	0.683		ND	1.01 (0.97 to 1.05)	0.695		ND
Endoscopic score	1.00 (0.89 to 1.12)	0.977		ND	1.01 (0.91 to 1.12)	0.878		ND
CT score	1.00 (0.97 to 1.03)	0.949		ND	1.00 (0.97 to 1.02)	0.917		ND

INCS=intranasal corticosteroids; CRS=chronic rhinosinusitis; IRR=incidence rate ratio; GMR=geometric mean ratio; CI=confidence interval; CT=computed tomography; ND=not done

presented in Table 3. The patients in the mid and late groups used 35% and 53% more INCS, respectively, than those in the early group, and their CRS-related medical costs were 35% and 48% higher, respectively, than those in the early group. Patients aged 18 to 60 years and older than 60 years used 62% and 67% more INCSs, respectively, compared than the younger patient group. Men used ~36% more INCS and paid ~21% higher treatment costs than women. After adjusting for other variables using a negative binomial model to identify independent factors affecting surgical outcomes, the authors found that the time to sinus surgery was not significantly associated with 2-year postoperative INCS use or CRS-related medication costs (p=0.056 and 0.058, respectively). In addition, age and male gender were significantly associated with INCS use (p=0.034 and 0.024, respectively).

Discussion

The present study investigated the effects of the timing of elective ESS for CRSsNP following medical failure on postoperative outcomes, including the number of ATB, INCS, and oral corticosteroid

prescriptions, OPD visits and CRS-related medication costs over a two-year period. The findings revealed significant postoperative differences in the use of INCS and CRS-related medication costs when compared with the time to surgery. There was a significant variation in the number of INCS prescriptions and the costs associated with CRS-related medications among the groups.

Several guidelines recommend that surgery should be considered when a 3-month trial of medical treatment fails[4] or there is insufficient symptomatic response to appropriate medical therapy[25]. In recent guideline[6], what constitutes an adequate trial of medical therapy in terms of therapeutic classes, modes of delivery, and duration is unclear. Few studies had attempted to standardize the indications for surgery. Although the timing of surgery has not been evaluated in a randomized trial, evidence suggests that lengthy delays in intervention are detrimental to symptom improvement. There are many reasons to support the hypothesis that earlier surgical intervention improves outcomes. Surgery improves sinus ventilation, allows for better irrigation and instillation of topical steroids, and significantly reduces biofilm density, leading to improved QoL and objective outcome measured[8]. Osteitis is associated with more severe inflammation and the worse disease severity[26]. There is also increasing evidence that irreversible mucosal changes may occur in direct correlation with duration of the disease[27].

To assess the impact of the timing of surgery on outcomes, the previous two studies demonstrated that patients in the less than one year group had significantly fewer postoperative healthcare visits and visit-related prescriptions than patients in the more than five years group[5,23]. However, the number of postoperative visits and drug prescriptions in the previous studies were dependent on individual practice and were not related to inflammation control after surgery.

The use of ATB and oral corticosteroids indicate postoperative acute exacerbated infection and the number of bottles of INCS indicate disease control. Although, the authors found the timing of surgery was a significant predictor of the number of bottles of INCS used, as also observed in the study by Hopkins et al.[5], the timing was not significantly associated with INCS use after adjusting for other variables. This could be explained by the small sample size of the present study. Surgery has been reported to reduce antibiotic utilization[28], but the timing of surgery in the present study was not significantly related to courses or days of ATB nor was it significantly related to the number of postoperative OPD visits, although, this latter was difficult to assess with confidence because the authors scheduled routine postoperative follow-up visits in their patients and the number of OPD visits was not significantly different between the groups. Surgical intervention has also been shown to be cost-effective. A cost-burden analysis of CRS showed a reduction in costs related to postsurgical CRS treatment[29]. The present study results found patients in the mid and late groups paid significantly higher medical costs than those in the early group, as also observed in a previous study[5]; however, the timing was not significantly associated with medical costs after adjusting for other variables. Over the 2-year follow-up period, although the revision surgery rate reached 2.9% in the early group, there were no differences in the reoperation rates among the groups. The 2-year follow-up period may be too short for an adequate analysis of revision surgery.

The present study found a similar number of men and women who underwent ESS, consistent with earlier studies from Europe, Korea, and Taiwan, which reported no differences in CRS prevalence by gender[30-33]. However, large national surveys from the U.S. and Canada found that CRS was twice as common in women as in men[34,35]. The authors also found no significant differences in age at the time of CRS diagnosis, preoperative serum eosinophil counts, endoscopic scores, and Lund-Mackay CT scores. No significant gender differences in endoscopic and CT scores were observed, similar to a study by Mendolia-Loffredo et al[36]. Their study also found that postoperative improvement did not differ by gender. However, in the present study, men used a significantly higher number of INCS bottles postoperatively than women. Although smoking was not a significant risk factor in the present study results, the indirect effects of smoking on a higher number of men INCS users could not be ruled out completely, even if the results are not shown. Older patients used the INCS more often than those younger than 18 years. The higher number of INCS bottles used in proportion to the increment with age can be explained by certain changes to the sinonasal tract and epithelium, including epithelial barrier function, reduced mucociliary function, and alterations in immune defense mechanisms[37-40]. One study found that elderly patients reported smaller improvements in disease specific and QoL after surgery[41].

The present study had limitations. First, this was a small sample size study, and the data were

obtained retrospectively from the HIS database, which was not specifically designed to study sinus disease. As a result, incomplete data collection or recordings from physicians, incorrect coding, or loss of information may have occurred. Medication compliance was assessed by monitoring the number of medications prescribed at each visit, but this may not accurately reflect true patient compliance. The present study did not assess patients lost to follow-up who may have stopped being lost because of clinical improvement. At the authors' institution, they did not routinely record sinonasal outcome tests (SNOT) or QoL scores. Second, the authors were uncertain of the timing of the first diagnosis and the duration of symptoms as CRSsNP poses a diagnostic challenge, and its symptoms may be attributed to other conditions. Therefore, these patients underwent a prolonged trial of medical therapy before surgery. It is possible that patients in the present study may have had a year without symptoms at the time of enrollment and would thus have been included in the early group, even though they may have had the disease for a longer period. Further research should involve a larger sample size and an extended follow-up period.

Conclusion

Time to sinus surgery was associated with 2-year postoperative INCS use and CRS-related medication costs. Early surgery after failed appropriate medical treatment was a better prognostic predictor for lower INCS use and medication costs after surgery and could be an effective option for improving postoperative inflammation control and managing chronic rhinosinusitis.

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Conflicts of interest

The authors declare no conflicts of interest.

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