

Original Research Article

Effect of topical furosemide on sinonasal polyposis relapse after endoscopic sinus surgery

Souvagini Acharya¹, Alka Kapil^{1*}, Kamalini Bepari¹, Sandrendu Rajan¹, Prachi Mohapatra³,
Ashima Mishra², Aishwarya Aparajita¹

¹Department of Otorhinolaryngology and Head Neck Surgery, VSSIMSAR, Burla, Odisha, India

²Department of Internal Medicine, VSSIMSAR, Burla, Odisha, India

³Department of Internal Medicine, IMS, BHU, Varanasi, Uttar Pradesh, India

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*Correspondence:

Dr. Alka Kapil,

E-mail: kapilalka1602@gmail.com

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ABSTRACT

Background: Chronic rhinosinusitis with nasal polyposis (CRSwNP) relapse is commonly seen during follow up period after endoscopic sinus surgery. Some studies claim the credibility of topical furosemide in preventing the polyposis recurrence after surgery. This randomised control trial was done to check the effectiveness of topical furosemide on sinonasal polyposis relapse after the endoscopic sinus surgery.

Methods: In the current study, 44 patients, attending ENT department, VSSIMSAR, for follow up after endoscopic sinus surgery, were evaluated clinically and endoscopically to demonstrate the prevalence and severity of polyposis relapse using Visual analogue scale (VAS) and meltzer endoscopic grading, before initiating the intervention. Patients were then randomised in two groups- one receiving topical furosemide nebulization and other intranasal normal saline spray, respectively. All patients were evaluated again at 1st, 2nd, 4th and 6th month follow-ups by VAS and MEG, setting statistical significance at $p < 0.05$.

Results: The MEG was grade 0 in 77% (17) patients of furosemide group and 32% (7) of normal saline group ($p = 0.0147$). Statistically significant improvement was also observed in VAS for nasal symptoms in former group ($p = 0.028$) than latter. The rate of relapse was less (23.81%) in furosemide group as compared to normal saline group (65%) but result not statistically significant at $p < 0.05$.

Conclusions: Topical furosemide can be used as a valid therapeutic approach for reducing the severity of sinonasal polyposis relapse after endoscopic sinus surgery with no known side effects of furosemide when administered topically.

Keywords: Topical furosemide, Sinonasal polyposis, Relapse, Endoscopic sinus surgery, VAS, Meltzer endoscopic grading

INTRODUCTION

Chronic rhinosinusitis with nasal polyposis (CRSwNP) represents a significant disease burden in the society with prevalence of about 11% in the western world.¹ It is observed that the patients with CRSwNP have more severe sinonasal symptoms than CRSsNP patients. The underlying etiopathogenesis is not completely defined but certainly it represents an end stage of chronic inflammation which is currently being treated by

pharmacotherapy in form of steroids and antibiotic or by surgical removal of the polypoidal mucosa. Both of the available management options are unable to control the disease relapse. Moreover, the treatment puts financial burden and escalates the morbidity. CRS is one of the top 10 most costly health conditions to US employers, with direct annual costs of \$8 billion US dollars. The total cost for treating 1 patient with CRS was estimated to be \$2600/year in the United States.²

The steroid therapy for long term produces its harmful effects and surgery alone does not give complete recurrence free results to the patients. One comprehensive analysis of a single-institutional cohort revealed short-term polyp recurrence in ~50% of patients 12 months following ESS.³ Supplementary medical treatment is always necessary to prevent the recurrence after surgery. The best approach to prevent this recurrence of sinonasal polyposis is to interfere with early phase of polyp development i.e. oedematous infiltration of nasal mucosa. Topical Furosemide aims at interfering with this stage of polyp formation by inhibiting the movement of water into the cell and subsequently into the interstitial tissue, causing oedema, which is one of the most prominent histopathological findings in nasal polyps.^{4,5} Though the polyposis relapse is taken care of by systemic and topical steroid or by revision surgery in recalcitrant cases. But all of these post-relapse treatments exhibit adverse effects which entails the research for effective treatment to decrease the prevalence and severity of this post-surgical relapse. So, our study aims at assessing the efficacy of topical furosemide on sinonasal polyposis relapse after the endoscopic sinus surgery.

METHODS

This double blinded, parallel group randomised control trial was planned and conducted in the Department of Otorhinolaryngology, VSSIMSAR, Burla. Ethical clearance for the same was obtained from the Institutional Ethical Committee VSSIMSAR, Burla and the time period for study was one and half years (July 2018 to December 2019).

All the patients, visiting the department of otorhinolaryngology, VSSIMSAR, Burla for follow up after endoscopic sinus surgery were considered for the study with more inclination for relapse cases of the surgery so as to observe the disease response to furosemide more distinctly.

Among those who fulfilled the inclusion and exclusion criteria and gave written informed consent after being described about the nature, potential risks and benefits of the treatment procedures were enrolled for the study. Prior set inclusion criteria was the post-operative cases of sinonasal polyposis, of age group between 15-60 years, coming for follow up after the endoscopic sinus surgery, with polyposis relapse or with high probability (based on clinical history) of polyposis relapse.

Exclusion criteria set were patients with coexistent systemic and chronic diseases like Wegener's granulomatosis, sarcoidosis, primary ciliary dyskinesia, any sinonasal tumour. Patients with known electrolyte imbalance, taking corticosteroids for any other disease, currently on diuretic therapy, hypersensitive to furosemide, unhealed nasal surgery or trauma or any other significant medical condition were also excluded from the study.

Subjects entering into the study were randomly divided into two groups- group A (interventional) and group B (control). Randomization was performed by assigning a random number according to a computer-generated code created by statistician. Patients were not provided with any information of the drug composition but counselled about the possible adverse effects and were encouraged to follow up for the study and subsequent treatment. They were also not concerned of the other parallel group of the present study. Washout period of 4 weeks was required before initiation of the study trial treatment as generally patients are given preoperative or postoperative systemic antibiotic, steroids and antihistamines along with topical steroids and decongestants. After their consent, all the patients were examined clinically and appropriate clinical history was obtained which provided us their VAS before initiation of the treatment. After that all the patients underwent endoscopic examination for assessment of pre-treatment Meltzer score. All the data was collected in the MS excel sheets for later interpretations. The two randomised groups were given the respective proposed treatment as follows:

In group A (27 patients), patients were administered topical furosemide by inhalation of 20 mg furosemide solution/10 minute through a jet nebulizer, BD for a duration of 4 months.

In group B (27 patients), patients were administered with isotonic normal saline nasal spray 2 puffs BD for 4 months.

The patients were asked to self-administer the drug and give periodic follow-up visit for 6 months. Their evaluation was again done using Meltzer endoscopic grading and VAS during follow up period at 1st, 2nd, 4th and 6th month after their enrolment in the study with a ± 7 day window for each visit. At each visit, patients' vitals and serum electrolyte levels were also checked to see for any systemic side effect of furosemide.

The Meltzer endoscopic grading is a clinical grading system to estimate the severity of sinonasal polyposis and can help in observing response to treatment and relapse in follow up period rather than using radiological investigations like CT scans, which have harmful effects when repeated frequently and are much costlier than the endoscopic assessment.⁶ This endoscopic assessment is easy to perform and gives required information. The grading system is described as: grade 0 (no polyp), grade 1 (polyps confined to middle meatus), grade 3 (polyps extending beyond middle meatus), grade 4 (polyps completely obstructing the nasal cavity). In cases of bilateral sinonasal polyposis, Meltzer grading from each nostril was taken and final grading was taken as sum of the two gradings.

Another analytical tool used in our study was VAS. It is a psychometric instrument used to subjectively quantify patient's symptoms severity ranging from 1 to 10 revealed by the patients seeing the scale. In CRSwNP, the VAS

helps in classifying the disease burden into mild (0-3 points), moderate (4-7 points), and severe (08-10 points). This type of scale is more reliable and sensitive while comparing with categorical scaling and is subjected to less distortion and well suited for measurement of continuous features like symptoms of allergic rhinitis or CRS (nasal obstruction, rhinorrhea, nasal irritation, sneezing, headache etc) gathered by VAS can be converted parametrically to interval level.⁷

All statistical analysis was performed using statistical package for social science (SPSS version 17) for Microsoft windows. A two-sided $p < 0.05$ was considered statistically significant. Data analysis was done utilising the data collected in excel sheets and represented using tables, bar graphs and pie charts. Appropriate mean values, percentage and statistical tests (test of homogeneity, independent t test, Mann-Whitney test) were applied to evaluate the data.

The patients who developed relapse after furosemide therapy were started with the current standard polyposis therapy of systemic and topical steroid, antibiotic and antihistamines for further management.

RESULTS

A total of 74 subjects were screened and assessed for eligibility. 13 patients did not meet inclusion criteria while 7 were unwilling for the study so excluded out. Allocation was started with 27 patients in each group but 6 lost to follow up or 4 became non-compliant to treatment. So, excluding them, the results were reproduced by utilizing the data obtained from 44 patients, thus $n=44$, of which 22 were in the study group and 22 in control group. Among the 44 patients, 16 were males (36.4%) and 28 were females (63.6%). The mean age of the patients in interventional group was 42.45 (21-72) years and in control group it was 37.13 (17-65) years (Table 1). This difference between the ages of patients in two groups was not significant. The requirement of homogeneity is met for the obtained demographic data with f -ratio value of 0.32138; $p=0.574$ which is not significant at $p < 0.05$.

While taking clinical history we could find out some possible etiopathological factor associated with the polyposis in our study population. In the taken population ($n=44$), asthma (06 i.e., 13.3% of patients), smoking (10 i.e., 22.7% of patients) and infection (05 i.e., 11.4% of patients) appeared to be the common etiopathological factor as compared to allergic rhinitis (01 i.e., 2.3% of patients), familial (4 i.e. 9.1% of patients), pollen allergy (02 i.e. 4.4% of patients), or aspirin intolerance (01 i.e. 2.3% of patients) (Table 1).

Most prevalent age group noted in our study was of females in age group ranging 35-44 years (11.36%) (Figure 1). Overall, the disease was observed commonly in the females in our study i.e. 63.65% (29.55%+34.1%).

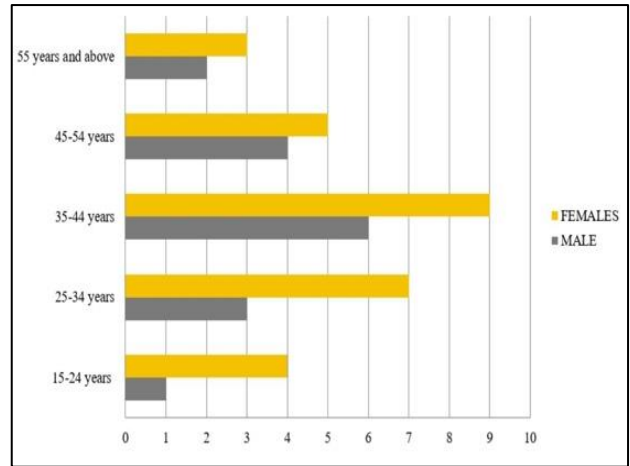


Figure 1: Demographic distribution of disease in study population.

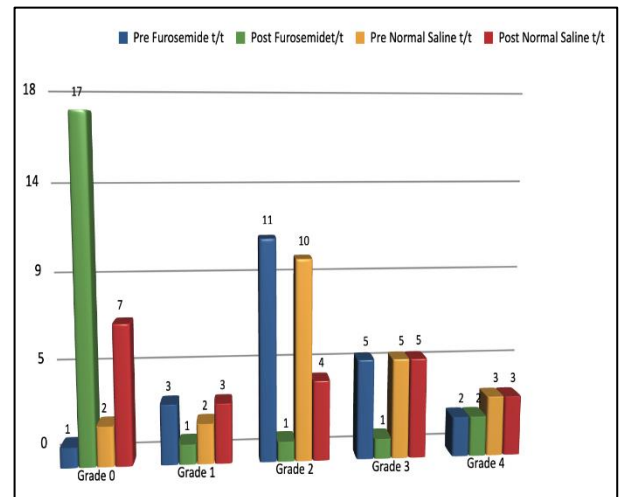


Figure 2: Meltzer endoscopic grading improvement after furosemide and normal saline treatment.

The study revealed significant improvement in the severity of the polyposis after treatment with intranasal furosemide as compared to intranasal normal saline spray (Figure 2). The severity was assessed in terms of Meltzer endoscopic grading which was grade 0 in 17 i.e. 77% of the patients of interventional group while it was grade 0 only in 7 i.e. 32% of patients of control group. This difference was statistically significant ($p=0.0147$) at $p < 0.05$ (Table 3).

The severity of polyposis was lowered in both the groups but it was notably lowered in patients taking topical furosemide treatment (Figure 2).

The evaluation of VAS reflected that nasal symptoms pertaining to sinonasal polyposis were more troublesome for the patients taking intranasal normal saline spray even after the treatment as compared to patients who were treated with topical intranasal furosemide. The difference in VAS before and after normal saline therapy was not statistically significant ($p=0.2187$). The post treatment

VAS for topical furosemide therapy was found to be significantly lowered when compared with its pre-treatment state in intervention group ($p=0.0001$). The furosemide spray also showed improved response in VAS as compared to topical normal saline therapy ($p=0.03$) all of which are statistically significant at $p<0.05$. Figure 3 representing average VAS on y-axis, represents the better outcome in terms of VAS in furosemide group.

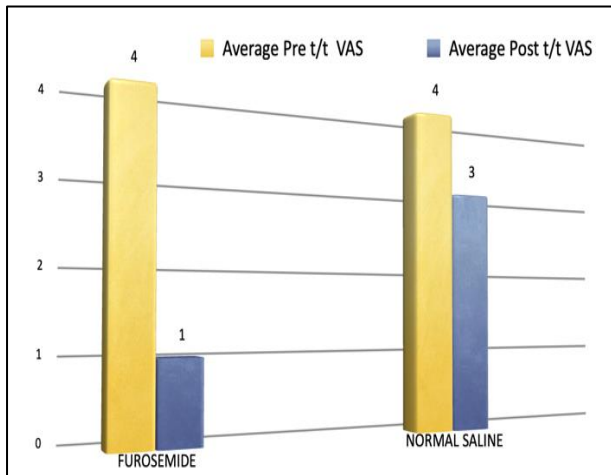


Figure 3: VAS improvement after furosemide and normal saline treatment.

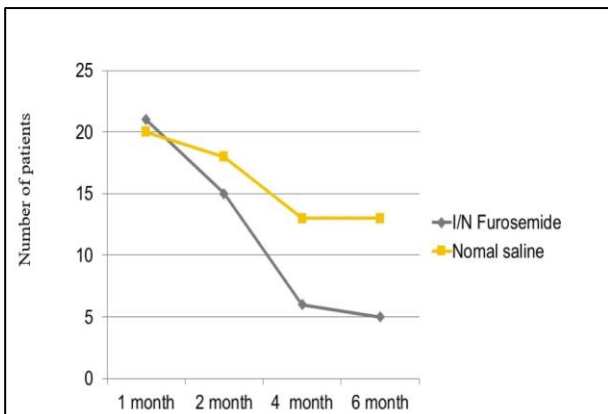


Figure 4: Nasal polyposis relapse after 6 months of topical furosemide therapy.

While evaluating the relapse rate, 5 patients out of 21 (i.e., 23.81%) patients in interventional group had polyposis relapse which was far lower than that of relapse in control group where it was seen in 13 (65%) patients (Table 4 and Figure 4).

The rate of relapse was lower in interventional group (23.81%) than of the control group (65%) but this difference was not statistically significant ($p=0.352$) at $p<0.05$. 5 out of 21 patients and 13 out of 20 patients who had Meltzer endoscopic grading of grade >0 had polyposis relapse after 6 months of therapy with topical furosemide and normal saline respectively.

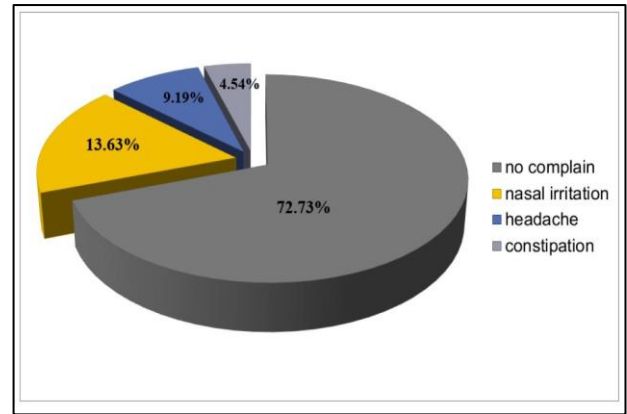


Figure 5: Adverse effects of topical furosemide therapy.

The safety related to the intranasal use of topical furosemide was notable. 16 (72.73%) patients did not complain of any adverse effect of the drug and were compliant to the therapy given. In seven patients receiving topical furosemide, treatment related adverse effects were reported, including 4 (18.18%) cases of nasal irritation, 2 (9.09%) cases of headache and 1 (4.54%) case of constipation (Figure 5). No systemic side effects of the drug (hypokalemia and hypotension) were observed during follow up period. In normal saline group, 5 (22.73%) reported nasal irritation and 2 (9.09%) complained of nasal congestion. There was no statistically significant difference ($p=1$) between the incidence of adverse reactions between the two groups convincing that furosemide is a safer drug in topical formulation for nasal polyposis.

DISCUSSION

This study investigated the effect of intranasal furosemide after endoscopic sinus surgery in preventing nasal polyposis relapse using Meltzer endoscopic grading and VAS. Although current medical and/or surgical interventions for CRSwNP achieve significant improvement in patient reported outcome measures, a significant portion of our patients fail to achieve endoscopic control of the disease.⁸

According to the current guidelines, the principle pharmacotherapeutic approaches for sinonasal polyposis and its relapse are corticosteroids and antibiotics. The primary goal of the therapy is to achieve and sustain clinical control. Control is defined as a disease state in which the patients do not have bothersome symptoms combined with a healthy or almost healthy mucosa and the need for local medication only.^{9,10} And relapse in our study is considered as more than or equal Meltzer endoscopic grading from the previous one during follow up periods.

In recalcitrant cases with no response to pharmacotherapy, surgical interventions are required. The surgery aims at restoring sinus ventilation and drainage by opening the key

areas and preserving the sinus mucosa. Presently, endoscopic sinus surgery (ESS) is the standard surgical procedure for chronic sinus disease and associated with better safety outcomes compared with previous more invasive procedures.¹¹ The need for revision surgery in patients with CRSsNP is estimated to be around 10%.¹²

Passali et al have shown that long-term application of intranasal furosemide, was at least as effective as topical steroid in the reducing the severity and rate of nasal polyp recurrence and significantly better than no treatment and saves the patients from adverse effects of steroid therapy.¹³ In our study, treatment with topical furosemide resulted in significant ($p=0.0147$) reduction in severity of sinonasal polyposis after ESS when compared with group of normal saline nasal spray. The severity of polyposis was estimated in terms of Meltzer endoscopic grading which was grade 0 in 17 (77.27%) patients who were taking topical furosemide therapy similar Meltzer endoscopic grading of grade 0 was observed only in 7 (32%). This result was comparable with the Passali et al study where it was grade 0 in 79% of patients in the furosemide group ($n=33$) compared with 38% in control group ($n=16$).¹³

The mode of action of furosemide in sinonasal polyposis is controversial but significant protection of polyp recurrence by furosemide demonstrated in controlled trials by Passali et al was achieved by 100 micrograms/nostrils/day.¹⁴ Furosemide may affect the nasal polyp growth by inhibiting fibroblasts by virtue of its NKCC inhibitory property. Furosemide is inhibitor of $\text{Na}^+/\text{K}^+/\text{2 Cl}$ cotransporter (NKCC), which leads to osmotically induced cell shrinkage by mediating the net influx of osmotically active ions and thus reduce the size of nasal polyposis.¹⁵

Although decrease in rate of relapse was observed in interventional group as compared to the control group but this was not statistically significant which is in contrast to the previous studies which found decrease in rate of relapse as well as severity of the polyposis relapse with topical furosemide therapy. The rate of relapse was lower in interventional group (23.81%) than the control group (65%) but this difference was not statistically significant ($p=0.352$) at $p<0.05$. 5 of 21 patients and 13 of 20 patients who had Meltzer endoscopic grading of grade >0 had polyposis relapse after 6 months of therapy with topical furosemide and normal saline respectively.

In the study, the dose of 20 mg of furosemide per inhalation did not induce any side effect, same results were obtained regarding the use of topical formulation of furosemide in other clinical trials as well.¹⁶

In conclusion we can say that topical furosemide can be used as a valid therapeutic approach for reducing the severity of sinonasal polyposis relapse after endoscopic sinus surgery with no severe adverse side effects of furosemide when administered topically.

Some limitations were observed while conducting our study and during interpretation of data like small sample size, lack of data on optimal dosage and duration of treatment, depriving study population of established postoperative treatment and non-compliance of patients.

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Ethical approval: The study was approved by the Institutional Ethics Committee

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