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Original Article

Effect of modified endoscopic sinus surgery combined with middle turbinate resection on olfactory function and stress response in patients with refractory chronic rhinosinusitis with nasal polyps

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Abstract: Objective: To investigate the effects of modified endoscopic sinus surgery combined with middle turbinate resection on olfactory function and stress response in patients with refractory chronic rhinosinusitis with nasal polyps (CRSwNP). Methods: We prospectively selected 92 patients with refractory CRSwNP who were treated in Tianjin 4th Central Hospital from June 2019 to June 2020 as the research subjects. According to the simple randomization of "flipping a coin", they were divided into the observation group (n=50) and the control group (n=42). The observation group was treated with modified endoscopic sinus surgery combined with middle turbinectomy and the control group underwent conventional surgery. The overall response rate, olfactory function, and stress responses of the two groups were compared. Results: A generalized linear model showed that the overall response rate at 2, 4, and 6 months after surgery in the observation group was higher than that in the control group (Wald χ^2 group =4.301, Wald χ^2 time =91.677, P group =0.038, P time <0.001). Repeated measurements of variance showed no significant differences in olfactory function scores before surgery (P=0.485). After 2, 4, and 6 months, the olfactory function scores of the observation group were higher than those of the control group (P<0.001). After surgery, patients in the observation group had lower Lund-Mackey, Lund-Kennedy, and SNOT-20 scores, and lower epinephrine (E), norepinephrine (NE), and cortisol (Cor) levels than those in the control group (all P<0.001). The observation group had a significantly lower incidence of complications than the control group (10.00% vs. 28.57%, χ^2=5.226, P=0.022). Conclusion: Modified endoscopic sinus surgery combined with middle turbinate resection significantly improved the olfactory function and reduced the perioperative stress response of patients with CRSwNP.

Keywords: Refractory chronic rhinosinusitis with nasal polyps, modified endoscopic sinus surgery, middle turbinate resection, olfactory function

Introduction

Chronic rhinosinusitis (CRS) is a common disease seen in otolaryngology. Affected by local or systemic factors, 5%-10% of CRS patients require a course of treatment of more than 6 months, and even after surgery or drug treatment, they still suffer from different degrees of nasal congestion, pus, facial pain, and olfaction disorders. Postoperative imaging has revealed sinus mucous edema, mucous purulent secretions, vesicles, polyps, and other chronic inflammatory changes in such patients; collectively this is defined as refractory CRS [1, 2]. The effect of conventional surgery on refractory CRS has been confirmed, but the destructive effect of surgery, combined with anesthetic drugs and the psychological burden on patients, often causes a strong intraoperative stress response, affecting the outcome of surgical treatment [3]. However, modified endoscopic sinus surgery and middle turbinectomy are minimally invasive surgical methods, and are characterized by a clear therapeutic field, less trauma, and better safety [4]. Currently, there are several clinical reports on the therapeutic effect of modified endoscopic sinus surgery combined with middle turbinectomy in patients with refractory nasal polyps and sinusitis, while there are only a few studies on intraoperative stress response and olfactory function in patients. Therefore, this study investigated the effects of

Table 1. Comparison of baseline data

Item		Observation group (50)	Control group (42)	t/χ^2	P
Gender (M/F)		32/18	28/14	0.072	0.789
Age (Y)		34.89±5.22	33.56±5.65	1.172	0.244
BMI (kg/m²)		23.12±2.56	23.42±2.22	0.594	0.554
Duration of disease (years)		11.4±1.4	10.8±1.6	1.918	0.058
Disease Type	Nasal polyp	28	24	0.012	0.912
	Sinusitis	22	18		
Surgical history	1-2	36	31	0.038	0.846
	≥3	14	11		
Comorbidities	Hypertension	16	14	0.018	0.892
	Diabetes	12	8	0.329	0.566
	Coronary heart disease	8	7	0.007	0.931
	Deviated septum	24	23	0.418	0.518
	Allergic rhinitis	14	13	0.096	0.757

Baseline data are expressed as number of cases or mean ± SD.

modified endoscopic sinus surgery combined with middle turbinate resection on olfactory function and stress response in patients with refractory CRS with nasal polyps (CRSwNP), thereby providing a reference for clinical treatment.

Materials and methods

Baseline data

Ninety two patients with refractory CRSwNP, who were treated in the Tianjin 4th Central Hospital from June 2019 to June 2020, were prospectively selected and divided into observation (n=50, undergoing modified endoscopic sinus surgery combined with middle turbinate resection) and control (n=42, receiving conventional surgery) groups according to the simple randomization of "flipping a coin". The observation group consisted of 32 males and 18 females, aged 22-58 years old, with a body mass index (BMI) of 18-28 kg/m². The control group consisted of 28 males and 14 females, aged 24-60 years old, with a BMI of 19-28 kg/m². Baseline data for both groups are shown in **Table 1.** The study was approved by the Medical Ethics Committee of the Tianjin 4th Central Hospital (Approval No. SZXLL-2019-KY02), and all patients provided written informed consent.

Inclusion criteria: (i) patients who met the diagnostic criteria for refractory nasal polyps, as set in the EPOS 2012 position paper as the presence of two or more specific symptoms together with endoscopic signs of nasal polyps [5]; (ii) patients with symptoms of nasal obstruction, purulent nasal discharge, and facial swelling after systematic surgery and drug treatment, and CT scans revealed abnormal thickening of the sinus mucosa; (iii) patients who underwent ≥1 nasal endoscopic surgery; (iv) patients who underwent >3 months of standardized treatment following surgery; and (v) patients whose symptoms and signs did not improve at a follow-up period of more than 6 months. Exclusion criteria were as follows: (i) those with heart, liver, or kidney dysfunction; (ii) those with malignant neoplastic diseases; (iii) those with immune dysfunction; (iv) those with hematological system diseases; (v) those with a history of middle turbinate resection; and (vi) those with psychiatric diseases that could not cooperate in the treatment.

The diagnostic criteria for refractory nasal polyps were: CRS patients still with nasal congestion, purulent nasal discharge, facial swelling or olfactory disturbance after systemic treatments such as surgery and drugs; chronic inflammatory changes such as sinus internal mucosal edema, mucopurulent secretions, vesicles, and polyps within the sinuses as indicated by CT examination.

Treatment options

Preoperative preparation: Smoking and alcohol were abstained from 2 weeks before surgery, and antibiotics and nasal irrigation were routinely administered. A preoperative CT scan of the sinuses was conducted to determine the area of CRSwNP and its relationship with the surrounding tissues, and to determine the surgical method. In addition, patients with comorbidities such as hypertension, diabetes, and coronary heart disease were given targeted treatment.

Surgical treatment: The patients in the control group underwent conventional surgery. The head of the bed was placed at a lower level than the foot, and local anesthesia was administered preoperatively. After anesthesia, the uncinate process and ethmoidal bulla were excised using the Messerklinger approach according to the results of nasal endoscopy. The frontal recess was removed to open the anterior and posterior ethmoid sinuses. Maxillary antrostomy was performed to enlarge the opening (ostium) of the maxillary sinus to completely remove the lesions and enlarge the entire sinus. Postoperatively, the surgical cavity was flushed with normal saline and filled with a gelatin sponge to stop bleeding [6].

Patients in the observation group underwent modified endoscopic sinus surgery combined with middle turbinate resection. Before surgery, the angular position of the head was adjusted to 15°-30° under general anesthesia. The patient's blood pressure was closely monitored during surgery. All the polyps, cysts, and swollen mucosal tissues were removed during surgery, and the nasal polyps as well as the surrounding tissues were partially or completely removed. The opening of the maxillary sinus was further enlarged so that the anterior and posterior ethmoid sinuses, ethmosphenoid, and sphenoid sinuses were open. The mucosa and bone of the anterior wall of the agger nasi cells were chipped to the nasal process of the frontal bone using 45° sinus thru-cut forceps. Subsequently, the parietal and posterior walls of the agger nasi cells and cells around the frontal sinus were completely removed until the frontal sinus of the patient was fully open. In patients with a deviated septum, localized deviated cartilage was removed. In patients with allergic rhinitis, localized nasal mucosa was electrocoagulated, or a vidian neurectomy was performed. In patients with nasal adhesions, the adhesions were removed. Postoperatively, the surgical cavity was flushed with normal saline and filled with a gelatin sponge to stop bleeding [7].

Postoperative treatment: Postoperative anti-infection treatment was routinely administered, and the stuffing was removed after 1-3 d. The nasal cavity was flushed with normal saline 2-3 times per day for 1 week. Patients were treated with glucocorticoids and mucokinetic agents. Meanwhile, nasal secretions, blood scabs, and granulation hyperplasia were removed using sinus endoscopy every 7 days after surgery until tissue epithelialization could be observed in the surgical cavity of the patient. After 6 months of follow-up, the outcomes of patients in both groups were recorded.

Outcome measurement

(1) The efficacy was assessed at 2, 4, and 6 months after surgery, according to the clinical classification and staging of CRSwNP and efficacy assessment criteria [8] for endoscopic sinus surgery established by the Otolaryngology Head and Neck Surgery Branch of the Chinese Medical Association. The assessment was categorized into three categories.

Markedly effective: all clinical symptoms disappeared; the ethmoid sinus was fully opened with re-epithelization of the nasal mucosa; and no purulent secretions were detected.

Effective: clinical symptoms improved, with partial edema of the sinus mucosa and a small amount of purulent secretions.

Ineffective: clinical symptoms improved, and endoscopy showed adhesions in the operative cavity with stenosis of the sinus as well as purulent secretions.

The overall response rate was calculated as (significant + effective)/N × 100%.

(2) The olfactory function was assessed using the Sniffin' Sticks examination before and 2, 4, and 6 months after surgery. Scores >30 were considered normal olfactory function, scores between 15-30 indicated diminished olfactory function, and scores <15 indicated loss of olfactory function.

(3) The nasal function was assessed using Lund-Mackey, Lund-Kennedy, and SNOT-20 scores before and 6 months after surgery.

Lund-Mackey score: corresponds to the frontal sinus, sphenoid sinus, and ostiomeatal com-

Table 2. Comparison of overall response rate after treatment (n, %)

Group	N	Overall response rate		
		2 months after treatment	4 months after treatment	6 months after treatment
Observation group	50	10 (20.00)	32 (64.00)[#]	45 (90.00)[#,*]
Control group	42	6 (14.29)	19 (45.24)[#]	30 (71.43)[#,*]
X^2	-	Wald χ^2_{group} =4.301, Wald χ^2_{time} =91.677		
P	-	P_{group} =0.038, P_{time} <0.001		

Note: Compared with 2 months postoperatively, [#]*P*<0.05; compared with 4 months postoperatively, [*]*P*<0.05.

plex, with a total of five items, with a lower score representing better condition of the paranasal sinus.

Lund-Kennedy score: corresponds to rhinorrhea, polyps, edema, scabs, and scars, with a lower score representing better mucosal condition.

SNOT-20 score: corresponds to dizziness, earache, and sneezing, with a total of 20 items, with a lower score representing better quality of life.

(4) To measure the stress response indicators, venous blood was extracted before and immediately after surgery, and epinephrine (E), norepinephrine (NE), and cortisol (Cor) levels were measured using ELISA.

Statistical analysis

Sample size determination: According to the sample estimation method of M. Kendall, the sample size estimation for the comparison of the mean of two independent samples is: $n = \frac{(u\alpha + u\beta)2(1 + 1/k)\sigma 2}{\sigma 2}$, and $\sigma^2=(S_e^2+{}_KS_c^2)/(1+1/k)$. In this study, we set as unilateral α=0.05, β=0.10, u_α=1.6449, u_β=1.2816; the olfactory function scores of the observation group and the control group after 6 months of treatment were used for sample size calculation (the olfactory function scores of the two groups were significantly different after surgical treatment), K=0.84, $\sigma^2=(S_e^2+{}_KS_c^2)/(1+1/k)=(3.4^2+0.84\times2.9^2)/(1+1/0.84)=8.502$. Thus, the observation group (N) sample size was estimated as $(u_\alpha+u_\beta)^2(1+1/k)\sigma^2/\delta^2=(1.6449+1.2816)^2(1+1/0.84)\times8.502/1.786^2=49.99\approx50$, and the control group sample size was estimated as 50×0.84=42.

SPSS 22.0 software was used for data analysis. Count data were expressed as (n, %) and the χ^2 test was performed. The normally distributed measurement data were represented as ($\bar{x}$ ± s), and an independent sample t-test was conducted. The count data for different time points were analyzed using repeated measurement-generalized estimation equation of graded count data [9]. The data measured at different time points were analyzed using repeated measurement variance analysis, and Bonferroni analysis was used for post-hoc comparison. The GraphPad Prism software was used for mapping analysis. Statistical significance was set at *P*<0.05.

Results

Comparison of baseline data

The comparison of baseline data showed no statistically significant differences in gender, age, BMI, duration, type of disease, surgical history, and comorbidities between the two groups (*P*=0.789, 0.244, 0.554, 0.058, 0.912, 0.846, 0.892, 0.566, 0.931, 0.518, and 0.757, respectively) (**Table 1**).

Comparison of overall response rate after treatment

Generalized estimation equation analysis showed that the overall response rate in the observation group was higher than that in the control group (Wald χ^2=4.301, *P*=0.038), with statistically significant differences among different time points (Wald χ^2=91.677, *P*<0.001), suggesting significant differences in the overall response rate of patients at different time points (**Table 2**).

Comparison of olfactory function before and after treatment

The olfactory function scores showed significant differences at time points and intergroup and group-by-time interaction effects between the two groups (all *P*<0.001). There was no

Table 3. Comparison of olfactory function before and after surgery (mean ± SD)

Indicator	Time pointc	Group		t	P
		Observation group (n=50)	Control group (n=42)		
Olfactory function score	Before surgery	23.2±2.0	23.5±2.1	0.700	0.485
	2 months after surgery	26.6±2.6[a]	24.3±2.2	4.530	0.000
	4 months after surgery	29.7±2.9[a,b]	26.9±2.7[a,b]	4.760	0.000
	6 months after surgery	33.4±3.4[a,b,c]	29.6±2.9[a,b,c]	5.706	0.000
	F	$F_{time\ point}$ =1150.142; $F_{intergroup}$ =20.895; $F_{interaction}$ =63.210		-	-
	P	$P_{time\ point}$ <0.001; $P_{intergroup}$ <0.001; $P_{interaction}$ <0.001		-	-

Note: Compared with preoperative, [a]*P*<0.05; compared with 2 months postoperatively, [b]*P*<0.05; compared with 4 months postoperatively, [c]*P*<0.05.

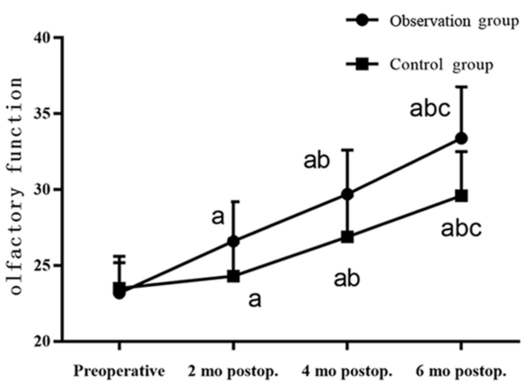

Figure 1. Comparison of olfactory function between the two groups before and after surgery. Note: Compared with preoperative, [a]*P*<0.05; compared with 2 months postoperatively, [b]*P*<0.05; compared with 4 months postoperatively, [c]*P*<0.05.

statistically significant difference in the preoperative olfactory function scores between the two groups (*P*=0.485). The olfactory function scores of the observation group at 2, 4, and 6 months after surgery were higher than those of the control group (all *P*<0.001) (**Table 3** and **Figure 1**).

Comparison of nasal function scores before and after treatment between the two groups

Before treatment, the Lund-Mackey, Lund-Kennedy, and SNOT-20 scores of the two groups were not significantly different (*P*= 0.928, 0.970, and 0.961, respectively). After treatment, the Lund-Mackey, Lund-Kennedy, and SNOT-20 scores of the observation group were significantly lower than those of the control group (all *P*<0.001) (**Table 4**).

Comparison of stress function before and after treatment between the two groups

There was no statistically significant difference in the levels of NE, E, and Cor between the two groups before surgery (*P*=0.812, 0.767, and 0.866, respectively). Immediately after surgery, the levels of NE, E, and Cor in the observation group were lower than those in the control group (all *P*<0.001) (**Table 5**; **Figures 2-4**).

Comparison of complications after treatment between the two groups

The incidence of complications in the observation group was significantly lower than that in the control group (10.00% vs. 28.57%, *P*= 0.022) (**Table 6**).

Discussion

The therapeutic effect of endoscopic sinus surgery on CRSwNP was verified clinically, and the results showed that endoscopic sinus surgery could effectively correct the abnormalities of the nasal cavity and sinus and fundamentally remove most of the inflammatory lesions of the nasal cavity and sinuses. However, patients with refractory CRSwNP are often accompanied by frontal sinus lesions, while traditional nasal endoscopic surgery preserves the mucosal flap of the frontal process of the maxilla, which easily leads to the opening and reclosure of the frontal sinus, and cells in the frontal recess region have an adverse effect on the frontal sinus drainage and are difficult to distinguish [10-12]. Hyperplastic and edematous connective tissue and inflammatory polyps contribute to abnormal breathing and can lead to a progressive loss of olfactory function [13, 14]. The main treatment principle of the modified endoscopic sinus surgery is to remove the edematous hyperplastic tissue and inflammatory polyps around the uncinate process, anterior and posterior ethmoid sinus, ethmosphenoid, and sphenoid sinus, all of which are open. However, the mucosa and bone of the an-

Table 4. Comparison of nasal function scores before and after treatment between the two groups (mean ± SD)

Group		Lund-Mackey	Lund-Kennedy	SNOT-20
Observation group (n=50)	Before treatment	7.29±2.68	8.39±1.29	18.53±6.89
	After treatment	3.62±1.63*	5.69±1.18*	7.91±3.48*
	T	8.273	10.920	9.729
	P	0.000	0.000	0.000
Control group (n=42)	Before treatment	7.24±2.6	8.38±1.24	18.6±6.81
	After treatment	4.47±1.61	6.76±1.19	10.41±3.49
	T	5.976	6.109	6.936
	P	0.000	0.000	0.000

Note: Compared with the control group after treatment, **P*<0.05.

Table 5. Comparison of stress function before and after surgery (mean ± SD)

Indicator	Group	Preoperative	Immediately after postoperative	$F_{Time\ point}$	$F_{Interaction}$	$F_{Intergroup}$
NE (ng/L)	Observation group (n=50)	252.76±19.61	346.81±33.35	2667.963	339.380	106.306
	Control group (n=42)	253.76±20.51	452.09±35.43			
	T	0.239	14.659			
	P	0.812	0.000	0.000	0.000	0.000
E (pmol/L)	Observation group (n=50)	260.13±37.38	548.17±44.31	6295.401	361.828	145.323
	Control group (n=42)	262.42±36.26	732.12±54.16			
	T	0.297	17.920			
	P	0.767	0.000	0.000	0.000	0.000
Cor (nmol/L)	Observation group (n=50)	409.75±36.35	612.66±62.37	2481.128	159.183	51.605
	Control group (n=42)	411.05±37.28	751.62±70.11			
	T	0.169	10.058			
	P	0.866	0.000	0.000	0.000	0.000

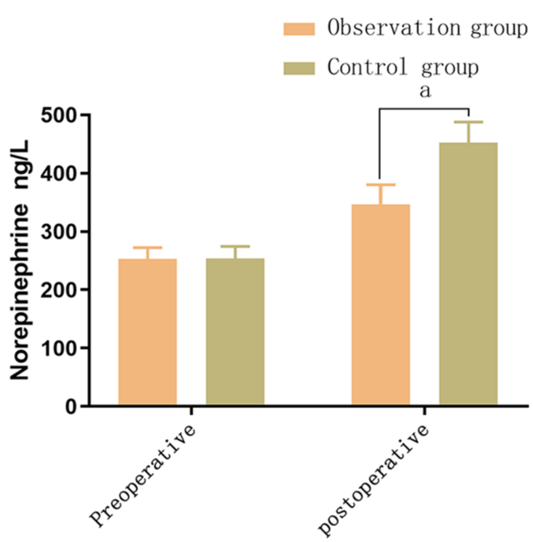

Figure 2. Comparison of norepinephrine level before and after surgery. After surgery, norepinephrine in the observation group was significantly lower than that in the control group. ^{a}P<0.05.

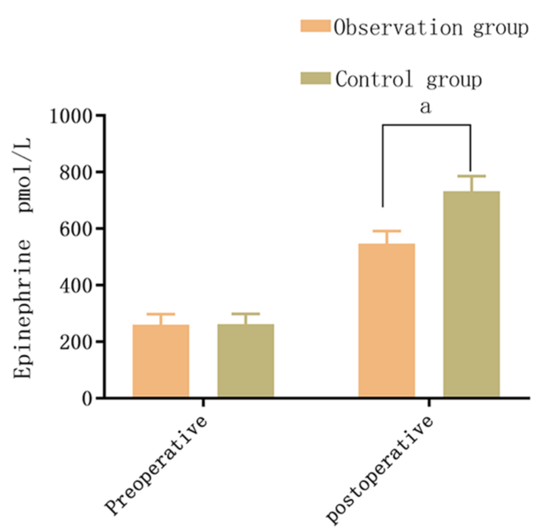

Figure 3. Comparison of epinephrine level before and after surgery. After surgery, epinephrine in the observation group was significantly lower than that in the control group. ^{a}P<0.05.

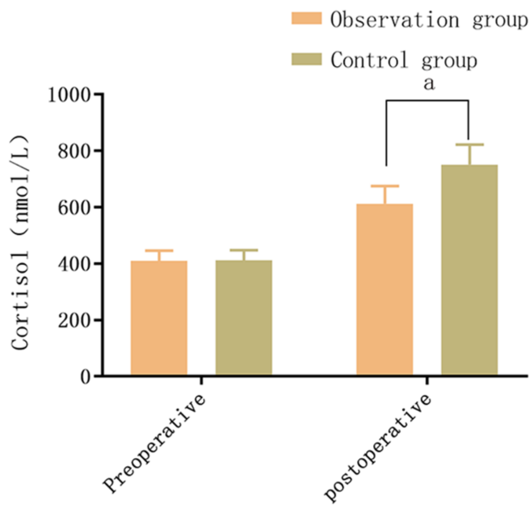

Figure 4. Comparison of cortisol level before and after surgery. After surgery, cortisol in the observation group was significantly lower than that in the control group. $^{a}P<0.05$.

terior wall of agger nasi cells are completely occluded during the surgery so that the anterior wall of agger nasi cells and the bottom of the frontal recess are open, which effectively prevents the closure of the frontal sinus and promotes the recovery of olfactory function. The middle turbinate is part of the lateral mass of the ethmoid bone, which protrudes from the external wall of the nasal cavity and contains a large distribution of glands that contribute to the secretion of antibodies. It protects the sinus ostia and stabilizes the nasal morphology, thus playing an important role in endoscopic sinus surgery [15, 16]. However, in recent years, studies have shown that the recurrence of polyps in the middle turbinate is higher in patients with refractory CRSwNP, while partial or total excision of nasal polyps is feasible for middle turbinate resection. This effectively reduces the recurrence, further improves the drainage of the middle nasal tract, and has a significant effect on the intraoperative observation and cleaning of the operative cavity, reducing nasal adhesions and removing lesions from the turbinates [17, 18].

In addition, Li et al. [19] showed that endoscopic sinus surgery in the treatment of refractory CRSwNP can achieve an efficacy rate of more than 80%. In this study, the total postoperative efficiency was 90%, higher than 71.43% of the control group, and at 2, 4, and 6 months after surgery, the Lund-Mackey, Lund-Kennedy, and SNOT-20 scores of the observation group were lower than those of the control group. These results are consistent with the findings of Wei et al. [20]. The results suggest that modified endoscopic sinus surgery combined with middle turbinate resection is effective in the treatment of patients with refractory CRSwNP and promoted the recovery of olfactory and nasal function.

The stress response is caused by injurious stimuli, which can trigger neuroendocrine dysregulation and increase sympathetic excitation and pituitary-adrenal cortical secretion [21]. Controlling the stress response is crucial for a successful surgery. A high stress response can affect the surgical process of patients, causing inappropriate procedures and increasing the risk of refractory CRSwNP. Therefore, it is vital to effectively reduce the stress response in perioperative patients [22, 23]. Epinephrine is mainly released by the adrenal glands, which promotes cardiac contractility and plays an important role in the contraction of the skin and mucosal vessels. NE is a hormone that is mainly synthesized and secreted by the adrenal medulla, but its normal levels are low. Cor is a glucocorticoid, which is the only inhibitory feedback regulator in the traumatic stress response and has a strong influence on glucose metabolism. It has been noted that a higher Cor level represents a more severe stress response [24]. In this study, although the postoperative levels of NE, E, and Cor in patients of the two groups increased, the postoperative levels of NE, E, and Cor in patients in the observation group were significantly lower than those in the control group. These results suggested that modified endoscopic sinus surgery combined with middle turbinectomy reduced the occurrence of intraoperative stress response and facilitate smooth surgery. The reasons are as follows. First, the modified endoscopic sinus surgery combined with middle turbinectomy does not involve the traditional destructive shaving of the simus mucosa, and while effectively removing the diseased tissue, the normal tissues of the nasal cavity, sinus, and mucosa of patients are preserved to the largest extent. This not only achieves effective treatment, but also reduces the intraoperative release of substances such as Cor and serotonin, promotes the stability of the patient's hemorheology, and reduces the stress response.

Table 6. Comparison of complications after treatment between the two groups (n, %)

Group	Nasal adhesion	Sinus atresia	Intraocular rectus injury	Black and blue eye socket	Others	Incidence
Observation group (n=50)	2 (4.00)	1 (2.00)	0 (0.00)	1 (2.00)	1 (2.00)	5 (10.00)
Control group (n=42)	4 (9.52)	3 (7.14)	1 (2.38)	1 (2.38)	2 (4.76)	12 (28.57)
X^2	1.142	1.452	1.204	0.016	0.552	5.226
P	0.285	0.228	0.273	0.901	0.458	0.022

In conclusion, the modified endoscopic sinus surgery combined with middle turbinate resection is effective in the treatment of patients with refractory CRSwNP and can effectively improve the olfactory function of patients and reduce their perioperative stress response. A shortcoming of this study was that it was from a single-center and it was a non-randomized control study, unlike the strict matching design of randomized control studies. It also had a short observation time, indicating that although improved endoscopic nasal surgery combined with middle turbinate resection was effective for refractory CRSwNP, patient olfactory function was not objectively examined. Therefore, multicenter prospective randomized controlled studies should be conducted in future to develop a more in-depth understanding.

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Disclosure of conflict of interest

None.

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