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RESEARCH ARTICLE
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COMPARISON OF NEBULIZED FRUSEMIDE WITH NEBULIZED BUDESONIDE ON POST-OPERATIVE SORE THROAT IN PATIENTS UNDERGOING SURGERY UNDER GENERAL ANAESTHESIA: A COMPARATIVE RANDOMISED, DOUBLE-BLIND PLACEBO-CONTROLLED STUDY.

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Abstract:

Background: Mucosal damage due to the endotracheal tube cuff can result in sore throat after the surgery. Our present placebo controlled study was planned to compare the effect of nebulised furosemide with nebulised budesonide on post operative sore throat in patients undergoing surgery under general anaesthesia.

Methods: In this randomized prospective study, 120 patients selected and were subjected to three interventions: group B (budesonide), group F (furosemide), and group C (control). Each group had 40 subjects. The primary objective was to determine whether budesonide or furosemide, through ultrasonic nebulization route, can cause any reduction in incidence of post operative sore throat, hoarseness and foreign body sensation.

Results: Out of 120, a total of 90 patients were analyzed. Demographically, all the groups were similar. On comparison to Group C, POST at rest was significantly lower in Group F and Group B at 2,4,6,8,10 hr time points ($p < 0.05$). On comparison to Group C, post operative hoarseness was significantly lower in Group F and Group B at 2,4,6,8,10 hr time points ($p < 0.05$). On group wise comparison, Group B had significantly lower incidence of hoarseness than Group F at 6, 8, 10 hr.

Conclusion: Topical use of budesonide or furosemide, through the nebulization route, effectively attenuated the incidence of post operative sore throat when compared to placebo. Either of them can be an alternative for suppression of post operative sore throat.

Keywords: Airway management, budesonide, cough, furosemide, peri-operative care, sore throat.

Introduction

Postoperative sore throat is one of the most troublesome compliant frequently reported following endotracheal intubation. Though typically transient, the incidence of POST has been reported as high as 70%.[1] POST may manifest in varying degrees of severity, yet it remains an uncomfortable ordeal for patients during the postoperative period. Often, patients recall it as one of the most distressing memories of their peri-operative experience. [2]

Several factors contribute to the risk of POST, including female gender, younger age, history of smoking, prolonged duration of anaesthesia, the presence of blood on the extubated endotracheal tube, procedures involving the head and neck mobilization, surgery done in lateral or prone position and high intra-cuff pressure during the surgery. [3,4] Although its etiology is not properly understood in literature, tracheal mucosal inflammation appears to be the main culprit. It releases local inflammatory mediators which exert local responses and lead to cell damage.[2] Typically, symptoms manifest within six hours post-surgery and resolve completely within 24 hours. However, for some patients, it persists until it is actively managed, causing considerable discomfort and mandating active intervention.

Various approaches have been explored to mitigate the effect of POST, utilizing different administration routes such as atomization, nebulization, intravenous infusion, and oral medications like lozenges or gargles, each yielding varied results. [5,6,7,8] Preemptive administration of drugs such as corticosteroids, local anesthetics (such as lignocaine and ropivacaine), and dexmedetomidine has shown efficacy. In asthmatic patients, inhaled budesonide, with its localized anti-inflammatory and analgesic properties, has gained popularity.

Budesonide, a steroid commonly used in asthmatic patients, has also demonstrated a beneficial effect through the inhalational route in reducing POST incidence.[9] Furosemide, a widely used diuretic, has been widely used for management of congestive heart failure, liver disease, and renal diseases. Various studies have documented the role of furosemide in mitigating airway edema, facilitating sputum drainage, suppressing inflammatory reactions, and reducing airway hyper-responsiveness, ultimately reducing post-operative sore throat after surgery under general anaesthesia. [3,10,11,12]

Both drugs have been documented to relieve POST, with more documentary evidence towards budesonide. However, literature exploring the comparative efficacy of furosemide and budesonide via nebulization in mitigating postoperative sore throat across various surgical procedures remains scarce. Hence, this study was undertaken with the primary objective to compare the severity of POST in patients in the postoperative period. The secondary objective was to compare the severity of hoarseness, foreign body sensation during rest and swallowing, the severity of cough, and any incidence of postoperative nausea and vomiting among the three groups.

Methodology

The study was designed as a randomized, double-blinded, placebo-controlled, parallel-arm clinical trial. Adult patients of either gender with an age of 18–60 years who were classified as American Society of Anesthesiologists grade I or II. This study was carried out under the guidance of the Department of Anaesthesia and Intensive Care, in a newly established medical college. After the approval of the Ethics Committee and written informed consent, patients scheduled to undergo elective surgery under general anaesthesia in neutral neck position and fulfilling the inclusion criteria were enrolled in the present study. Any patient with with a preoperative sore throat or upper respiratory tract infection, a history of cardiac, liver, or renal disorders, with an anticipated difficult airway and an anticipated duration of laryngoscopy > 15 seconds or already taking systemic corticosteroids or furosemide, gave history of known allergy to the test medications, traumatic extubation were excluded from the study.

The Institutional Ethics Committee approved the study (AIMS/IEC/13/2023), and written informed consent was obtained from each participant. The study was registered prospectively in the Clinical Trials Registry of India (CTRI) (trial registration number: CTRI/2023/10/058963, trial registration

date: 20/10/2023). This clinical research was done following the ethical principles for medical research involving human subjects in accordance with the Helsinki Declaration of 2013.

Randomization and allocation concealment

A total of 120 patients who were posted for elective surgery under general anaesthesia were randomly allocated to three groups of 40 (Group F, Group B, and Group C) using a computer-generated random number table (www.randomization.com). The randomized subject numbers were sealed in coded opaque envelopes 1:1:1 to the three groups: furosemide in Group F, budesonide in Group B, and 0.9% sodium chloride solution in Group C. (Figure 1)

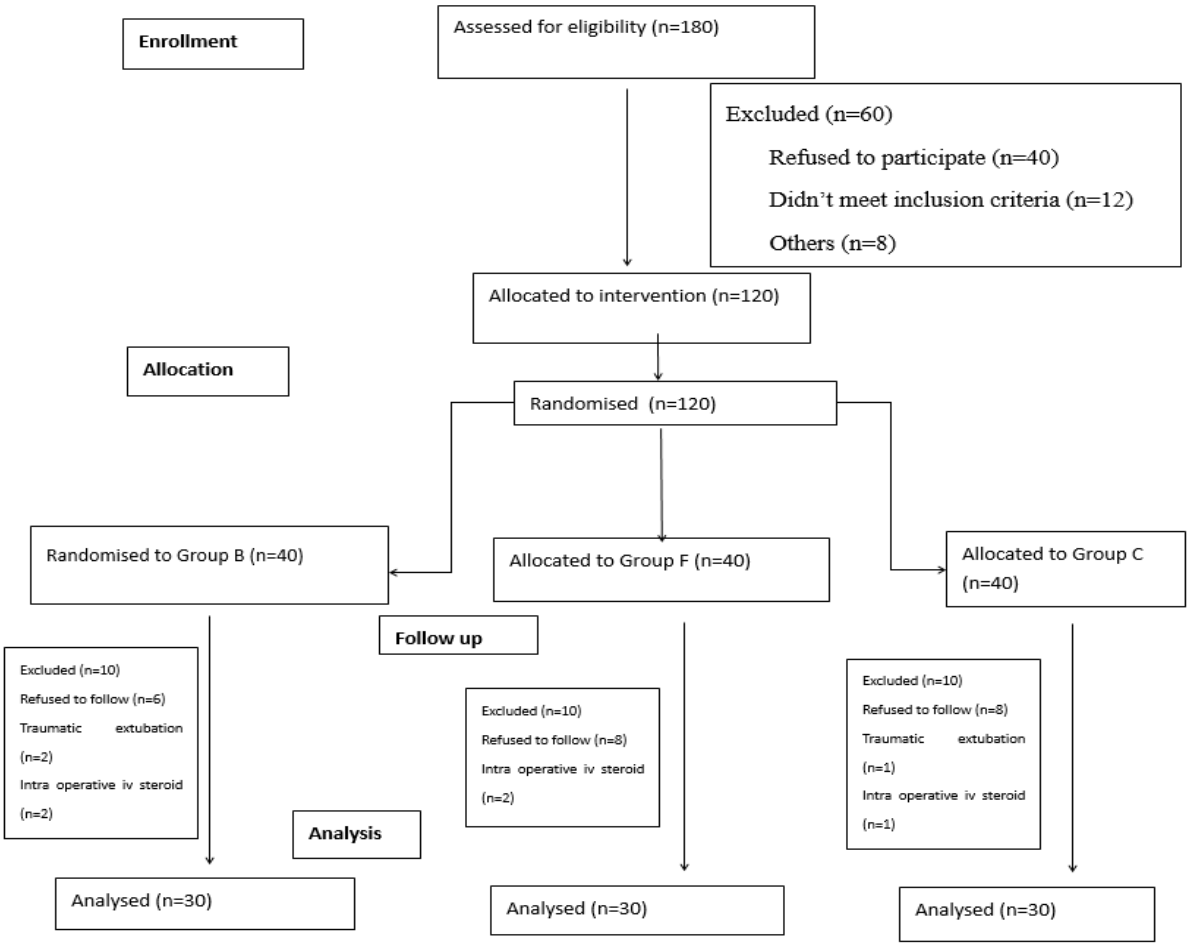

Figure no 1: CONSORT diagram

Group F (n = 40) received ultrasonic nebulization with furosemide 40 mg (Alpa Laboratories Ltd., Lot no. AV3538) (total volume used: 6 ml).

Group B (n = 40) received ultrasonic nebulization with budesonide 2 mg (Cipla Ltd., batch no. T020219) (total volume used: 6 ml).

Group C (n = 40) received ultrasonic nebulization with 0.9% normal saline (total volume used: 6 ml).

The rationale for choosing the said dosages of the drugs was based on the study conducted by J. An et al. [3] Both of the drugs used were within therapeutic limits.

The primary anesthesiologist with at least 3 years of experience blinded to the randomization group prepared the randomized drug for patients in the three groups. The second blinded anesthesiologist administered the drug and recorded the study variables. All participants, anesthesiologists, postoperative follow-up assessors, and statisticians were blinded to the treatment allocation.

Preparation of the patient: All the patients were prepped for surgery under general anaesthesia as per the institutional protocol. Detailed physical and systemic examination alongwith relevant investigations was done one day prior in our Pre Anaesthesia Checkup room. After clearance for surgery, patients were advised to be NPO for 6 hours for solids and 2 hours for plain, clear water. They were prescribed an anti anxiety and antacid early on the day of the surgery. Consent for the surgery under anaesthesia alongwith the enrollment for the surgery was taken one day prior in their preferred language.

The patient was operated on under general anaesthesia as per the institutional protocol. After identification and implementation of surgical safety checklist, patient was shifted to the OT table. Premedication with iv midazolam (0.04 mg/kg) was done 5 minutes before induction. All standard ASA monitoring were attached in the supine position. Pre-oxygenation was done for standard three minutes with 100% oxygen. Induction was done with inj morphine 0.1 mg/kg iv and inj propofol 2 mg/kg iv. After confirmation of adequate bag and mask ventilation, inj vecuronium 0.1 mg/kg was used as muscle relaxant. Endotracheal intubation was adequately sized endotracheal tube (7.0 or 7.5 mm ID for female, 7.5 or 8.0 mm ID for male) was inserted after direct laryngoscopy. Afterwards patient was put on Volume controlled assisted ventilation on N2O:O2 in ratio of 66:33. For maintenance of anaesthesia, inhalation agent isoflurane along with intermittent boluses of muscle relaxant was used. For post operative pain, 15 mg/kg of paracetamol was given and anti-emetic (ondansetron 0.1 mg/kg) was given before extubation. After adequate respiratory efforts, neuromuscular blockade was reversed with 0.05 mg/kg of neostigmine and 0.01 mg/kg of inj. glycopyrrolate. Trachea was extubated when the patient demonstrated the ability to follow verbal commands or showed purposeful movements in addition to the resumption of regular spontaneous respiration. After the extubation of the trachea, the patient was shifted to the PACU, where the nebulization procedure was done. Ultrasonic nebulization was done with Yuwell ultrasonic nebulizer 402AI^{TM} while the patients breathed normally until the complete drug was nebulized (approximate time 10 minutes), which created a fine mist of size < 5 microns. The anesthetist blinded to the study recorded the following parameters:

Postoperative sore throat at 0, 2, 4, 6, 8, 10, 12, and 24 hours was assessed with the following grade [13]: Grade 0: patient complained of no sore throat since the extubation, Grade 1: Minimal; patient answered in the affirmative only when asked, Grade 2: Moderate; patient complained of a sore throat on his or her own, Grade 3: Severe change in voice associated with throat pain.

Postoperative cough was assessed at the same time points: [3]. Grade 0: no cough, Grade 1: minimal (<5 cough bouts) Grade 2: moderate (> 5 cough bouts) Grade 3: severe (continuous bouts requiring intervention)

Postoperative hoarseness of voice was assessed at the same time points: Grade 0: No complaint of hoarseness at any time since the operation, Grade 1: Minimal, minimal change in quality of speech, Grade 2: Moderate, moderate change in quality of speech of which the patient complains on his or her own, Grade 3: Severe, gross change in the quality of voice perceived by the observer .

The other parameters which were observed such as foreign body sensation in the pharynx, dry mouth, post-operative nausea and post-operative vomiting were rated as either present or absent. [3] After the patients were observed in the PACU for 2 hours, they were shifted to their respective wards in stable conditions. All the patients received standard post operative monitoring and analgesia (inj. Paracetamol 1 gm iv 8 hourly) as per the institutional policy.

Sample size calculation:

The sample size was calculated from https://clincalc.com/Stats/SampleSize.aspx, based on a study by Jin An et al., where nebulized furosemide had an incidence of 56% of postoperative hoarseness at 1 hour as compared to 88.5% in the control group. [3] The effect size is calculated from this study, taking into consideration the difference in percentage. With a power of 80% and an alpha error of 0.05, the sample size was calculated to be 29 patients in each group, and a total of 120 patients were recruited for the study, including those who resigned or dropped out due to various reasons. All data

were expressed as mean (SD), median (range), or number (proportion). The data was analyzed using SPSS version 25.0 (SPSS Inc., Chicago, IL, USA). We used an unpaired, two-tailed Student's t-test to compare normally distributed continuous variables. Continuous data that was not normally distributed was analyzed using the Kruskal-Wallis test. Categorical data was analyzed using the Fisher's exact test where appropriate. A p-value < 0.05 was considered statistically significant. All the observations were noted in the prescribed proforma and subjected to appropriate statistical analysis.

Results:

A total of 120 enrolled patients were enrolled in the study over a five-month period (study start date: October 30, 2023; end date: March 31, 2024). 90 patients were analyzed for statistical analysis (30 in each group). Patient demographics are presented in Table 1. Surgeries were from various specialties (general surgery, orthopaedics, gynecology). There were no significant differences between the groups with respect to demographic data (age, height, weight, gender, and ASA PS grade), duration of anaesthesia, duration, and type of surgery. (Table No. 1)

Table no 1: Demographic characteristics.

	Group B	**Group F**	**Group C**	**P value***	**Group B: Group F**	**Group F: Group C**	**Group C: Group B**
Age	34.76±10.48	38.46±12.63	35.06±8.48	0.333	0.375†	0.993†	0.436†
Gender(M/F)	12/18	8/22	9/21	0.516	0.411‡	1‡	0.58‡
Height	165.5±7.5	161.66±5.55	165.03±6.67	0.055	0.07†	0.95†	0.12†
Weight	72.16±12.52	67.83±13.74	72.53±11.28	0.2711	0.379†	0.992†	0.32†
ASA PS	20/10	20/10	27/3	0.05	1‡	0.05‡	0.05‡
Duration of surgery	62.83±25.31	63±21.91	60±14.20	0.824	0.99†	0.86†	0.84†
General Surgery	12	14	14	-	-	-	-
Orthopaedics **Gynaecology**	11 7	10 8	11 5				
	Values are presented as Mean ± SD, number of patients. ASA PS:American Society of Anaesthesiologists Physical status, Group B: Group Budesonide, Group F: Frusemide, Group C: Control. *ANOVA, †Student T test, ‡ Fisher Exact test						

Post-grading was assessed both at rest and during swallowing at various time points (before nebulization, 0 hr), 2, 4, 6, 8, 10, 12, and 24 hr based on the scales tabulated (Table 2). In our study, on Kruskal-Wallis test analysis of all the groups, post-grading at rest decreased statistically significantly ($p < 0.05$) at all time points up to 12 hours. Only 1 patient in Group B and 2 patients in Group F had Grade II POST in comparison to 8 patients in Group C. None of the patients had grade III in the interventional group, whereas one patient developed distress in Group C and was treated accordingly. In subgroup comparison, Group B and Group F were comparable at most of the time points, but a statistically significant decrease was noted when Group B and Group F were compared with the control group, establishing an advantage over their use. Though Group B had a significant decrease at all time points, Group F became comparable after 12 hours in comparison to the control group.

Table no 2: Comparison of post operative sore throat

POST at Swallowing Grade 0/1/2/3	**GROUP B (n=30)**	**GROUP F (n=30)**	**GROUP C (n=30)**	**P value***	**Group B: Group F P value‡**	**Group F: Group C P value‡**	**Group C: C: Group B P value‡**
0 Hr	19/11/0/0	20/8/2/0	19/10/1/0	0.99	0.818	1	0.8

2 Hr	23/7/0/0	20/10/0/0	16/12/1/1	0.24	0.398	0.147	0.03§
4 Hr	25/5/0/0	22/8/0/0	13/15/2/0	0.015†	0.355	0.01§	0.0008§
6 Hr	28/2/0/0	22/8/0/0	17/12/0/1	0.046†	0.03§	0.144	0.001§
8 Hr	29/1/0/0	21/9/0/0	18/11/1/0	0.03†	0.004§	0.37	0.0005§
10 Hr	28/2/0/0	24/6/0/0	19/10/1/0	0.126	0.133	0.12	0.004§
12 Hr	30/0/0/0	26/4/0/0	20/10/0/0	0.08	0.03§	0.06	0.0003§
24 Hr	30/0/0/0	28/2/0/0	25/5/0/0	0.534	0.155	0.234	0.019§
POST At Rest Grade 0/1/2/3							
0 Hr	20/10/0/0	18/10/2/0	18/11/1/0	0.832	0.359	0.494	0.79
2 Hr	25/5/0/0	20/10/0/0	14/14/2/0	0.003†	0.14	0.008§	0.0001§
4 Hr	25/5/0/0	21/9/0/0	13/16/1/0	0.003†	0.229	0.003§	0.0001§
6 Hr	26/3/1/0	21/9/0/0	13/14/2/1	0.012†	0.269	0.015§	0.0001§
8 Hr	26/4/0/0	22/8/0/0	15/14/1/0	0.007†	0.203	0.04§	0.001§
10 Hr	30/0/0/0	26/4/0/0	17/12/1/0	0.011†	0.03§	0.008§	0.0001§
12 Hr	30/0/0/0	26/4/0/0	21/9/0/0	0.133	0.03§	0.12	0.0008§
24 Hr	30/0/0/0	30/0/0/0	26/4/0/0	0.59	0.876	0.155	0.03§
	Values are presented in patients numbers. Group B: Group Budesonide, Group F: Frusemide, Group C: Control, * Kruskal Wallis test,† Statistically significant, ‡ Fisher Exact test, § Statistically significant						

POST at swallowing also observed similar results, where the overall group comparison revealed a significant decrease at 4, 6, and 8-hour time points. In group-wise comparison, Group B excelled and was better than Group F and Group C at all time points, therefore establishing a clear role in the attenuation of POST at swallowing. 100% of patients in Group B and 94% in Group F had grades 0–1, whereas grade 2–3 was seen in a few patients in Group C. Group F and Group C were comparable and offered no clear advantage when POST was compared at swallowing.

Compared to Group C, the incidence of cough was not significantly lower in any of the other two groups (p value > 0.05). So none of the groups had reduced the incidence of coughing in the patients. Compared to Group C, the incidence of postoperative hoarseness was significantly lower in Group B at 2, 4, 6, 8, 10, and 12 hr (p value < 0.05) and significantly lower in Group F at 2, 4, 6, 8, 10, and 12 hr (p value < 0.05). On comparison of Group B and Group F, the incidence of hoarseness at 6, 8, and 10 hours in Group B was significantly lower than that in Group F (P value < 0.05). (Table no. 3)

Table no 3: Comparison of incidence of cough and hoarseness

COUGH Grade 0/1/2/3	**GROUP B (n=30)**	**GROUP F (n=30)**	**GROUP C (n=30)**	**P value***	**Group B: Group F P value‡**	**Group F: Group C P value‡**	**Group C: Group B P value‡**
0 Hr	22/6/2/0	28/2/0/0	28/2/0/0	0.289	0.03‡	1	0.03‡
2 Hr	27/3/0/0	30/0/0/0	28/2/0/0	0.793	0.07	0.155	0.647
4 Hr	26/4/0/0	27/2/1/0	28/2/0/0	0.907	1	0.47	0.398
6 Hr	26/4/0/0	27/2/1/0	29/1/0/0	0.795	1	0.249	0.166

8 Hr	27/3/0/0	28/2/0/0	29/1/0/0	0.905	0.647	0.561	0.308
10 Hr	26/4/0/0	27/3/0/0	29/1/0/0	0.793	0.693	0.308	0.166
12 Hr	27/3/0/0	28/2/0/0	30/0/0/0	0.793	0.647	0.155	0.07
24 Hr	28/1/1/0	29/1/0/0	30/0/0/0	0.904	0.412	0.321	0.178
HOARSENESS Grade 0/1/2/3							
0 Hr	22/8/0/0	18/12/0/0	17/11//2/0	0.439	0.281	0.49	0.1
2 Hr	26/4/0/0	21/9/0/0	12/15/3/0	0.004†	0.121	0.008‡	0.0001‡
4 Hr	26/4/0/0	23/7/0/0	12/17/1/0	0.003†	0.325	0.002‡	0.0001‡
6 Hr	28/2/0/0	21/8/1/0	12/16/1/1	0.001†	0.01‡	0.02‡	0.0001‡
8 Hr	29/1/0/0	24/6/0/0	12/17/1/0	0.0004†	0.04‡	0.001‡	0.0001‡
10 Hr	30/0/0/0	26/4/0/0	15/14/1/0	0.002†	0.03‡	0.001‡	0.0001‡
12 Hr	30/0/0/0	29/1/0/0	23/6/1/0	0.242	0.321	0.02‡	0.004‡
24 Hr	30/0/0/0	30/0/0/0	28/2/0/0	0.876	1	0.155	0.155
	Values are presented in patients numbers. Group B: Group Budesonide, Group F: Frusemide, Group C: Control, * Kruskal Wallis test,† Statistically significant, ‡ Fisher Exact test, § Statistically significant						

The incidence of foreign body sensation both at rest and swallowing also observed similar results, where overall group comparison revealed a significant decrease at 2, 4, 6, 8, 10, and 24 hr time points (p value < 0.05) for foreign body sensation at rest and at 6, 8, 10, 12, and 24 hr time points (p value < 0.05) for foreign body sensation at swallowing. In group-wise comparison, Group B was better at attenuating foreign body sensation than Group C, and the results were statistically significant at all time points. (p value < 0.05), whereas the results were comparable between Group B and Group F. Group F and Group C were comparable and offered no clear advantage. (Table no. 4) .

Table no 4: Comparison of foreign body sensation

FOREIGN BODY SENSATION AT REST (Y/N)	**GROUP B (n=30)**	**GROUP F (n=30)**	**GROUP C (n=30)**	**P value***	**Group B: Group F P value‡**	**Group F: Group C P value‡**	**Group C: Group B P value‡**
0 Hr	6/24	12/18	13/17	0.12	0.15	1	0.09
2 Hr	1/29	8/22	12/18	0.003†	0.02§	0.411	0.001§
4 Hr	2/28	6/24	12/18	0.007†	0.25	0.15	0.004§
6 Hr	3/27	6/24	11/19	0.04†	0.47	0.25	0.03§
8 Hr	2/28	7/23	10/20	0.03†	0.14	0.56	0.02§
10 Hr	2/28	7/23	10/20	0.03†	0.14	0.56	0.02§
12 Hr	2/28	5/25	8/22	0.115	0.42	0.532	0.07
24 Hr	1/29	1/29	8/22	0.004†	1	0.02§	0.02§
FOREIGN BODY SENSATION							

AT SWALLOWING (Y/N)							
0 Hr	10/20	10	14/16	0.46	1	0.42	0.42
2 Hr	8/12	10	12/18	0.83	0.76	0.78	1
4 Hr	5/25	6	12/18	0.08	1	0.15	0.08
6 Hr	4/26	8	12/18	0.04†	0.33	0.411	0.03§
8 Hr	2/28	6	11/19	0.01†	0.25	0.25	0.01§
10 Hr	2/28	5	11/19	0.01†	0.42	0.14	0.01§
12 Hr	2/28	4	10/20	0.01†	0.67	0.12	0.02§
24 Hr	1/29	2	10/20	0.001†	1	0.02§	0.005§
	Values are presented in patients numbers. Group B: Group Budesonide, Group F: Frusemide, Group C: Control, * Chi Square test,† Statistically significant, ‡ Fisher Exact test, § Statistically significant						

The incidence of dry mouth was comparable in all the groups, and the results were statistically non-significant at all time points (p value > 0.05). (Table no. 5)

Table no 5: Incidence of Dry mouth

DRY MOUTH (Y/N)	**GROUP B (n=30)**	**GROUP F (n=30)**	**GROUP C (n=30)**	**P value***
0 Hr	13/17	19/11	17/13	0.285
2 Hr	19/11	15/15	19/11	0.479
4 Hr	18/12	13/17	17/13	0.391
6 Hr	15/15	8/22	15/15	0.107
8 Hr	9/21	5/25	11/19	0.212
10 Hr	11/19	5/25	6/24	0.154
12 Hr	8/22	5/25	5/25	0.535
24 Hr	4/26	4/26	3/27	0.901
	Values are presented in patients numbers. Group B: Group Budesonide, Group F: Frusemide, Group C: Control, * Chi Square test			

Only 2 patients in Group B and 3 patients in Group C complained of nausea and/or vomiting in the postoperative period, which was statistically non significant. (p value > 0.05)

Discussion:

Postoperative sore throat and hoarseness are common complications following general anaesthesia, affecting patient comfort and satisfaction in the postoperative period. Predisposing factors for POST and hoarseness include female gender, younger age, smoking habits, prolonged anaesthesia duration, the presence of blood on the endotracheal tube, and procedures involving the head and neck region. [3,4] The incidence of POST and hoarseness is also affected by the type of surgery, e.g., laparoscopic surgeries are associated with more due to pneumo-peritoneum and intracuff changes, surgeries done in prone or lateral positions, the type of anaesthesia (use of inhalation anaesthesia or total intravenous anaesthesia), and any laryngeal manipulation like multiple attempts at intubation or difficult extubation.

Many studies have utilized various pharmacological and non-pharmacological methods to attenuate the incidence of POST and hoarseness. Non-pharmacological methods that are commonly employed include the use of a small ETT, lubricating of the tracheal cuff with water-soluble jelly like lignocaine

jelly, gentle laryngoscopy with a duration <15 seconds, low intracuff pressure, intermittent monitoring of intra-cuff pressure, and smooth extubation. [14] Various pharmacological interventions have been explored to mitigate these adverse effects, including the use of nebulized medications such as local anesthetics (lignocaine, ropivacaine), corticosteroids, alpha-agonists like dexmedetomidine, furosemide, etc.

Hoarseness and coughing are usually associated with POST. Larger endotracheal tubes and laryngeal trauma are the common reasons for postoperative coughs. Usually, it is intermittent in nature and resolves within 72 hours. In our study, we did not use any non-pharmacological method, as mentioned above; only the intubation time was kept within 15 seconds (so as to avoid any induced mucosal trauma). Few of these methods can be incorporated into the daily routine of anesthesiologists, but various confounding factors, like the non-availability of resources, always pose a challenge.

Today, nebulization therapy is being widely explored due to the local deposition of the drug directly at the tracheal site. It is highly recommended because of the small volume of drugs required for the desired effect, the easy way of administering them, their easy availability, good patient compliance, and, most importantly, the low risk of adverse events compared with other methods (such as gargles, intravenous, etc.). [15]

In this present study, we have used two interventions through the nebulization route, furosemide (a loop diuretic) and budesonide (a corticosteroid), and compared them with a placebo. Furosemide acts by inhibiting the reabsorption of sodium and chloride in the renal tubules, leading to increased diuresis. Some studies suggest that its localized effect may reduce inflammation and mucosal irritation in the airways, thereby alleviating postoperative symptoms. On the other hand, budesonide acts as a potent anti-inflammatory agent by inhibiting multiple steps in the inflammatory cascade. It suppresses the production of pro-inflammatory cytokines such as interleukins and tumor necrosis factor-alpha, thereby reducing mucosal edema, vascular permeability, and leukocyte infiltration in the airways. [3] Its use in the prevention of POST has been investigated, with promising results when used through atomizing inhalation. [9] While furosemide may target mucosal inflammation through non-specific pathways, budesonide offers targeted suppression of inflammatory mediators implicated in airway irritation and edema.

Many studies have compared the efficacy of nebulized furosemide or budesonide individually in preventing postoperative sore throats and hoarseness. [3,9,16] Factors such as dosage, timing of administration, patient characteristics, and surgical procedures may influence the outcomes. A study by An J et al. compared both of these drugs in comparison to a control group in patients undergoing maxillofacial surgery under general anaesthesia. [3] They found that postoperative administration of aerosolized furosemide is a new alternative to nebulized budesonide while avoiding the adverse effects of the latter. They had been used in maxillo-facial surgery, which itself is a risk factor for POST, but in our study, we included patients who underwent surgery under general anaesthesia, positioned with their neck in a neutral position. Lateral movements of the neck itself predispose to mucosal damage and POST.

Our study reports similar results where both furosemide and budesonide decrease the incidence of POST at rest, with statistically significant ($p<0.05$) results from 2 hours to 12 hours. On subgroup analysis, both interventional groups (Group B and Group F) had documented significant reductions until 12 hours of the postoperative period. The incidence of hoarseness, foreign body sensation, and cough was also statistically significantly reduced in both intervention groups in comparison to the control group.

Similarly, Ranjan et al. used budesonide through a metered-dose inhaler (MDI) at a dose of 200 micrograms. They found it to be significantly effective in reducing POST, hoarseness, and cough after endotracheal intubation. [9] As with our results, in their study, 96% relief from POST was seen in the budesonide group at 12 hours as compared to our study, which had 100% relief in comparison to 30% in the control group. Use of MDI also leads to local administration of the drug in the airway while avoiding systemic effects. Similarly, the use of nebulized budesonide in patients undergoing

elective middle ear surgeries under general anaesthesia has documented a reduced incidence and severity of sore throat, cough, and hoarseness. [16]

Our results were comparable to those documented by Sneha et al., where non-significant results with relation to postoperative cough have been documented, similar to our study. None of the groups were able to attenuate the incidence of cough. [16]On the contrary, our study reported a statistically significant reduction ($p<0.05$) at all time points from 2 to 10 hours for postoperative hoarseness in both interventional groups when compared to the control group, but Sneha et al. reported no significant change with budesonide. On subgroup analysis, Group B was able to attenuate more at 6, 8, and 10 hours than Group F.

A systemic review by Juan Yu compared various drugs through the nebulization route and found that nebulized corticosteroids, magnesium, and ketamine have been shown to be effective in preventing POST, and nebulized corticosteroids appeared to be the best among the vast armamentarium. [17]

Furosemide has been widely explored in lung diseases such as dyspnea, COPD, and COVID-19 patients through various routes, namely intravenous, oral, and recently through nebulization. [18,19,20] But very few studies have explored its role in POST, and that is through the nebulization route. Local administration of the drug provides local effects by reducing mucosal edema, reducing airway hyper-responsiveness, and attenuating airway mucosal inflammation. It has been found to be a good alternative to other pharmacological agents and to avoid the unnecessary systemic side effects associated with them.

Both nebulized furosemide and budesonide are generally well-tolerated with minimal systemic side effects when administered in appropriate doses. Furosemide may cause electrolyte disturbances such as hypokalemia and metabolic alkalosis, especially at higher doses or with prolonged use. Budesonide, being a corticosteroid, carries a risk of local fungal infections, dysphonia, and adrenal suppression, although these risks are low with nebulized administration. The safety profiles of furosemide and budesonide should be carefully considered, particularly in patients with co-morbidity such as electrolyte imbalances, hypertension, diabetes, or respiratory infections. Clinicians should weigh the potential benefits of symptom relief against the risks of adverse effects when choosing between these agents for postoperative prophylaxis.

The strengths of our study were that all the intubations were done by experienced anesthesiologists and the laryngoscopy duration was <15 seconds. Most of the studies have nebulized their intervention prior to the intubation in the preoperative period. While the action of the drug onsets and the intra-operative time are not beneficial to the patient, in our study, we nebulized our patients in the postoperative period after extubation. In this way, we were available to exclude any patients who did not meet the inclusion criteria. Moreover, in the postoperative period, the effects of the drugs will remain for a longer period in comparison to the preoperative period. But such hypotheses need more studies to establish any conclusion.

Limitations: There are some limitations to our study. The evaluation of a postoperative sore throat is based primarily on the patient's subjective feelings. Objective indicators to evaluate the grades should be included. The patients were followed only up to 24 hours post operatively, as the incidence of POST declined mostly within this time frame. The long-term effects of the interventions were not assessed. POST should be explored in future studies, and the impact of the interventions should be analyzed, which was lacking in our study.

Conclusion: Nebulization of furosemide or budesonide is better than normal saline to prevent postoperative sore throats. Both are equally suitable as an alternative to each other.

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