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Original Article

Treating moderate-to-severe persistent allergic rhinitis by endoscopic posterior nasal neurectomy: a study of efficacy and effects on autophagy

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Abstract: Objective: This study aimed to analyze the efficacy of endoscopic posterior nasal neurectomy (EPNN) in treating patients with moderate-to-severe persistent allergic rhinitis (PAR), and its effects on autophagy. Methods: A total of 63 patients with moderate-to-severe PAR in our hospital from July 2018 to June 2019 were randomized into the Control Group (CG, n=31, conservative medication) and the Surgery Group (SG, n=32, EPNN) by drawing lots. Clinical efficacy was compared between the two groups. Results: (1) At 1 month, 3 months, 6 months and 12 months after treatment, the VAS and QOL (quality of life) scores were significantly lower in the SG ($P<0.05$) while no intergroup and intragroup significance was found in the length of wetted tear test strip ($P>0.05$). (2) At 12 months after treatment, the IL-4, IL-13 and IL-17A levels were significantly lower in the SG ($P<0.05$). (3) According to IHC, the expressions of autophagy-related proteins ECP and LC3 were weakened. Conclusion: In patients with moderate-to-severe PAR, EPNN can mitigate pain intensity, improve QOL and inhibit autophagy.

Keywords: PAR, moderate-to-severe, EPNN, treatment, autophagy

Introduction

Allergic rhinitis (AR), is known as a non-infectious inflammatory disease of the nasal mucosa, and it has clinical symptoms of sneezing, rhinorrhea, nasal congestion and itching. Its development is mediated by IgE mainly after the body has contact with an allergen, and it involves many types of cell factors and inflammatory factors [1]. According to epidemiological surveys, AR is a global health concern with an incidence between 10% and 20% worldwide and rising, especially in China in recent years, affecting patients' work, study and life [2, 3].

Ordinary therapies for AR include avoidance or minimization of contacting allergens, medication, specific immunotherapy and surgery [4]. Previous studies have evidence for the good efficacy of non-surgical conventional therapies in most of the AR cases [5, 6]. However, a considerable number of AR patients are not tolerant to the adverse reactions caused by the drugs or their long-term application, and conventional non-surgical therapies failed to demonstrate ideal efficacies in some moderate-to-severe PAR patients in whom, the clinical syndromes were robust [7]. For such a group of patients with refractory AR, operation has become the first choice, including vidianneurectomy and Vidian nerve electrofulguration [8]. In recent years, with the development in functional sinus endoscope and image navigation technology, there are a lot of domestic and foreign reports on the clear efficacy of posterior nasal neurectomy in moderate-to-severe PAR [9, 10], which has failed to investigate the relevant molecular mechanisms. Regardless of the reports on the hygiene hypothesis, Th1/Th2 imbalance theory, IgE and its receptor, and clasmatoblasts and their roles as mediators of inflammation and regulators of nerves, the real molecular mechanism is unclear.

In recent studies, the impacts of autophagy on apoptosis of fibroblasts and eosinophils, differ-

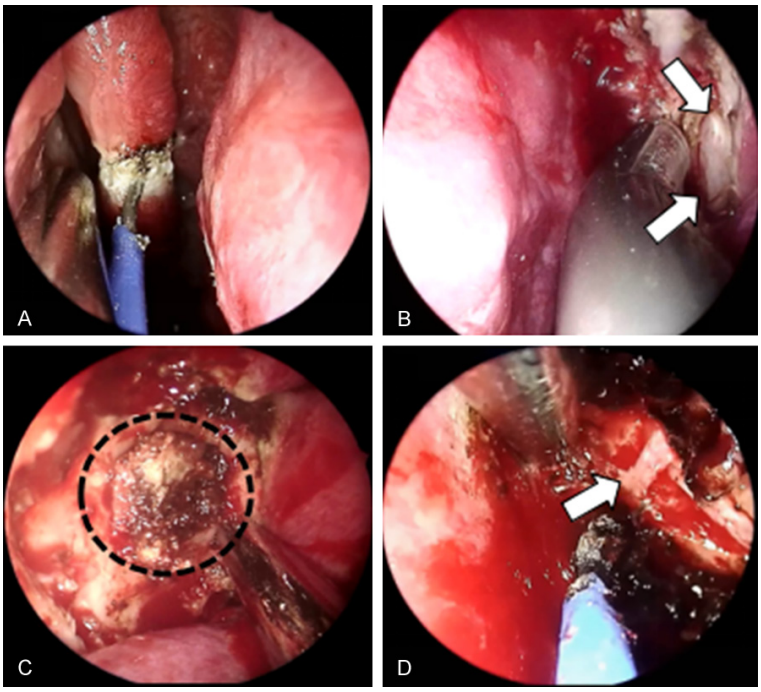

Figure 1. Steps of Bilateral EPNN. A. Cut off the posterior part of the free margin of concha nasalis media; B. Cut open the mucous membrane in an arc shape at the anterior lower part of the root of concha nasalis media to expose the foramina sphenopalatinum; C. Cut off the neurovascular bundle of foramina sphenopalatinum at 360°, namely, dissecting the PNN plexus and its branches; D. Adequate hemostasis and cut off the branch pharyngeal nerve.

entiation of eosinophils in bone marrow and their secretion were observed. This is an important process of our body to adapt to the environment and maintain internal environment stability. Abnormal autophagy has its advantages and disadvantages in the development of many diseases. On the one hand, it induces apoptosis and inhibits cell survival; on the other hand, it inhibits apoptosis and promotes cell growth. According to the most recent studies, inhibiting autophagy can be a way to suppress the Eosinophilic esophagitis in severe asthma, and a new target in the treatment of respiratory diseases. In addition to efficacy, this study also explored the surgical method's effects on autophagy.

Materials and methods

Materials

A total of 63 moderate-to-severe PAR patients in our hospital from July 2018 to June 2019 were randomized to the CG (n=31) and the SG (n=32) by drawing lots. All patients have been informed of the study content and provided their consent. The study was approved by the Ethics Committee of our hospital. (1) Inclusion criteria: compliance with the relevant criteria specified in the *Guides to the Diagnosis and Treatment of Allergic Rhinitis (Tianjin, 2015)* [11]; treated by non-surgical methods for at least 2 years; bilateral EPNN assisted by image navigation required; compliance with surgical indications; normal cognition; guarantee to complete the follow-up. (2) Exclusion criteria: incompliant with the moderate or severe criteria; surgical contradictions; failure of follow-up; mental disorders; changed nasal structure due to nasal surgeries in the past.

Methods

Patients in the CG were treated by spraying nasal glucocorticoids and oral administration of antihistamines for 3 months. Budesonide Nasal Spray (specification: 32 ug/spray, 120 sprays/dose, approval no. J20040082, manufactured by AstraZeneca AB) was selected for nasal glucocorticoids treatment, with the dosage of 128 ug each side and once daily in the morning. Loratadine (specification: 10 mg*6 tablets, approval no. H20080105; manufactured by Shanxi Zhendong Taisheng Pharmaceutical Co., Ltd.) was used for antihistamine treatment, which was taken 5 mg orally every night before sleep.

Patients in the SG received a bilateral EPNN assisted by image navigation (**Figure 1**) after CT examination of paranasal sinus and in a general anesthesia state. Under the nasal endoscope at an angle of 0° or 30°, the middle nasal meatus mucosa was cut open along the long axis of middle turbinate at about 0.5 cm ahead of the attachment site of the posterior end of concha nasalis media until the bone surface. Detachment was performed at the posterior superior direction with a detacher in con-

Table 1. Intergroup Comparison of General Materials ($\bar{x}$ ± s)/[n (%)]

Materials		SG (n=32)	CG (n=31)	t/X^2	*P*
Gender	Male	17 (53.13)	18 (58.06)	0.156	0.693
	Female	15 (46.87)	13 (41.94)		
Age (y)		35.16±12.28	37.94±13.12	0.869	0.389
Course of disease (y)		7.45±3.61	6.97±3.50	0.534	0.595
BMI (kg/m^2)		22.43±1.16	23.08±1.24	2.149	0.036
Early duration of therapy (y)		2.34±0.20	2.40±0.22	1.133	0.262

tact with the bone surface. The posterior end of concha nasalis media was lifted, and an area of about 1 cm^2 was exposed on the foramina sphenopalatinum to show the neurovascular bundle projecting therefrom, and the nerve bundle passing through the independent bone canal. The bundles were slightly separated to identify each PNN branch and arteries in the combined course. The neurovascular bundle was coagulated and cut off with a plasma knife. The broken end of foramina sphenopalatinum neurovascular bundle required coagulation, too. Intravenous drip of antibiotics maintained for 2 days after the surgery, and the nasal fillers were removed to clean the nasal cavity regularly and when necessary.

After treatment, both groups received continuous follow-up, with the longest follow-up period of 12 months. The follow-up methods were mainly telephone follow-up and outpatient follow-up.

Observation indices

Pain intensity: before, at 1 month, 3 months, 6 months and 12 months after the surgery, the visual analogue scale (VAS) [12] was used to evaluate the pain intensity. It is a movable scale with 11 numbers from 0 to 10, of which, 0 represents no pain and 10 the worst possible pain. Patients were guided to select a number from the scale to indicate the pain they were suffering from.

Schirmer test [13]: a tear test strip was placed in the lower fornix at the junction of lateral 1/3 and medial 2/3. Patients were asked to close their eyes for 5 minutes. Tears caused progressive wetting of the paper strip and the length was accurately recorded before, at 1 month, 3 months, 6 months and 12 months after the test.

QOL: the Rhinoconjunctivitis Quality of Life Scale (RQLQ) [14] was used for evaluation before, at 1 month, 3 months, 6 months and 12 months after treatment. The scale includes 7 items, namely, practical problems, emotional function, limited activity, nasal symptoms, non-nasal symptoms, eye symptoms and sleep quality, each containing four entries scored between 0 and 6. The total score of the scale is between 0 and 168, and positively reflects the quality of life.

Enzyme-linked immunosorbent assay (ELISA): nasal mucosa samples were collected from all patents before and at 12 months after treatment, cleaned in normal saline to remove the blood and nasal secretions, and kept in Formalin solution. Nasal mucosa tissue was thawed, cut into pieces, mixed with normal saline at the proportion of 1 g/10 ml, and centrifuged at 3,000 rpm under 4°C for 5 minutes. The supernatant was recycled, stored at 4°C, and tested by ELISA for the levels of IL-4, IL-13, and IL-17A.

Immunohistochemistry (IHC): nasal mucosa tissues were collected, fixed, dehydrated, sliced, and waxed. The primary antibody was added into the processed tissue for incubation overnight after antigen repair and serum blocking. The incubated mixture was then placed in PBS, with secondary antibody was added, rinsed again and DAB developer was added (Dako Inc, California, UAS), and then visualized by haematoxylin to test autophagy-related proteins through observation.

Statistical analysis

Statistical analysis was performed with SPSS 22.0. In case of numerical data expressed as Mean ± Standard Deviation, comparison studies were carried out through independent-samples *t* test; in case of nominal data expressed as [n (%)], comparison studies were carried out through X^2 test for intergroup comparison. Intergroup comparison at multiple points was done by ANVOA. For all statistical comparisons, significance was defined as $P<0.05$.

Table 2. Intergroup Comparison of VAS Scores before and after Treatment ($\bar{x}$ ± s, score)

Group	n	Before treatment	At 1 month after treatment	At 3 months after treatment	At 6 months after treatment	At 12 months after treatment
SG	32	7.12±1.36	5.02±1.53*	3.61±1.08*	2.03±1.27*	0.67±0.31*
CG	31	7.23±1.39	6.32±1.45*	4.84±1.33*	2.84±1.46*	1.33±0.58*
t		0.317	3.459	4.036	2.352	5.658
P		0.752	0.001	0.002	0.022	0.000

Note: *P<0.05 vs conditions before treatment.

Table 3. Intergroup Comparison of Changes in Schirmer Test Results before and after Treatment ($\bar{x}$ ± s, mm)

Group	n	Before treatment	At 1 month after treatment	At 3 months after treatment	At 6 months after treatment	At 12 months after treatment
SG	32	15.62±1.06	16.82±1.21	15.91±1.12	16.02±1.18	15.73±0.98
CG	31	15.43±1.02	16.38±1.27	16.01±1.13	15.94±1.32	15.89±1.07
t		0.725	1.408	0.353	0.254	0.619
P		0.472	0.164	0.726	0.801	0.538

Table 4. Intergroup Comparison of Improvements in QOL before and after Treatment ($\bar{x}$ ± s, score)

Group	n	Before treatment	At 1 month after treatment	At 3 months after treatment	At 6 months after treatment	At 12 months after treatment
SG	32	98.45±12.34	85.23±10.19*	76.31±8.92*	61.42±7.48*	43.28±5.13*
CG	31	102.31±13.28	95.42±11.64*	83.64±10.17*	73.61±9.35*	56.31±6.39*
t		1.196	3.700	3.044	5.723	8.939
P		0.237	0.001	0.003	0.000	0.000

Note: *P<0.05 vs conditions before treatment.

Results

General materials

Statistical difference was not found between the two groups in the proportions of male and female patients, average age, average course of disease, average BMI, and early duration of therapy (P>0.05) (**Table 1**).

Bilateral EPNN assisted by image navigation alleviates pain intensity

Before treatment, the two groups were not significantly different in VAS score (P>0.05). At 1 month, 3 months, 6 months and 12 months after treatment, the VAS scores were (5.02±1.53), (3.61±1.08), (2.03±1.27) and (0.67±0.31) (P<0.05) respectively, in the SG; and (6.32±1.45), (4.84±1.33), (2.84±1.46) and (1.33±0.58) P<0.05) respectively, in the CG (P<0.05) (**Table 2**).

Schirmer test

Significant difference in the length of tear moistened test strip was not observed in and between the two groups before and after treatment (P>0.05). Values based on the recorded data at 1 month, 3 months, 6 months and 12 months after treatment the SG had wetted the test strips to (16.82±1.21) mm, (15.91±1.12) mm, (16.02±1.18) mm, and (15.73±0.98) mm respectively; and the CG had (16.38±1.27) mm, (16.01±1.13) mm, (15.94±1.32) mm, and (15.89±1.07) mm respectively (P>0.05) (**Table 3**).

Bilateral EPNN assisted by image navigation improves QOL

Before treatment, the two groups were not significantly different in RQLQ score (P>0.05). At 1 month, 3 months, 6 months and 12 months after treatment, the RQLQ scores were (85.23±10.19), (76.31±8.92), (61.42±7.48),

Table 5. Intergroup Comparison of IL-4, IL-13 and IL-17A Levels ($\bar{x} \pm s$)

Group	Time	IL-4 (ng/L)	IL-13 (ng/L)	IL-17A (ng/ml)
SG (n=32)	Before treatment	121.35±54.13	485.61±153.62	42.61±5.85
	At 12 months after treatment	50.34±16.64*	230.65±127.49*	8.42±1.30*
CG (n=31)	Before treatment	118.76±50.38	462.15±150.38	40.85±6.05
	At 12 months after treatment	75.51±34.52*	384.76±261.24*	16.37±3.07*
t		3.705	2.990	13.458
P		0.001	0.004	0.000

Note: *t* and *p* as the comparative statistical values of the two groups at 12 months after treatment. *P<0.05 vs conditions before treatment.

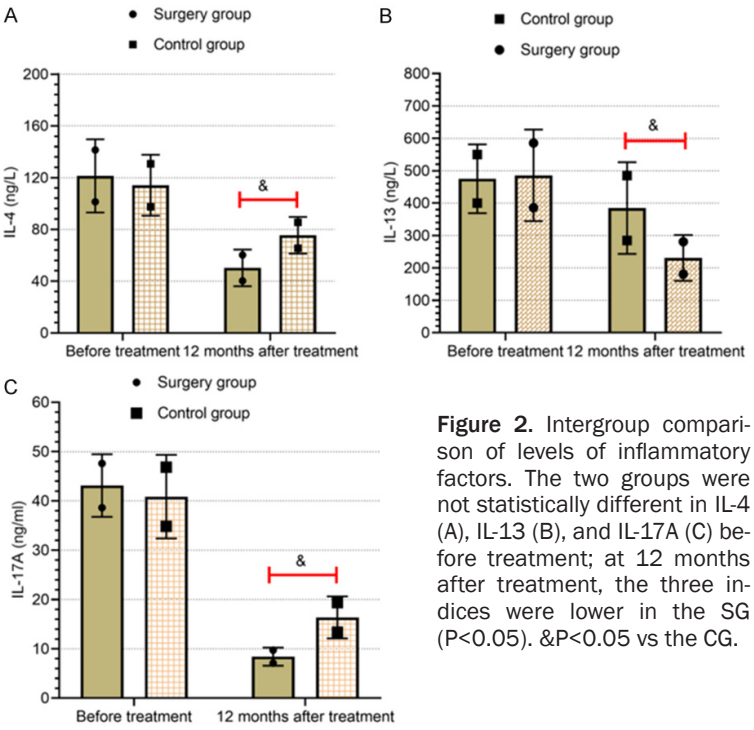

Figure 2. Intergroup comparison of levels of inflammatory factors. The two groups were not statistically different in IL-4 (A), IL-13 (B), and IL-17A (C) before treatment; at 12 months after treatment, the three indices were lower in the SG (P<0.05). &P<0.05 vs the CG.

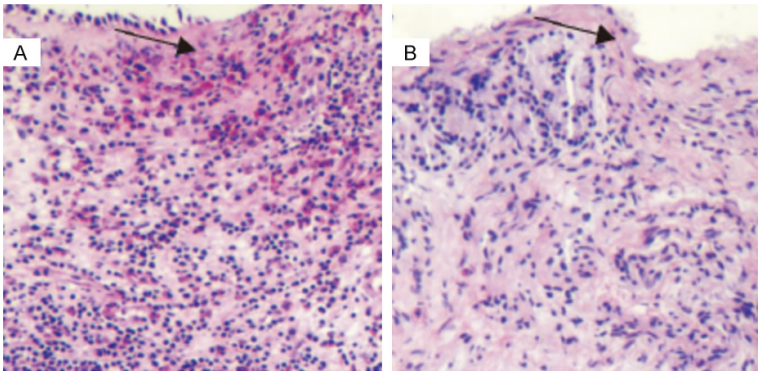

Figure 3. Analysis of immumohistochemical staining results. A. CG at 12 months after treatment, showing thickened mucosa and large amount of EOS and lymphocyte infiltration; B. SG at 12 months after treatment, showing pseudostratified ciliated columnar epithelium.

and (43.28±5.13) (P<0.05) respectively, in the SG; and (95.42±11.64),(83.64±10.17), (73.61±9.35), and (56.31±6.39) (P<0.05) respectively, in the CG (P<0.05) (**Table 4**).

Bilateral EPNN assisted by image navigation improves ELISA results

The intergroup difference in IL-4, IL-13 and IL-17A was not statistically different before treatment (P<0.05). At 12 months after treatment, they were (50.34±16.64) ng/L, (230.65±127.49) ng/L and (8.42±1.30) ng/ml respectively, in the SG; and (75.51±34.52) ng/L, (384.76±261.24) ng/L and (16.37±3.07) ng/ml respectively, in the CG (P<0.05) (**Table 5** and **Figure 2**).

Bilateral EPNN assisted by image navigation changes IHC results

According to IHC, the epithelial layer of mucous membrane of the anterior nasal cavity in the CG was thickened at 12 months after treatment, and marked inflammatory cell infiltration (EOS and leukomonocytes) was observed in the tissue (**Figure 3A**). Clear inflammatory cell infiltration was not found in nasal mucosa tissue in the SG at 12 months after

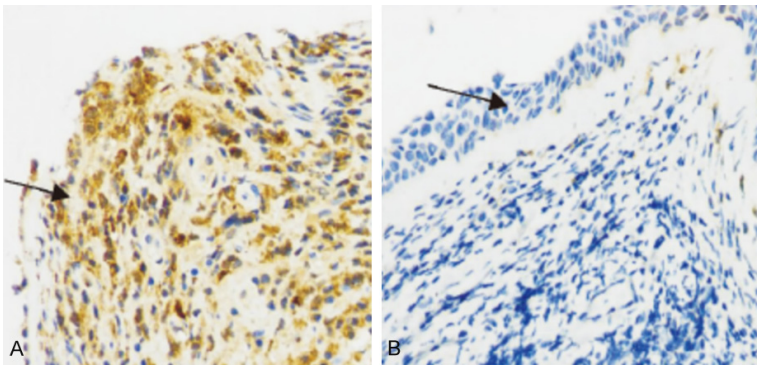

Figure 4. IHC detection of autophagy-related protein ECP expression. A. CG at 12 months after treatment, showing a large amount of cytoplasmic staining of the mucosal epithelial layer (arrow) and submucosal cells; B. SG at 12 months after treatment, showing slight staining of cells.

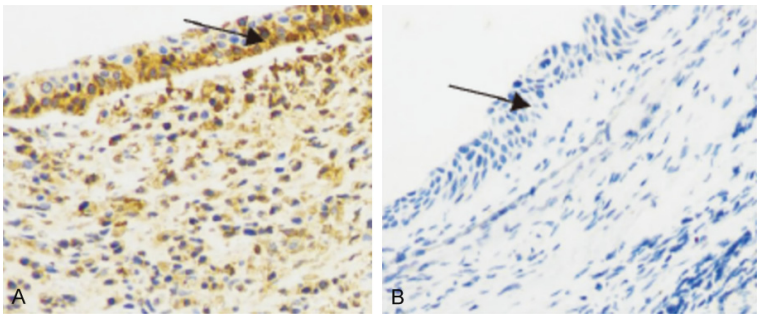

Figure 5. IHC detection of autophagy-related protein LC3 expression. A. CG at 12 months after treatment, showing a large amount of cytoplasmic staining of mucosal epithelial cells (arrows) and submucosal cells; B. SG at 12 months after treatment, showing slight staining of epithelium.

treatment (**Figure 3B**). The expression of ECP, an autophagy-related protein, was also observed under a light microscope with IHC. At 12 months after treatment, a large amount of dyed brown-yellow or brown particles were found in the cytoplasm of epithelial cells of nasal mucosa in the CG (**Figure 4A**), which faded or became colorless in the SG after treatment of 12 months (**Figure 4B**). Another autophagy-related protein, LC3 was found in large amounts in the epithelial cells of nasal mucosa or in glands in the CG at 12 months after treatment under the light microscope (**Figure 5A**). It was found in the cytoplasm mainly, or cytoskeleton in some cases, and existed as brown yellow or brown particles which faded or became colorless in the SG at 12 months after treatment (**Figure 5B**).

Discussion

Both immune mechanism and neuroregulatory mechanism are closely related to the onset mechanisms of AR. Studies have revealed the increased activity of the parasympathetic nerve is an important factor in the development of AR [15]. The Vidian nerve consists of sympathetic fibers and parasympathetic nerve fibers. It can regulate gland secretion and vasoconstriction, and dominate the greater part of lacrimal gland, palatum durum, nasal cavity and sinuses [16]. On these grounds, it is believed in this study that in treating AR, selectively blocking the Vidian nerve can accelerate the contraction of small vessels in the nasal mucosa, mitigate the mucosal swelling, and effectively improve the microcirculation [17]. With a microscope, Fizzano KM et al [18] discovered that after surgery, the number and proportion of glands, and the mucous layer in the nasal mucosa have recovered to the normal levels; serous glands were reduced and mucous glands formed. However, the difference between specific operating methods resulted in varying efficacies in different reports. In some operations, the Vidian nerve was accurately cut off, and the efficacy was good. In some cases, methods including cauterization and thermocoagulation failed to achieve these efficacies as expected [19, 20].

In recent years, clinical diagnosis and treatment techniques have achieved marked progress, including nasal endoscopy. As a result, clinical understanding on the Vidian canal and the Vidian nerve is improved, and vidianneurectomy is increasingly improved [21]. However, in practice, vidianneurectomy is also associated with obvious complications and effects on prognosis. Doctors may have different understanding of the Vidian nerve and its adjacent anatomic structure, and during the operation significant difficulty exists in exposing the Vidian canal opening, accurate nerve cutoff and avoidance of neuranagenesis [22, 23]. As studies continue, PNN is gradually applied in the clinic. Benkhatar H et al [24] found in a H&E

IHC study that after PPN, the number of glands in the infraturbinal mucosa significantly reduced from (3.86±1.08) to (2.61±0.88), and the local infiltration of inflammatory cells also reduced. In this study, patients in the SG were treated by EPNN, and yielded lower VAS and QOL scores at 3 months, 6 months and 12 months after treatment; and the levels of IL-4, IL-13 and IL-17A were (50.34±16.64) ng/L, (230.65±127.49) ng/L, (8.42±1.30) ng/ml, respectively in the SG, which were lower than those of (75.51±34.52) ng/L, (384.76±261.24) ng/L and (16.37±3.07) ng/ml in the CG. However, compared with the above similar results, there are some differences in the specific data results, which can be attributed to the differences in the included subjects, detection methods and technical levels. Nevertheless, EPNN can control pain and inflammatory levels, and improve patients' quality of life. Furthermore, no obvious time-dependent change in the length of the wetted tear test strip was observed in the Schirmer test, evidence that the operation did not have significant impact on the functions of parasympathetic fibers dominating the lacrimal glands. EPNN is a minimally invasive operation characterized by simple positioning to obtain clear visual field, also having a low difficulty in operation and minimal wounding. It can control the symptoms of AR by inhibiting inflammatory cytokine levels [25]. To maximize the efficacy and safety of the operation, the posterior lower part of the middle nasal meatus can be completely exposed, and the back end of concha nasalis media may be internally shifted when necessary to enlarge the operating space. Besides, surgeons can fully concentrate on processing the PNN vascular bundles. An ontological microscopic right ankle hook shall be used to dissociate the blood vessel surface and cut off the PNN branches at a length of at least 5 mm. In such a process, attention needs to be paid to the cutoff of the independent branches of PNN.

Autophagy is a natural phenomenon in eukaryotic cells. It is an important mechanism for cells to maintain the stability of their internal environment, and it can help cells to adapt to environmental changes and prevent the invasion of pathogenic microorganisms. ECP is an important agent for eosinophils to exert their biological functions. Clinical methods for the determination of ECP expression include serum, nasal lavage fluid and nasal secretions. It was found that the severity and duration of nasal obstruction in children with persistent allergic rhinitis were closely related to serum ECP level. Studies have shown that patients with allergic rhinitis have significantly higher levels of ECP in nasal mucosal tissues compared with healthy people, suggesting that ECP plays a role in promoting the occurrence and progression of allergic rhinitis. LC3 is an important method for autophagy detection, which has high specificity and can accurately reflect autophagy activity. LC3 is a homologue of autophagy-related genes in yeast in mammalian cells. It exists on the surface of the anterior autophagosome and the membrane of the autophagosome, and is a participant in the formation of autophagosomes. It is found that the level of LC3 in the peripheral blood of asthmatic patients was significantly higher than that of healthy people, and the level of LC3 was significantly decreased after treatment, indicating that LC3 was a participating factor of asthma. In this study, IHC detection showed that ECP faded or became colorless in the SG at 12 months after treatment. In the surgery group, 12 months after treatment, IHC detection showed that autophagy-related protein LC3 faded or became colorless in the SG at 12 months after treatment. After surgical treatment, both ECP and LC3 showed improvement under IHC, suggesting that ECP and LC3 are correlated with the severity of allergic rhinitis, which can be regarded as indicators of the efficacy and prognosis of allergic rhinitis.

In conclusion, for patients with moderate-to-severe PAR, EPNN can mitigate the pain intensity, improve QOL and inhibit autophagy. However, this study is defective in some points, such as limited number of samples, insufficient study of autophagy, and possible biased results to a certain degree. Future studies shall be based on more samples, and autophagy will be studied in detail and more comprehensively, in order to obtain specific scientific conclusions as reference for treating patients with moderate-to-severe PAR.

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Disclosure of conflict of interest

None.

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