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ORIGINAL ARTICLE

Effect of Silver Nitrate Cauterisation of Nasal Mucosa on Quality-of-Life and Histology in Patients with Intractable Chronic Rhinitis

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Abstract Patients with chronic rhinitis causing intractable sneezing which is non-responsive to conventional medication require alternative therapies. The aim of the study was to ascertain the effect of topical 10% silver nitrate solution on the inferior turbinate mucosa as well as quality of life in such patients. Patients with severe chronic rhinitis who failed conventional therapy had application of 10% silver nitrate solution to inferior turbinate mucosa. The number of sneezes/day and mini Rhinoconjunctivitis Quality of Life Questionnaire (RQLQ) score was noted before and 8 to 16 weeks after treatment. Pre- and post treatment turbinate biopsies were performed to assess histological changes. At baseline, 67 patients had a mean of 36.6 sneezes/day and mean mini RQLQ score of 4.0 ± 0.7. Pre-treatment biopsies showed epithelial denudation and hyalinization of basement membrane. Following 10% silver nitrate application, 64/67 (95.5%) patients showed significant reduction in number of sneezes both at 1 week ($p < 0.001$) and 8–16 weeks (mean = 5.5 ± 7.8; $p < 0.001$). Post- treatment mean global mini RQLQ score was also significantly reduced (mean = 1.3 ± 1.1; $p < 0.001$). A single application was sufficient in 70.1% patients. There were no complications. Squamous metaplasia ($p = 0.005$) and epithelial hyperplasia ($p = 0.013$) as well as epithelial and basement membrane restoration occurred following therapy. 10% silver nitrate solution application is an effective and safe office- based procedure which significantly reduces sneezing improves QoL with corresponding histological changes.

Keywords Silver nitrate · Chronic rhinitis · Squamous metaplasia · Quality-of-life

Introduction

Guidelines for medical therapy in chronic rhinitis of allergic or vasomotor etiology have been developed largely based upon the severity of the disease and the symptoms that are predominant. Available standard first and second line pharmacotherapy includes oral and topical antihistamines and intranasal steroid and antihistamine nasal spray or drops [1]. In severe cases, combination therapy has been recommended. Ipatropium bromide has been suggested for cases of vasomotor rhinitis with rhinorrhoea as the predominant symptom [2]. Not all patients respond to first or second line therapies, however. An interest in trying alternative therapies for these difficult-to-treat patients is evident in the literature. There is evidence supporting the benefit of turbinate reduction in patients with chronic rhinitis [3, 4]. This surgical procedure addresses the problem of nasal congestion primarily and

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that of rhinorrhoea and sneezing secondarily. Procedures like Vidian neurectomy have been found to be useful in reducing excessive nasal discharge and obstruction in cases of vasomotor rhinitis but side effects of crusting and dry eyes occur [5]. More recently, posterior nasal neurectomy, which does not produce these unpleasant side-effects, has been found effective in reducing nasal discharge and sneezing [6].

The use of topical intranasal chemical cautery with chemicals like trichloroacetic acid and silver nitrate is an alternative form of therapy that has not been extensively studied. Application of a chemical cautery to the nasal mucosa is a simple, convenient and cost-effective mode of therapy for this small subset of patients with chronic rhinitis with persistent sneezing or rhinorrhoea who have not responded to or do not wish to continue conventional oral or topical medication [7]. It is less invasive than submucous diathermy and can be performed effortlessly in the out-patient setting with the same equipment that is used for diagnostic nasal endoscopy.

The histological effects of topical therapies have not been extensively studied [8, 9]. In an earlier study we showed that epithelial denudation and basement membrane thickening was reduced and ciliary presence enhanced when patients with allergic rhinitis and inferior turbinate hypertrophy were subject to either submucous diathermy or had endoscopic resection of the turbinate [10].

In the present study, we sought to ascertain whether topical application of a 10% silver nitrate solution could effectively reduce or abolish the symptoms of sneezing and rhinorrhoea in those patients with chronic rhinitis in whom these two symptoms were predominant. We further wished to ascertain the duration of this effect as well as any change in quality of life (QoL) in these patients using a standard QoL instrument. The histological effects of silver nitrate cauterisation on the nasal mucosa were also studied.

Materials and Methods

We conducted a prospective, cohort study in the Department of ENT of our tertiary care hospital between May 2019 to March 2020. Patients aged $\geq$ 18 years diagnosed with allergic or vasomotor rhinitis with predominant sneezing (> 10 sneezes/ day) $\pm$ watery rhinorrhoea not responding to conventional therapy were recruited to the study (Fig. 1).

Patient Screening

After clinical history, diagnostic nasal endoscopy, skin allergy testing and radiological assessment as per ARIA guidelines [11], where indicated, patients with chronic rhinitis were screened and those with evidence of sinusitis or any other nasal pathology were excluded.

Pre-treatment Assessment

Informed consent was taken for patients recruited to the study. The total number of sneezes/day was specifically noted. All patients were administered the mini Rhinoconjunctivitis Quality of Life Questionnaire (RQLQ).

Procedure

Cotton strips soaked in 4% xylocaine and 0.05% oxymetazoline solution were first inserted into both nasal cavities for anesthesia and decongestion. A silicon splint coated with xylocaine jelly was placed against the nasal septum to avoid any damage to the mucosa during the procedure. A 2–3 mm biopsy was taken from the anterior end of the inferior turbinate on one side. All biopsy specimens were preserved in 10% formalin and sent to the Anatomy Department for histological examination.

Thereafter, a swab stick soaked in 10% silver nitrate solution was applied on the anterior one centimeter of the medial aspect of both inferior turbinates until a white discoloration of the mucosa covering the turbinates was observed.

Post-procedure Instructions

Patients were advised to avoid picking the nose. They were instructed to apply normal saline nasal drops thrice daily for a week. If they developed sneezing or rhinorrhoea during the following 7 days, they were advised to take one tablet of fexofenadine 120 mg daily as rescue medication. Those who complained of pain were prescribed analgesics. Patients were asked to diarise the number of sneezes and the presence of rhinorrhoea over the next 16 weeks.

Patients were reviewed at 1 week following the procedure and also at 8–16 weeks.

Follow up after 1 week: If patients continued to have less than 50% improvement in symptoms of sneezing and rhinorrhea, a second application of 10% silver nitrate was performed. The same post-procedure instructions were given. If patients had persistent symptoms, a 3rd session was advised but if they refused, they were prescribed topical steroids and antihistamines as before. Follow up after 8–16 weeks: Frequency of sneezing and rhinorrhoea was documented. Mini RQLQ questionnaire was re-administered. Those patients who were willing underwent repeat biopsy of the anterior end of inferior turbinate.

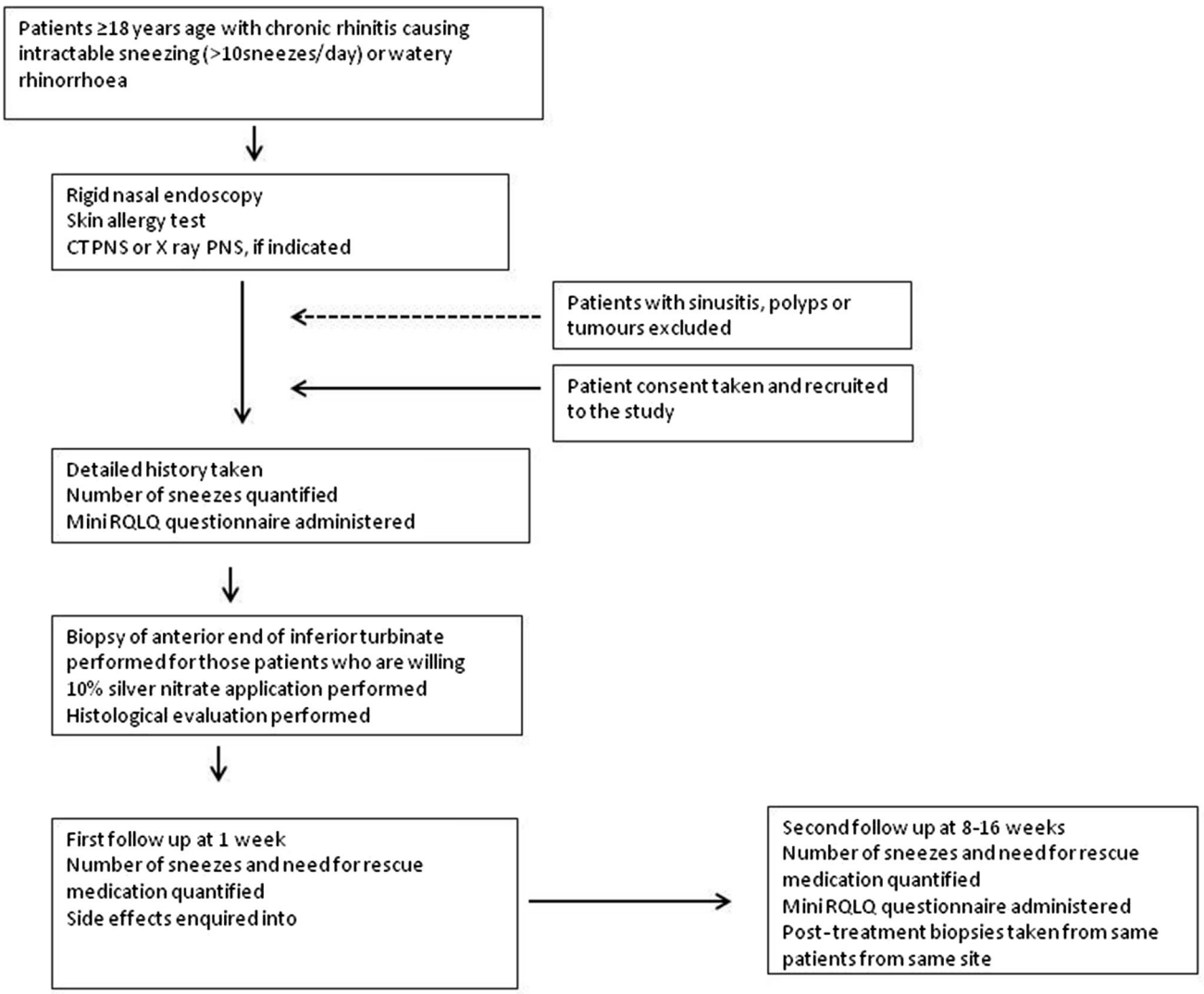

Fig. 1 Flow chart of patient recruitment, treatment and follow up

Final follow up: Follow up was continued as long as possible and at each follow up details of sneezing frequency and QoL were ascertained.

Histological examination: About 5–6 μm thick serial sections were taken and every 10^{th} section was stained with eosin and hematoxylin visualized and studied under 40 × objective. Histological examination of the tissue was done both qualitatively and quantitatively using Cellsens image processing software. The quantitative analysis was done to look at the number of goblet cells for a total length 20 mm for each sample and the number of eosinophils, blood vessels including capillaries, arterioles, venules, high endothelial venules (HEVs) were noted for a total area of $1.25mm^2$ for each sample. The maximum and minimum thickness of the epithelium was measured and in addition the basement membrane thickness was measured in five different regions which had areas of complete, partial denudation, squamous metaplasia and intact epithelium. The total length of the epithelium with regions of intact epithelium, partial denudation, complete denudation, hyperplasia and squamous metaplasia were measured along the basement membrane and expressed as percentages.

Qualitative assessment was done to assess epithelial integrity, presence or absence of basement membrane thickening, subepithelial fibrosis and perivascular fibrosis.

Statistical Methods

For continuous variables, mean, range and standard deviation was calculated. For categorical variables, frequency was calculated. Comparison of pre- and post-procedure improvement in nasal symptoms, mini RQLQ scores and qualitative histological changes was performed using the

paired t test. Comparison of mean pre- and post-procedure quantitative assessment of histological samples was performed using Mc Nemar test.

Institutional Review Board approval

The study was approved by the Institutional Review Board and Ethics committee of Christian Medical College, Vellore (IRB number: 11857).

Results

Demography

A total of 67 patients (38 males and 29 females) with a mean age of 33.9 years (range = 18–64 years) were included. There was only one smoker. All patients had been on nasal steroid sprays and/or antihistamines for a minimum of 3 months.

Preoperative Diagnostic Nasal Endoscopy Examination

Features consistent with allergic rhinitis like pale mucosa with/without cobblestone appearance of inferior turbinate mucosa was seen in all patients. No coexistent pathology was present.

Pre-procedure Assessment of Patients

Patients reported 25 to 85 sneezes/day(mean ± SD = 36.6 ± 11.3; median = 55) with 70.1% having 25- 35 sneezes/ day. Rhinorrhoea was associated with sneezing in all patients. The baseline global mean mini RQLQ score was 4.0 ± 0.7. Analysing the score for individual domains (Table 1), it was found that patients had the highest scores for practical problems and activities followed by nasal symptoms. They were less affected by eye symptoms.

Post-procedure Follow-up of Patients

Follow up at 1 week

Reduced sneezing and rhinorrhoea was noted in 64/ 67 patients (95.5%). The mean number of sneezes had come down to < 5 in 61 patients (91%) and less than 10 in 3 (4.5%) patients. This reduction was significant ($p < 0.001$). Overall, 95.5% of patients had > 80% reduction in the number of sneezes per day at the 1 week follow up.

Three (4.5%) patients did not report any improvement and wished to continue the medication they were taking earlier. No serious complications were noted following the procedure. Some patients complained of burning sensation in the nose soon after the procedure which resolved with analgesics over the next 2 to 3 days.

Follow up at 8 to 16 weeks

The mean number of sneezes in these patients was 5.5 ± 7.8 and the improvement over baseline values was both sustained and significant ($p < 0.001$) Overall, 92.2% of patients had > 80% reduction in the number of sneezes per day at the 8 to 16 week followup. The post-treatment mean global mini RQLQ scores was 1.3 ± 1.1. There was a statistically significant reduction in mini RQLQ scores following the procedure ($p < 0.001$) in each domain (Table 1).

Late follow up (17 to 76 weeks)

Follow up of patients continued for upto 76 weeks in those 49 patients (73.4%)who could be contacted. Even at last follow up, there was a sustained reduction in sneezing ($p < 0.001$).

Number of applications of silver nitrate

Most patients (70.1% patients) improved with a single sitting of silver nitrate cauterisation. The patients with longest duration of relief of 72 and 76 weeks had only 1

Table 1 Pre -and post -therapy mean scores in each domain of mini RQLQ questionnaire

Mini RQLQ Domain	Pre therapy mean score ± SD	Post therapy mean score ± SD	*p* value (paired t test)
Global mean	4.0 ± 0.7	1.3 ± 1.1	< 0.001
Activities	4.4 ± 1.1	1.3 ± 1.2	< 0.001
Practical problems	5.1 ± 1.0	1.9 ± 1.4	< 0.001
Nose symptoms	4.3 ± 0.6	1.5 ± 1.2	< 0.001
Eye symptoms	2.6 ± 1.8	0.7 ± 0.8	< 0.001
Other symptoms	3.8 ± 1.3	1.1 ± 1.2	< 0.001

sitting each. The sole patient who had 25 sneezes/ day after the first sitting, underwent a second sitting of silver nitrate cauterisation at review. She had a good response when followed up at 16 weeks after the second sitting of silver nitrate, with a mean of 2.5 sneezes/ day. The 2 patients who had upto 20 sneezes/day could not return for a second sitting of silver nitrate cauterisation because of the COVID-19 pandemic as well as other factors, and were asked to resume steroid nasal sprays. However, it was noted that in both the above patients, the mean number of sneezes had reduced and they appeared to be satisfied with their improvement.

Histological changes

Pre-treatment (Fig. 2) (Table 2)

The pre-treatment biopsy specimen showed areas of pseudostratified ciliated columnar epithelium with unevenly distributed goblet cells. Areas of complete or epithelial denudation were seen in 56.9% and 24.3% of specimens respecively. Basement membrane hyalinization was present in all cases (Fig. 2). Perivascular fibrosis was seen in the lamina propria in 12 cases (66.6%) and subepithelial fibrosis in 16 cases (88.9%).

Post-treatment (Figs. 3 and 4) (Table 2)

The significant changes in the epithelium post-treatment were the presence of squamous metaplasia ($p = 0.005$), epithelial hyperplasia ($p = 0.013$) (and partial epithelial denudation ($p < 0.001$). All post- treatment specimens showed a 100% reversion of basement membrane thickening. In the lamina propria, capillaries and arterioles showed no significant change in distribution following therapy. The number of venules showed a marked reduction post-therapy, however ($p = 0.006$).

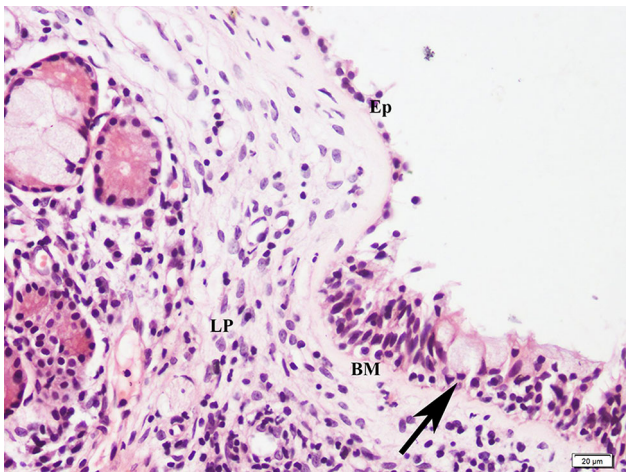

Fig. 2 Pre-treatment specimen showing pseudostratified ciliated columnar epithelium with goblet cells (black arrow), thickened basement membrane (BM) and underlying lamina propria (LP). The epithelium shows areas of partial denudation (Ep) in some areas

Discussion

The results of our study show that topical 10% silver nitrate application is an effective treatment for reducing symptoms of sneezing and rhinorrhoea in those patients with allergic or vasomotor rhinitis who do not respond adequately to conventional therapy or are unwilling to continue with pre-existing topical and/or systemic therapy. In our observation, this population comprises < 2% of patients who attend a Rhinology clinic at our hospital on a single day. These patients are quite severely affected and look for a therapy which offers quick and reasonable control of these troublesome symptoms, requires a single, or at most, two/ three applications and is cost-effective. Topical 10% silver nitrate application clearly addresses these issues. Additionally, the patients in our series experienced significant improvement in QoL (Table 1).

Of the few studies on the use of topical silver nitrate in chronic rhinitis, the studies by Bhargava et al. [7, 12] stands out as this treatment was introduced in India at a time when steroid nasal sprays were unavailable. The authors showed a benefit in 79.4% of patients with allergic rhinitis using multiple applications of 15% silver nitrate solution [12]. In another study, the use of a higher concentration (20%) of silver nitrate solution showed a benefit in 88.5% patients [13]. In our study, we used a concentration of 10% silver nitrate which was well tolerated and effective in 92.2% of patients even on long-term follow up. We felt, however, that a higher concentration may be associated with severe irritation in patients and may not be tolerated.

Silver nitrate has been shown to produce a local astringent action by coagulating albumin [14]. The excitability and sensitivity of mucous membrane is reduced due to this action. The anterior part of inferior turbinates and septum are believed to be trigger points for stimulation of sneezing and rhinorrhoea and desensitising this area brings about relief of symptoms [7, 12, 13]. Though other studies [7, 12, 13] describe cauterisation of the septum also, we opted not to to do so to avoid synechiae between the raw areas on the septum and inferior turbinate. These studies also carried out repeated cauterisation once a week for 1–5 sittings. We performed repeat cauterisation only if patients did not have benefit with the first sitting. Most patients 47(70.1% patients) had a single sitting of 10%

Table 2 Comparison of pre and postoperative changes in epithelium and lamina propria (n = 36)

Parameter	Pre -treatment values (n = 18) Mean (SD)	Post- treatment values (n = 18) Mean (SD)	p value
Quantitative analysis			
Length of epithelium studied (micrometres)	10,728.3 ± 2033.9	10,063.7 ± 1997.4	
Epithelial changes			
Percentage of intact epithelium	7.2 (11.5)	2.3 (4.4)	0.125
Percentage with partial denudation	24.3 (21.7)	31.9 (28.1)	0.001*
Percentage with complete denudation	56.9 (19.7)	27.3 (15.5)	0.237
Percentage with epithelial hyperplasia	9.3 (8.6)	28.4 (28.6)	0.013*
Percentage with squamous metaplasia	0.1 (0.1)	10.8 (14.0)	0.005*
Maximum epithelial thickness (micrometres)	86.6 (57.9)	107.3 (74.8)	0.275
Minimum epithelial thickness (micrometres)	14.2 (19.7)	15.2 (10.8)	0.853
Number of Goblet cells	44.1 (78.5)	37.5 (112.2)	0.853
Lamina Propria			
Number of eosinophils	20 (27.8)	18.4 (16.4)	0.822
Number of blood vessels			
Capillaries	85.2 (26.9)	87.9 (36.1)	0.746
Arterioles	5.8 (5)	4.6 (4.5)	0.396
Venules	18.7 (11.5)	10.6 (8.2)	0.006
High endothelial venules	6.9 (5.7)	9.7 (10.1)	0.203
Qualitative analysis			
Perivascular fibrosis	12(66.7)	12(66.7)	1
Subepithelial fibrosis	16 (88.9)	13(72.2)	0.25

*significant

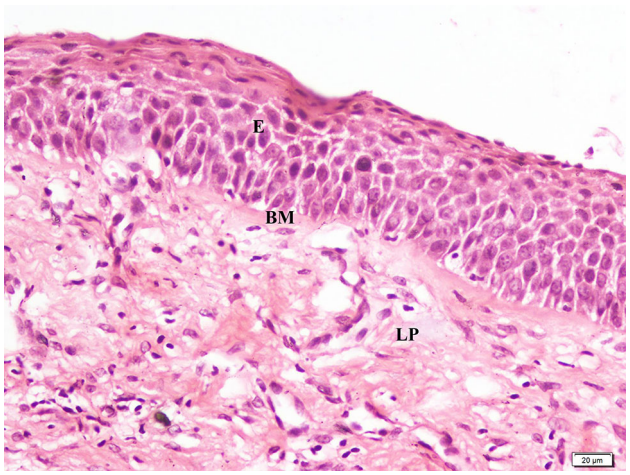

Fig. 3 Post-treatment specimen showing squamous metaplasia of the epithelium (E) with reduction of basement membrane thickening (BM) with underlying lamina propria (LP)

silver nitrate cauterisation and only 2 patients required upto 3 sittings which were several weeks apart.

The salient feature seen histologically in this study was the development of squamous metaplasia and epithelial hyperplasia after therapy. Squamous metaplasia is usually the result of chronic irritative processes on the mucosa and is an adaptive change to prevent further damage to the mucosa. Peric et al. [15] described squamous metaplasia in nasal polyps which are associated with chronic rhinosinusitis, aspirin-exacerbated respiratory disease and exposure to heavy metals, especially nickel and copper. In the present study, squamous metaplasia most likely occurred in the cauterized areas of mucosa and this was accompanied by restoration of epithelium in the adjacent areas. These two histological changes are the probable cause for reduction of nasal secretions that occurred following treatment with silver nitrate cautery. Another feature noted post-therapy in the present study, was a marked reduction in complete denudation of epithelium along with increased presence of partial denudation. In allergic rhinitis, features of epithelial denudation are typically seen. The improvement in epithelial integrity suggests that restoration of epithelium is occurring following therapy. Similar results were noted by Lukka et al. in patients who had undergone submucous diathermy for inferior turbinate hypertrophy [10].

Lamina propria fibrosis has been noted in patients with allergic rhinitis in several studies [10, 16]. In our study, subepithelial fibrosis was present in 88.9% of cases. Following procedures like coblation, increased sub-epithelial

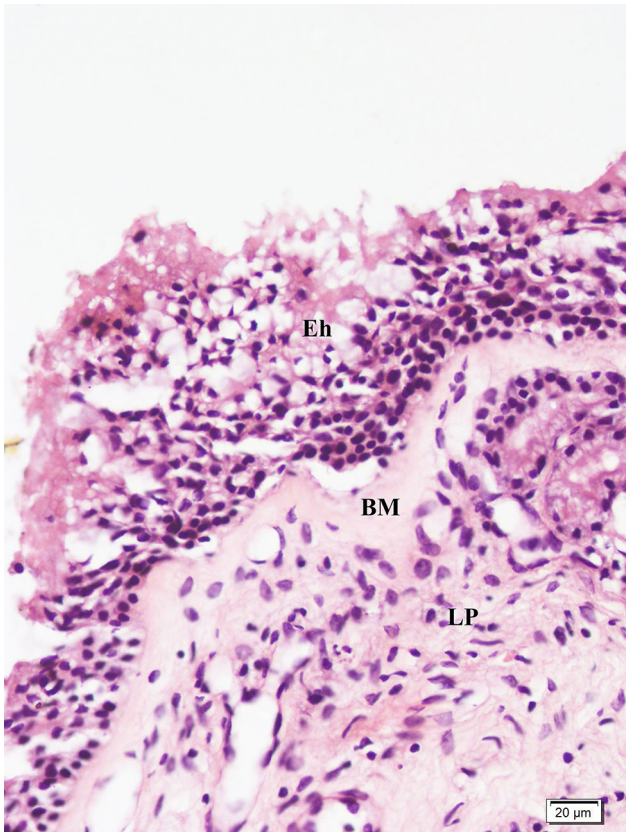

Fig. 4 Post-treatment specimen showing areas of hyperplastic epithelium (Eh) resting on basement membrane (BM) with underlying lamina propria (LP)

fibrosis has also been noted by some authors [17], while reduction in fibrosis following diathermy has been noted by others [10]. In our study, no significant difference was noted in either perivascular or subepithelial fibrosis, following 10% silver nitrate application, however.

Studies have shown the presence of an increased network of venous sinusoids which possesses an exaggerated expansile capacity in allergic rhinitis [18, 19]. Schmidt et al. also reported an increased number of blood vessels in the inferior turbinate in cases of vasomotor rhinitis and related this to the phenomenon of neoangiogenesis [20]. Two other studies, however, did not support a finding of greater vascular density in perennial allergic rhinitis [16, 19].

The mini RQLQ questionnaire, a QoL instrument, measures symptoms, functional limitations, practical problems encountered on a daily basis and psychological well-being [21]. There was a statistically significant improvement in mini RQLQ questionnaire scores when compared to baseline ($p < 0.001$). Thus, topical 10% silver nitrate therapy treatment not only resulted in reduction of sneezing and rhinorrhoea but also improved the patient's quality of life and this improvement was sustained even upto 76 weeks after the procedure.

Conclusion

Topical application of 10% silver nitrate solution over the inferior turbinate mucosa is a simple, safe and cost-effective office- based procedure that may be used to treat the small category of patients with intractable sneezing and rhinorrhoea who do not wish to continue conventional anti-allergy medication. Further, the treatment significantly improves QoL. Our study highlights the histological changes in the epithelium and lamina propria in patients with chronic rhinitis and their reversal after therapy. These findings correlated well with reduction in symptoms in these patients.

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Author contribution All authors contributed to the study conception and design. Material preparation, data collection and analysis were performed by Jenny Jacob, Nedha Joy, Suganthy Rabi and V. Rupa. The first draft of the manuscript was written by Jenny Jacob and Nedha Joy and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

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Availability of data Data is stored within the institution and is available on request.

Declarations

Conflicts of interest The authors have no relevant financial or non-financial interests to disclose. The authors have no conflicts of interest to declare that are relevant to the content of this article.

Ethics approval The study was approved by the Institutional Review Board and Ethics committee of Christian Medical College, Vellore (IRB number: 11857).

Consent to participate All patients recruited to the study gave informed consent prior to participation in the study.

Consent for publication All patients recruited to the study gave consent for publication of the results of the study.

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