Association of Comorbid Asthma and the Efficacy of Bioabsorbable Steroid-eluting Sinus Stents Implanted After Endoscopic Sinus Surgery in Patients with Chronic Rhinosinusitis with Nasal Polyps*

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[Abstract] Objective: To identify factors affecting the efficacy of steroid-eluting sinus stents implanted after endoscopic sinus surgery (ESS) in patients with chronic rhinosinusitis with nasal polyps (CRSwNP). **Methods:** We performed a post-hoc analysis of a randomized self-controlled clinical trial on post-operative implantation of bioabsorbable steroid-eluting stents in patients with CRSwNP. Univariate logistic regression analysis was conducted to identify which of the following factors affect the response to post-operative stent implantation: sex, serum eosinophil levels, history of prior surgery, endoscopic scores, and comorbid conditions (asthma and allergic rhinitis). The primary outcome was the rate of post-operative intervention on day 30, and the secondary outcome was the rate of polypoid tissue formation (grades 2–3) on days 14, 30, and 90. **Results:** A total of 151 patients with CRSwNP were included in the post-hoc analysis. Asthma was identified as the only risk factor for a poor response to steroid-eluting sinus stents on post-operative day 30, with an odds ratio of 23.71 (95% CI, 2.81, 200.16; *P*=0.004) for the need for post-operative intervention and 19 (95% CI, 2.20, 164.16; *P*=0.003) for moderate-to-severe polypoid tissue formation. In addition, the asthmatic group showed higher rates of post-operative intervention and polypoid tissue formation than the non-asthmatic group on post-operative day 30. Blood eosinophil levels were not identified as a risk factor for poor outcomes after stent implantation. **Conclusion:** Comorbid asthma, but not blood eosinophil level, impairs the efficacy of steroid-eluting sinus stents in the short term after ESS in patients with CRSwNP.

Key words: chronic rhinosinusitis; asthma; nasal polyps; outcome; steroid-eluting sinus stent

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*This study was supported by grants from the National Natural Science Foundation of China (No. 81873694), the Key Research and Development Program of Hubei Province (No. 2021BCA119 and No. 2022BCA005), and Knowledge Innovation Program of Wuhan-Basic Research (No. 2022020801010446).

Electronic supplementary material The online version of this article (https://doi.org/10.1007/s11596-023-2786-6) contains supplementary material, which is available to authorized users.

Chronic rhinosinusitis with nasal polyps (CRSwNP) is a common phenotype of chronic rhinosinusitis (CRS) that has a high relapse rate after medical and surgical treatments[1]. CRSwNP is usually treated with conventional medications such as systemic glucocorticoids and nasal surgery. Monoclonal antibodies including dupilumab, mepolizumab, and omalizumab are emerging therapeutic methods. Several clinical studies have demonstrated the remarkable effect of monoclonal antibodies in the treatment of CRSwNP[2–4], but the high cost of continuous medication

restricts their use[5]. Endoscopic sinus surgery (ESS) is the preferred treatment for CRSwNP in patients who have failed to respond to conventional medical therapy[1, 6]. However, the occurrence of post-operative complications remains a barrier to the rehabilitation of patients. For example, sinus ostial stenosis and middle turbinate (MT) lateralization require debridement or lysis of adhesions during post-operative outpatient visits, resulting in a painful experience for patients[7]. Mucosal edema or polypoid mucosal changes indicate persistent inflammation, which worsens long-term outcomes[8]. Although topical or oral steroids can help alleviate post-operative abnormalities, the use of such pharmaceutical interventions has limitations[1]. The effect of topical steroids is influenced by factors such as patient compliance, nasal discharge, and efficiency of drug deposition[9]. Meanwhile, even short-term use of oral corticosteroids carries systemic risks, including sepsis, venous thromboembolism, and fracture[10].

Implantation of steroid-eluting sinus stents is an emerging novel therapy for CRSwNP, and, thus far, only bioabsorbable stents coated with mometasone furoate have been used in clinical settings[11–13]. Several clinical trials have confirmed the promising efficacy of steroid-eluting sinus stents in alleviating post-operative complications such as mucosal edema, polypoid tissue formation, MT lateralization, tissue adhesion, and sinus ostial restenosis[11, 12, 14, 15]. However, some patients showed poor responses to post-operative implantation of steroid-eluting sinus stents. For example, a meta-analysis showed that polypoid tissue formation occurred in 18.4% of patients even with the implantation of steroid-eluting sinus stents after ESS[16], which may be related to the heterogeneous features of CRSwNP. Previous studies have demonstrated that comorbid asthma, blood eosinophil percentage, and sinus computed tomography scores could affect the response to systemic and topical glucocorticoid treatments in patients with CRSwNP[17, 18]. Nevertheless, the risk factors for a poor response to steroid-eluting sinus stents have not been thoroughly investigated. Identifying factors that affect the treatment efficacy of steroid-eluting sinus stents is crucial to improving treatment efficacy and avoiding improper treatment. This study aimed to investigate factors associated with a poor response to post-operative implantation of steroid-eluting sinus stents in patients with CRSwNP, based on a post-hoc analysis of data from a prospective, multicenter, randomized, single-blind, intrapatient, controlled clinical trial that compared the efficacy of stents and NasoPore[14].

1 MATERIALS AND METHODS

1.1 Study Design and Patients

This study was a post-hoc analysis of a previously published multicenter, randomized, single-blind, intrapatient, controlled clinical trial that recruited 181 patients with CRS between September 2012 and November 2015[14]. The clinical trial was registered in the Chinese Clinical Trial Registry Center of the World Health Organization (No. ChiCTR-IIR-17013832). All ESS procedures were performed bilaterally under general anesthesia. The sinus stent was first compressed in the press holder and then loaded into a funnel, through which the catheter tip of the delivery system was connected, and the stent was pushed along the funnel into the cavity of the sheath tube at the catheter tip of the delivery system with a push tool to complete the entire stent loading process. The stent or NasoPore was implanted in the ethmoid sinus. The treatment-side sinus cavity received one bioabsorbable steroid-eluting sinus stent and the contralateral side received a NasoPore pack (Stryker Corporation, USA), in a randomized manner, at the end of ESS[14].

There were no restrictions on preoperative oral or intranasal steroid use. Use of saline sprays or irrigation was permitted as needed both before surgery and during follow-up. A 7-day course of antibiotics was required after the ESS. Nasal saline irrigation and oral mucolytics were routinely used during the follow-up period. Intranasal steroid sprays were allowed from 30 days after the ESS.

The BISORB bioabsorbable steroid-eluting sinus stent [Puyi (Shanghai) Biotechnology Co., Ltd., China], which is composed of a bioabsorbable polylactide-co-glycolide polymer coated with 652 mg mometasone furoate, was used for this study. The mometasone furoate content of the stent coating was released in a controlled manner into the sinus mucosa over approximately 30 days.

This study was approved by the institutional review boards of all participating hospitals. All patients provided informed consent before participation.

1.2 Definition of Asthma, Allergic Rhinitis, CRS, and Eosinophilic CRSwNP

The diagnosis of asthma was based on clinical history and physician diagnosis according to the Global Initiative for Asthma guidelines[19]. In addition, the diagnosis of allergic rhinitis (AR) was based on the concordance between a typical history of allergic symptoms and the result of a skin prick test. CRS was diagnosed according to the European Position Paper on Rhinosinusitis and Nasal Polyps 2020 criteria[1]. Our previous study has shown that an absolute blood eosinophil count of $\geq 0.215\times10^9$/L has a sensitivity of 74.2% and a specificity of 86.5% for diagnosing eosinophilic CRSwNP[20]. We used this criterion to define eosinophilic CRSwNP.

1.3 Definition of Post-operative Endoscopic Evaluation

In post-operative evaluations, we used the

endoscopic grading systems described in the original study for the polypoid tissue score (0 = none, 1 = minor polypoid tissue within the middle meatus, 2 = multiple polypoid tissues within the middle meatus, and 3 = polypoid tissue beyond the middle meatus), MT lateralization score (0 = medialized, 1 = normal, 2 = partially lateralized, and 3 = completely lateralized), and adhesion score (0 = none, 1 = mild, 2 = moderate, and 3 = severe)[14].

1.4 Definition of Outcomes

The primary outcome of this clinical trial was the rate of post-operative debridement interventions within 30 days after ESS[14]. Post-operative debridement interventions were recommended when at least one of the endoscopic scores was ≥2 or 3 (polypoid tissue score ≥2, adhesion score ≥2, or MT lateralization score of 3). The secondary outcomes were the rates of endoscopic polypoid tissue formation (grades 2–3), MT lateralization (grade 3), and moderate-to-severe adhesion (grades 2–3) on post-operative days 14, 30, and 90.

1.5 Post-hoc Analysis Objective

The main objective of this post-hoc analysis was to ascertain which of the following baseline factors affect the efficacy of steroid-eluting sinus stents implanted after ESS for the treatment of CRSwNP: sex, baseline serum eosinophil levels, history of prior surgery, preoperative Lund-Mackay score, preoperative nasal polyp score, preoperative MT lateralization score, preoperative adhesion score, and comorbid asthma and allergic rhinitis.

1.6 Statistical Analysis

Statistical analyses were performed using SPSS for Windows (version 26.0; SPSS Inc., USA). The level of significance was set at 0.05 in a two-tailed test. The Kolmogorov-Smirnov test was used for normality testing. A paired *t*-test was used to assess significant intergroup variability and the Mann-Whitney *U* two-tailed test or covariance analysis was used for between-group comparisons. The Chi-square test or Fisher's exact test was used to compare differences in proportions between groups, and the McNemar test was used for intergroup comparisons. Post-operative intervention frequency, polypoid tissue score, MT lateralization score, and adhesion score were analyzed as continuous variables in the logistic regression model. Logistic regression analysis was performed to identify predictors of treatment effect, and odds ratios (ORs) with 95% confidence intervals (CIs) are reported.

2 RESULTS

2.1 Factors Affecting the Efficacy of Stent Implantation

In the original study[14], a total of 181 patients with CRS without nasal polyps or CRSwNP were enrolled. Because of their small number, we excluded patients with CRS without nasal polyps (*n*=7) from this post-hoc analysis and included only the remaining 174 patients with CRSwNP. We further excluded 23 patients with CRSwNP who had incomplete data (e.g., lack of routine blood test results), and 151 patients with CRSwNP on post-operative day 14 were enrolled in this post-hoc analysis. We compared the baseline patient characteristics and clinical outcomes between this post-hoc cohort and the original cohort and found no significant differences (tables S1 and S2). Owing to follow-up loss, only 144 and 91 patients were analyzed on post-operative days 30 and 90, respectively.

Using univariate logistic regression analysis, we investigated the baseline characteristics affecting the primary outcome after stent treatment (table 1). Comorbid asthma was the only factor associated with a higher frequency of post-operative intervention on post-operative day 30, with an OR of 23.71 (95% CI, 2.81, 200.16; *P*=0.004). Other factors, including sex, absolute serum eosinophil count, serum eosinophil percentage, serum eosinophil count ≥0.215×10^9/L (the cutoff value for defining eosinophilic CRSwNP), history of prior surgery, preoperative Lund-Mackay score, preoperative nasal polyp score, preoperative MT lateralization score, preoperative adhesion score, and comorbid AR, were not significantly associated with the primary outcome after stent treatment.

We also investigated factors affecting polypoid tissue formation on the stent side on days 14, 30, and 90 as response variables. Similarly, comorbid asthma was identified as the only risk factor for a poor response to implantation of a steroid-eluting sinus stent, with an OR of 19 (95% CI, 2.20, 164.16; *P*=0.003) for moderate-to-severe polypoid tissue formation (grades 2–3) on post-operative day 30; however, no significant association was found for moderate-to-severe polypoid tissue formation (grades 2–3) on days 14 and 90 (table 1). Because no or only a few patients had complete MT lateralization (grade 3) or moderate-to-severe adhesion (grades 2–3) on the stent side, we did not analyze such outcomes.

2.2 Factors Affecting the Efficacy of NasoPore

We also investigated baseline characteristics that might influence the outcome on the NasoPore side using univariate logistic regression analysis (table S3). Preoperative nasal polyp score (OR, 2.34; 95% CI, 1.45, 3.76; *P*<0.001) and preoperative adhesion score (OR, 1.72; 95% CI, 1.10, 2.68; *P*=0.016) were identified as predictors of the need for post-operative intervention on day 30.

Preoperative nasal polyp and adhesion scores were also predictors of grades 2-3 polypoid tissue formation on day 14 (OR, 1.68; 95% CI, 1.08, 2.61; *P*=0.022 and OR, 1.57; 95% CI, 1.08, 2.29; *P*=0.019, respectively) and day 30 (OR, 2.31; 95% CI, 1.44, 3.72; *P*=0.001 and

Table 1 Univariate logistic regression analysis of baseline characteristics affecting the efficacy of stents on post-operative days 14, 30, and 90

Characteristics	Endoscopic efficacy results on day 14 (*n*=151)			Endoscopic efficacy results on day 30 (*n*=141)						Endoscopic efficacy results on day 90 (*n*=91)		
	Polypoid tissue (2–3 grade)			Need for post-operative intervention			Polypoid tissue (2–3 grade)			Polypoid tissue (2–3 grade)		
	OR	95% CI	*P*	OR	95% CI	*P*	OR	95% CI	*P*	OR	95% CI	*P*
Gender (female)	1.456	0.542–3.913	0.456	0.724	0.327–1.603	0.426	0.649	0.291–1.449	0.292	0.76	0.169–3.423	0.721
History of prior surgeries (≥1)	0.713	0.288–1.767	0.465	0.484	0.214–1.097	0.082	0.484	0.21–1.10	0.082	0	–	0.998
AR	1.192	0.498–2.851	0.693	1.183	0.546–2.565	0.67	1.327	0.607–2.901	0.478	0.691	0.131–3.654	0.664
Asthma	2.587	0.603–11.095	0.201	**23.71**	**2.81–200.16**	**0.004**	**19.00**	**2.20–164.16**	**0.003**	0	–	0.999
Serum eosinophils ≥0.22 cells/L	1.344	0.563–3.213	0.505	0.853	0.391–1.861	0.69	0.957	0.435–2.101	0.912	1.172	0.246–5.584	0.842
Serum eosinophil count, cells/L	3.182	0.269–37.653	0.359	0.449	0.047–4.342	0.489	0.563	0.057–5.558	0.623	0.226	0.001–41.504	0.576
Serum eosinophil percentage, %	1.026	0.875–1.204	0.75	0.925	0.798–1.073	0.303	0.939	0.81–1.09	0.41	0.961	0.703–1.313	0.801
Preoperative Lund-Mackay score	0.89	0.694–1.142	0.36	0.962	0.776–1.192	0.723	0.943	0.757–1.174	0.599	1.549	0.938–2.559	0.087
Preoperative nasal polyp score	1.165	0.643–2.11	0.614	1.262	0.745–2.137	0.387	1.237	0.725–2.111	0.436	1.064	0.392–2.889	0.904
Preoperative middle turbinate lateralization	1.145	0.697–1.882	0.593	0.936	0.593–1.479	0.777	0.946	0.594–1.506	0.814	0.338	0.117–1.288	0.122
Preoperative adhesion	1.336	0.895–1.993	0.165	1.04	0.706–1.532	0.841	1.084	0.763–1.597	0.683	1.146	0.515–2.548	0.738

Logistic regression analyses were performed to evaluate the association between predictors and endoscopically assessed efficacy. Bold font indicates statistical significance. AR, allergic rhinitis; CI, confidence interval; OR, odds ratio

OR, 1.73; 95% CI, 1.11, 2.70; *P*=0.015, respectively).

2.3 Differences between CRSwNP Patients with and without Asthma

To further clarify the impact of asthma on the outcome of stent implantation, we examined the differences between CRSwNP patients with (*n*=9) and without (*n*=142) asthma. No significant differences in demographic or baseline characteristics were found between the asthmatic and non-asthmatic groups (table 2). Consistent with the logistic regression analysis, we found that the rate of post-operative intervention on the steroid-eluting sinus stent side within 30 days after ESS was significantly lower in the non-asthmatic group than in the asthmatic group (22.79% *vs*. 87.5%, *P*<0.001) (table 3). In addition, the percentage of cases with grades 2-3 polypoid tissue formation on the stent side was significantly lower in the non-asthmatic group than in the asthmatic group on post-operative day 30 (21.32% *vs*. 87.5%, *P*<0.001), whereas no significant difference was observed on days 14 and 90 (table 3). No, or few patients developed MT lateralization (grade 3) and moderate-to-severe adhesion (grades 2–3) on the stent side, irrespective of the asthma status (table 3).

In addition, We compared the changes in post-

Table 2 Baseline characteristics of the asthmatic and non-asthmatic CRSwNP groups

Characteristics	Asthmatic group	Non-asthmatic group	*P*
n	9	142	–
Male gender, *n* (%)	6 (66.67%)	101 (71.13%)	0.720
History of prior surgeries (≥1), *n* (%)	2 (22.22%)	32 (38.03%)	0.486
AR, *n* (%)	5 (55.56%)	48 (33.8%)	0.279
Serum eosinophils ≥0.22 cells/L, *n* (%)	5 (55.56%)	51 (35.92)	0.302
Serum eosinophil count (10^9/L), mean ± SD	0.27±0.17	0.20±0.17	0.149
Serum eosinophil percentage (%), mean ± SD	3.80±1.93	3.00±2.70	0.179
Lund-Mackay score, mean ± SD			
Stent side	9.5±2.07	8.69±1.77	0.224
NasoPore side	9.27±1.73	8.5±1.69	0.242
Nasal polyp score, mean ± SD			
Stent side	2.44±0.53	2.31±0.76	0.768
NasoPore side	2.44±0.53	2.27±0.79	0.690

The Mann-Whitney *U* test (two-tailed) was used to analyze continuous variables, and the Chi-square or Fisher's exact test was used to assess categorical variables. *P*<0.05 indicates a significant difference between the two groups. AR, allergic rhinitis; CRSwNP, chronic rhinosinusitis with nasal polyps; SD, standard deviation

Table 3 Comparison of outcomes between the asthmatic and non-asthmatic groups

Endpoints	Stent side		*P*	NasoPore side		*P*
	Asthmatic (*n*=9)	Non-asthmatic (*n*=142)		Asthmatic (*n*=9)	Non-asthmatic (*n*=142)	
Primary outcome						
Need for post-operative intervention on day 30, *n* (%)	7 (87.5)	31 (22.79)	<0.001	7 (87.5)	78 (57.35)	0.14
Secondary outcomes						
Endoscopic efficacy results on day 14						
Polypoid tissue (grade 2–3), *n* (%)	3 (33.33)	23 (16.20)	0.186	6 (66.67)	64 (45.07)	0.304
Middle turbinate lateralization (grade 3), *n* (%)	0	0	–	0	1 (0.70)	1.0
Severe adhesion (grade 2–3), *n* (%)	0	0	–	0	0	–
Endoscopic efficacy results on day 30						
Polypoid tissue (grade 2–3), *n* (%)	7 (87.5)	29 (21.32)	<0.001	7 (87.5)	77 (56.62)	0.14
Middle turbinate lateralization (grade 3), *n* (%)	0	1 (0.74)	1.0	0	0	–
Severe adhesion (grade 2–3), *n* (%)	0	0	–	0	3 (2.21)	1.0
Endoscopic efficacy results on day 90						
Polypoid tissue (grade 2–3), *n* (%)	0	8 (9.30)	1.0	0	24 (27.91)	0.32
Middle turbinate lateralization (grade 3), *n* (%)	0	0	–	0	0	–
Severe adhesion (grade 2–3), *n* (%)	0	2 (2.33)	1.0	0	15 (17.44)	0.586

Chi-square test or Fisher's exact test was applied to compare the difference in proportions between groups.

operative polypoid tissue scores over time between stent and NasoPore treatments. As shown in fig. 1, in the asthmatic group, the polypoid tissue scores on the stent side showed no significant difference from those on the NasoPore side on post-operative days 14, 30, and 90 (fig. 1A). By contrast, in the non-asthmatic group, the scores on the stent side was significantly improved as compared with those on the NasoPore side at all time points (fig. 1B). When the stent and NasoPore sides were separately analyzed, we found that the polypoid tissue scores in the non-asthmatic group were significantly lower than those in the asthmatic group on post-operative day 30 on both sides (fig. 1C and 1D).

2.4 Differences between Patients with Eosinophilic CRSwNP and Those with Non-eosinophilic CRSwNP

Eosinophilic inflammation may influence the treatment efficacy of systemic glucocorticoids and intranasal glucocorticoid spray[21]; however, our logistic regression analysis revealed no association between serum eosinophil levels and the primary and secondary outcomes on the stent side. We further examined the differences between patients with eosinophilic CRSwNP and those with non-eosinophilic CRSwNP, which were classified based on blood eosinophil levels (table 4). The demographic and clinical characteristics of the eosinophilic and non-eosinophilic CRSwNP groups are presented in table S4, and patients with eosinophilic CRSwNP showed a higher prevalence of comorbid AR. In line with the results of logistic regression analysis, no significant difference in the primary or secondary outcome was found between the eosinophilic and non-eosinophilic CRSwNP groups at all time points (table 4).

3 DISCUSSION

In this post-hoc analysis of a clinical trial, we evaluated the effectiveness of steroid-eluting sinus stents implanted after ESS in patients with CRSwNP. According to endoscopic examinations, we found that comorbid asthma negatively influenced the response to stent implantation in terms of the rates of post-operative intervention and moderate-to-severe polypoid tissue formation on post-operative day 30. Nevertheless, this negative impact was not observed on days 14 and 90 after ESS. Our results indicate that comorbid asthma may impair the efficacy of steroid-eluting stents in the short term and delay the recovery of the sinus mucosa.

A previous study described that the sinus mucosa remains in the "stage of clean cavity" on post-operative day 14 after complete lesion resection, and

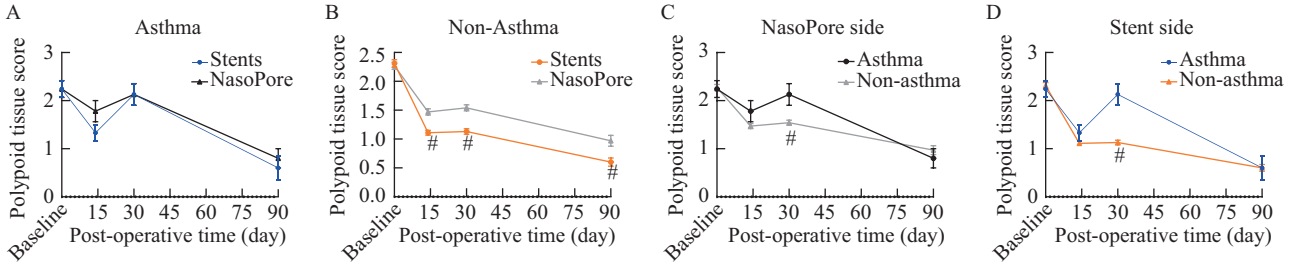

Fig. 1 Comparison of changes in post-operative polypoid tissue scores over time between the asthmatic and non-asthmatic groups (A and B) and between the stent and NasoPore sides (C and D) ($^{\#}P$<0.05)

Table 4 Comparison of outcomes between the eosinophilic and non-eosinophilic CRSwNP groups

Endpoints	Stent side		*P*	NasoPore side		*P*
	Eosinophilic (*n*=56)	Non-eosinophilic (*n*=95)		Eosinophilic (*n*=56)	Non-eosinophilic (*n*=95)	
Primary outcome						
Need for post-operative intervention on day 30, *n* (%)	13 (25.00)	25 (27.17)	0.776	31 (58.49)	54 (58.70)	0.981
Secondary outcomes						
Endoscopic efficacy results on day 14						
Polypoid tissue (grade 2–3), *n* (%)	11 (19.64)	15 (15.79)	0.545	26 (46.43)	44 (46.32)	0.989
Middle turbinate lateralization (grade 3), *n* (%)	0	0	–	0	1 (1.05)	1.0
Severe adhesion (grade 2–3), *n* (%)	0	0	–	0	0	–
Endoscopic efficacy results on day 30						
Polypoid tissue (grade 2–3), *n* (%)	13 (25.00)	23 (25.00)	1.0	31 (59.62)	53 (57.61)	0.815
Middle turbinate lateralization (grade 3), *n* (%)	0	1 (1.09)	1.0	0	0	–
Severe adhesion (grade 2–3), *n* (%)	0	0	–	1 (1.92)	2 (2.17)	1.0
Endoscopic efficacy results on day 90						
Polypoid tissue (grade 2–3), *n* (%)	3 (8.57)	5 (8.93)	1.0	8 (22.86)	16 (28.57)	0.547
Middle turbinate lateralization (grade 3), *n* (%)	0	0	–	0	0	–
Severe adhesion (grade 2–3), *n* (%)	0	2 (3.57)	1.0	6 (17.14)	9 (16.07)	0.893

The Chi-square test or Fisher's exact test was used to compare differences in proportions between groups. CRSwNP, chronic rhinosinusitis with nasal polyps

the mucosa disorders such as edema or adhesion are yet to develop[22]. Similarly, in our current post-hoc study, the proportion of patients with moderate-to-severe polypoid tissue formation on the stent side was lower on day 14 (17.22%) than on day 30 (25%). We did not identify any factor that influenced the effect of stent implantation on polypoid tissue formation on day 14 after ESS, possibly because of the low rate of polypoid tissue formation during this time. The operative cavity progresses to the "stage of mucosal transitional competition" on post-operative days 14 to 30[22]. During this period, vesicles, granulation tissues, polypoid tissue, and adhesion develop, resulting in the need for post-operative intervention[22]. In our study, the stent was coated with 652 mg mometasone furoate, which was released into the surrounding mucosa in a controlled manner over approximately 30 days. Controlled release potentially enabled the steroid-eluting stent to control undesirable inflammation during post-operative sinus mucosal recovery. Thus, the primary outcome was the rate of post-operative intervention for moderate-to-severe polypoid tissue formation or adhesion and severe MT lateralization. We found that on the stent side, the main issue leading to intervention was moderate-to-severe polypoid tissue formation, which occurred in 25% of patients on post-operative day 30. As only a few patients had moderate-to-severe adhesion and severe MT lateralization on the stent side at all post-operative time points, logistic regression analysis of factors affecting such secondary outcomes was impossible.

Among the 11 analyzed baseline demographic and clinical features, only comorbid asthma was identified as a risk factor for a poor response to steroid-eluting sinus stents on post-operative day 30, with a high OR for the need for post-operative intervention (primary outcome) and moderate-to-severe polypoid tissue formation (secondary outcome). Accordingly, the asthmatic CRSwNP group had higher rates of post-operative intervention and moderate-to-severe polypoid tissue formation than the non-asthmatic CRSwNP group. We also found no difference in polypoid tissue scores between the stent and NasoPore sides in patients with asthma, suggesting that stent implantation may not bring additional benefits for patients with CRSwNP with comorbid asthma on post-operative day 30. Asthma has also been identified as a risk factor for polyp recurrence, uncontrolled disease after surgery, and poor response to topical corticosteroids[23–25]. Previous studies reported that patients with CRSwNP with asthma had higher levels of interleukin (IL)-13, immunoglobulin E (IgE), and eosinophil cationic protein in the local mucosa than patients with CRSwNP without asthma[26–28]. The high inflammation load in patients with CRSwNP with asthma may impair the treatment efficacy of steroid-eluting stents by delaying the recovery of the sinus mucosa[29, 30]. The high local and systemic inflammation load in patients with asthma indicates the need for more potent stents that release higher doses of steroids that requires further investigation.

The stent used in our study was biodegradable and lasted only 30 days in the sinus cavity; therefore, intranasal steroid sprays were allowed starting 30 days after ESS. In our post-hoc analysis, none of the analyzed factors, including comorbid asthma, were associated with outcomes on the stent side on day 90. The results suggest that asthma may not affect the long-term outcomes after stent treatment. Regular post-operative debridement to clean the regenerated

lesions is essential to restore normal mucosal function; however, violent tearing and excessive cutting should be avoided, as it may cause injury to the epithelium and result in a painful experience for patients[22]. For patients with CRSwNP without asthma, stent implantation has the advantage of reducing the need for post-operative intervention, which corresponds to reduced healthcare costs and increased patient compliance.

Previously, nasal tissue IL-8 and immunoglobulin G3 (IgG3) levels, baseline headache visual analog scale scores, blood eosinophilia, and comorbid acetylsalicylic acid tolerance, asthma, as well as, allergy have been reported as risk factors in a poor response to topical corticosteroids[31–34]. Blood eosinophilia may be used as a surrogate for tissue eosinophilic inflammation, considering the significant positive correlation between conditions[20]. In this study, blood eosinophil levels were not identified as a risk factor for poor outcomes of stent implantation, and no significant differences in outcomes were observed between the eosinophilic and non-eosinophilic CRSwNP groups. The inconsistency between asthma comorbidities and eosinophilic inflammatory outcomes may be due to asthma being a heterogeneous immunological disease, rather than presenting with skewed eosinophilic inflammation alone[35]. The results here suggest that implantation of steroid-eluting stents is suitable for both patients with eosinophilic CRSwNP and those with non-eosinophilic CRSwNP.

The post-hoc analysis herein has several limitations that cannot be ignored. First, the small number of patients with asthma might have led to a statistical deviation. A previous study reported that only 2%–6% of patients with CRS in southern China have concurrent asthma[36], which is closely related to our study (5.96%). Second, the original trial did not consider quality-of-life outcomes. This limits the extent of determining whether stent implantation can improve CRS symptoms. Third, we were unable to obtain data on the asthma severity and medication use of patients with asthma after ESS because of the lack of documentation in the original clinical study, and this may have biased our final results. Fourth, we did not collect sufficient mucosal or secretory samples in the original trial. Therefore, we were unable to monitor the changes in mucosal inflammation after stent treatment and investigate the mechanisms underlying the negative effects of asthma. Moreover, we could not define the eosinophilic inflammation in tissue directly for every CRSwNP patient. However, previous studies have found that peripheral blood eosinophilic counts are correlated with tissue eosinophilic inflammation and can predict eosinophilic CRSwNP[20], we therefore, used peripheral blood eosinophilic counts to reflect eosinophilic inflammatory load and found that blood eosinophilic level was not correlated with the therapeutic effect of sinus stents. Last, our findings need to be confirmed by a randomized clinical trial owing to the inherent limitations of post-hoc analyses.

To sum up, this study demonstrated that comorbid asthma impairs the short-term efficacy of steroid-eluting sinus stents in patients with CRSwNP. In patients with CRSwNP with concomitant asthma, stent implantation after ESS failed to bring additional benefits on post-operative day 30. Stent implantation showed similar efficacy between patients with eosinophilic CRSwNP and those with non-eosinophilic CRSwNP. Further randomized clinical trials are needed to confirm our findings and guide clinical practice.

Conflict of Interest Statement

All authors declare no conflict of interest regarding the publication of this article.

Author Zheng LIU is a member of the Editorial Board for Current Medical Science. The paper was handled by other editors and has undergone rigorous peer review process. Author Zheng LIU was not involved in the journal's review of, or decisions related to, this manuscript.

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(Received May 16, 2023; accepted Aug. 3, 2023)