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Research Article

A prospective, randomized, double blind, placebo controlled clinical trial to study efficacy and safety of benzydamine 0.15% gargles in prevention of postoperative sore throat

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ABSTRACT

Background: Postoperative sore throat (POST) is an undesirable outcome of general anesthesia. The aim of the study was to evaluate the effectiveness of benzydamine preoperative gargles in reducing the incidence and severity of POST.
Methods: A randomized double blind prospective study involving 200 adult male and female patients was performed to assess the incidence of sore throat, cough and hoarseness of voice following tracheal intubation. The patients were randomly divided into two groups (group B and group C) of 100 each. Group B patients received benzydamine 0.15% gargles while group C received placebo. Patients were asked to gargle for 30 seconds, five minutes before induction of anesthesia. The patients were examined for sore throat, cough and hoarseness of voice at intervals of 0, 2, 4, and 24 hours post-extubation.
Results: The incidence of POST was significantly high ($p<0.05$) in the group C (controls) as compared to group B (cases) at all the durations of time after extubation. The peak incidence was noted at 0 and 2 hours post extubation, in both the groups, where 89% in group C and 47% reports of sore throat in group B were observed. The benzydamine group B had no evidence of sore throat at 24 hours duration whereas group C had 36% of patients who still complained sore throat. The incidence and severity of hoarseness of voice was found to be significantly low in group B at all the times as compared to group C ($p<0.05$).
Conclusions: A simple technique of gargling performed preoperatively with benzydamine hydrochloride was effective in reducing POST with no evidence of any side effects.

Keywords: POST, Benzydamine, Post-extubation, Sore throat, Cough, Hoarseness of voice

INTRODUCTION

Postoperative sore throat (POST) is one of the minor yet very common complications after general anaesthesia, which affects the quality of anaesthesia care and patient satisfaction. The expression of "sore throat" is well known to a common person and the typical symptoms of scratchiness in throat, pain while swallowing, cough and change in voice are very uncomfortable. POST compiles of the same constellation of signs and symptoms, like laryngitis, tracheitis, hoarseness of voice, cough, or dysphagia.[1] The symptoms are the result of mucosal injury secondary to airway instrumentation leading to inflammatory changes (i.e. trauma during laryngoscopy and suctioning) or the irritating effects of a foreign object (i.e., airway devices used like endotracheal tube, laryngeal mask airway (LMA), or oropharyngeal airway). Airway injuries are well-recognized complications of

general anaesthesia, and claims for airway injuries are frequent in the "American Society of Anesthesiologists Closed Claims database".[2] According to this database, the most common site of injuries to the airway is the pharynx and larynx, representing 33% of all airway injury claims, giving rise to hoarseness of voice.

In present study, an attempt was made to study use of a simple technique of gargling, very commonly known to laymen, can help to avoid this morbidity of sore throat that leads to patient dissatisfaction. In our study, a topical non-steroidal anti-inflammatory drug (NSAID) called benzydamine hydrochloride 0.15% (BH) is used for preoperative gargles. BH has been widely used to cure mucositis, due to radiation exposure mainly in cancer patients receiving radiation therapy.[3] Studies have been done to know the efficacy of this drug peri-operatively to reduce sore throat. Preemptive topical BH has been reported to decrease the incidence of sore throat from tracheal intubation and LMA use in general anaesthesia.[4] There are no contraindications to its use except any known hypersensitivity. Occasionally oral tissue numbness or stinging sensations may occur. The present study is an attempt to investigate whether preoperative gargling with BH solution is effective in reducing severity or preventing occurrence of POST, cough and hoarseness of voice following tracheal intubation.

METHODS

A prospective randomized double blind comparative study was conducted during the period of September 2008- August 2010. The study was approved by the Ethical Committee of Institutional Postgraduate Review Board.

A total of 200 adult male and female patients of age group between 16-60 years performed surgeries under general anesthesia were included in our study. Subsequently two groups were divided randomly containing 100 each using random number table method. The patients were selected on the basis of aforementioned criteria.

Inclusion criteria

- Patients age group between 16-60 years.
- Patients undergoing general surgical, gynaecological and orthopaedic procedures under general anaesthesia were included.
- ASA (American Society of Anesthesiologists) grade I and II with duration of surgery 1-3 hours and patients with or without naso-gastric (Ryle's tube) in situ (inserted post induction, intraoperatively).

Exclusion criteria

- Unwilling Patients,
- Mallampatti classification (MPC) >2, Patients with preoperative sore throat or URTI within last 7 days of surgery, Allergies to Benzydamine Hydrochloride
- All pregnant mothers and patients with gastro-esophageal reflux/ regurgitation.

After a thorough pre anaesthesia check-up, the inclusion and exclusion criteria were taken into consideration and patients fulfilling them were invited to participate in this study.

A qualified anesthesiologist, who was not a part of the investigating team, prepared the gargling solutions for the two groups. For group B (cases) benzydamine hydrochloride (0.15%) 15 ml was diluted upto 30 ml in mineral water (BH solution) and for group C (controls) edible color tartrazine (easily available in the market) along with sugar in incremental quantity to match the sweetness with BH solution, was added in 30 ml mineral water, stirred well, thus giving it similar taste and color as that of BH solution. This helped in blinding the patient as well as the investigating anaesthetist.

Patients were divided into two groups by random number table method and coding done. It was ensured that none of the patients received any sedative premedication drugs on the night before surgery.

Patients were asked to gargle for 30 seconds. Those who were unable to perform gargling appropriately or who were uncomfortable doing gargles were excluded from the study. A nasogastric tube was inserted as per the requirement of the surgery. Post extubation vitals were checked and then the patient was shifted to the Post-operative recovery room. An anaesthetist, who was blind to the groups, was then assigned the work of assessing the patient with the questionnaire methods given in Table 1 (by providing direct questions, as suggested by Harding and McVey) at 0, 2, 4, and 24 hours post extubation. Side effects like dysgeusia, irritation if any were also asked.

Patients with more than one attempt of laryngoscopy or intubation, or patients in whom blood was seen during laryngoscopy or nasogastric tube insertion/removal or while oropharyngeal suctioning with sterile red rubber catheter were excluded from the study. The next patient was allotted the number according to random number table. Decoding was done at the completion of the study, for the purpose of statistical analysis.

Statistical analysis was done by SPSS (Statistical package for social sciences), PASW (Predictive Analysis Software Statistics) version 18.0 (SPSS Inc, Chicago, Illinois). The independent student t test was used to compare demographic data, duration of surgery and cuff pressures in both groups. Ordinal data were analyzed using contingency table analysis with Chi Square Test with trend. A value of $p<0.05$ was considered significant. Unless otherwise indicated,

continuous variables are presented as mean (±S.D.), while ordinal data are presented as number (%).

Table 1: Scoring system for sore throat, cough and hoarseness of voice.

Please grade any sore throat you may have according to the following scale:
0 No sore throat at any time since your operation (until now).
1 Minimal sore throat, less severe than with cold, occurring at any time since your operation.
2 Moderate sore throat, similar to that noted with a cold, occurring at any time since your operation.
3 Severe sore throat, more severe than noted with a cold, occurs at any time since your operation.
Please grade any cough that you may have according to the following scale:
0 No cough or scratchy throat occurring at any time since your operation.
1 Minimal scratchy throat or cough, less than noted with a cold, occurring at any time since your operation.
2 Moderate cough, as would be noted with a cold, occurring at any time since your operation.
3 Severe cough, greater than would be noted with a cold, occurring at any time since your operation.
Please grade any hoarseness that you have according to the following scale:
0 No evidence of hoarseness occurring at any time since your operation.
1 No evidence of hoarseness at the time of interview, but hoarseness was present previously.
2 Hoarseness at the time of interview that is noted by the patient only
3 Hoarseness that is easily noted at the time of interview

RESULTS

The parameters of gender, MPC classification and ASA grades in group B and C, were compared using Pearson's Chi square test. The male: female ratio of patients was comparable in both the groups. The mean (±SD) age in group B was 38.08 (±9.819) years and that in group C was 35.45 (±10.556) years (Table 2). The age factor was comparable in both the groups and statistically found to be non-significant by using independent student "t" test.

ASA grade: 95 patients in group B and 93 patients in group C were ASA I, 5 patients in group B and 7 patients group C were ASA II. MPC classification: In both the groups we found that 95 patients each were MPC Class I and 5 patients each were MPC Class II. This data when compared statistically was found to be non-significant ($p>0.05$). Thus the demographic profile of the patients in both the groups was comparable.

The types of surgeries that patients underwent were compared and shown in Table 3. A group wise analysis of the types of surgeries, whether general surgical, gynaecological or orthopaedic procedure, which both group patients underwent, showed that out of 100 procedures in group B, 86 were general surgery, 11 were gynaecological and 3 were orthopaedic procedures. As compared to this, in group C, out of 100, 81 were general surgery, 13 gynaecological, and 6 orthopaedic procedures and the data was found to be statistically non-significant ($p>0.05$).

The mean duration of surgery in both the groups was also compared. Table 4 shows that the mean duration of surgery was 143.20±29.512 (mean±SD) minutes in group B and in group C it was 136.80±34.049 (mean±SD). Both the groups were comparable with respect to duration of surgery.

The mean endotracheal cuff pressure (cm of H2O) in both the groups, were found to be 20.05±1.226 cm of H2O in group B and 19.71±1.049 cm of H2O in group C as shown in Table 5. There was no significant difference between the endotracheal cuff pressures of the two groups. Thus the two groups were comparable with respect to the endotracheal cuff pressure.

Table 2: Demographic data.

Parameters		Group B	Group C	p-value
Age (Mean±SD)		38.08±9.819	35.45±10.556	>0.05
Gender n (%)	M	39 (55.7)	31 (44.3)	>0.05
	F	61 (46.9)	69 (53.1)	
ASA grade n (%)	I	95 (50.5%)	93 (49.5%)	>0.05
	II	5 (41.7%)	7 (58.3%)	
MPC class n (%)	I	95 (50.5%)	95 (50.5%)	>0.05
	II	5 (41.7%)	5 (41.7%)	

p>0.05- not significant.

Ryle's tube was inserted according to the requirement of the surgery that the patient underwent. The presence and absence Ryle's tube in both the study cases was studied. The number of patients in whom RT (Ryle's tube) was inserted was shown in Table 6. Group B had 69% patients with RT present and 31% without RT, whereas in group C 67% had RT inserted and 33% were without RT as per the requirement of the surgeries they underwent. Thus the two groups were comparable as regards to the presence or absence of Ryle's tube.

Table 3: Types of surgery done.

Type of surgery	Group B (cases)	Group C (controls)	p-value
General surgery	86	81	>0.05
Gynaecological	11	13	
Orthopaedic	3	6	
Total	100	100	

Pearson's chi square test showed p value>0.05- not significant.

Table 4: Group wise duration of surgery in minutes.

Duration of surgery (mins)	N	Mean±SD	p-value
Group B	100	143.20±29.512	>0.05
Group C	100	136.80±34.049	

Independent t test shows p>0.05 -Not significant.

Table 5: Endotracheal tube cuff pressures.

Endotracheal tube cuff pressures (cm of H_2O)	N	Mean±SD	p-value
Group B (Cases)	100	20.05±1.226	>0.05
Group C (Controls)	100	19.71±1.049	

Table 6: Ryle's tube in study groups.

Ryle's tube	Group B	Group C	p-value
Present [%]	69	67	>0.05
Absent [%]	31	33	
Total [n=%]	100	100	

From the 0th hour of extubation when the patient was kept in the post-surgery recovery room, by the direct questionnaire method, severity and incidence of sore throat, cough and hoarseness of voice and side effects was assessed at the intervals of 0 hour, 2nd, 4th and 24th hour post operatively.

Sore throat

The incidence of sore throat in the study groups was observed. As shown in Table 7 the incidence of sore throat was significantly high ($p<0.05$) in the group C as compared to group B at all the durations of time after extubation. The peak incidence was noted at 0 and 2 hours post extubation, in both the groups, where group C had 89% and group B had 47% reports of sore throat. However group B showed a significant decrease in the incidence to 14% at 4 hours, as compared to group C having 74% at 4 hours.

Table 7: Incidence of sore throat.

Incidence of sore throat		0 hours	2 hours	4 hours	24 hours	p-value
Present (%)	Group C	77	89	74	36	<0.05
	Group B	36	47	14	0	
Absent (%)	Group C	23	11	26	64	
	Group B	64	83	56	100	

The benzydamine group B had no evidence of sore throat at 24 hours duration whereas group C had 36% of patients still complained sore throat. Thus we can conclude that BH gargles are effective in reducing the incidence of sore throat post operatively and preventing the occurrence of sore throat at 24 hours post extubation.

Table 8 shows the severity of sore throat in the study groups. The overall severity of sore throat was low in group B as compared to group C at all the durations of post extubation. The benzydamine group shows only 14% occurrence of mild sore throat at 4 hours as compared to control group which had 53% mild sore throat, 18% moderate and 3% had severe sore throat. At 24 hours however there is no incidence of sore throat in benzydamine group. Hence it has been observed that benzydamine hydrochloride is effective in reducing the severity of POST with a relief of symptoms at 24 hours in comparison to the placebo group.

Table 8: Severity of sore throat.

Severity	0 hours		p- value	2 hours		p-value	4 hours		p-value	24 hours		p-value
	Group			Group			Group			Group		
	B	C		B	C		B	C		B	C	
Mild	16	49	<0.005 **	23	49	<0.005 **	14	53	<0.005 **	0	28	<0.005 **
Moderate	14	21		21	30		0	18		0	7	
Severe	6	7		3	10		0	3		0	1	
Total	100	100		100	100		100	100		100	100	

** Highly significant.

Cough

The occurrence and severity of cough in the benzydamine and the placebo group was shown in Table 9. These findings showed that the overall incidence of cough was less in both the groups. However it was seen that the incidence was significantly less in group B (42%) as compared to group C (66%) at 0 hours. But the findings were statistically non-significant at 2, 4 and 24 hours in both the groups as the incidence was only 5, 4 and 2 percent in group C while in group B it was 14, 2, 2 percent at 2, 4 and 24 hours. Hence it can be commented that the incidence of cough in both the groups was noted maximum just after extubation at 0th hour.

Table 10 shows the severity of cough at 0, 2, 4, and 24 hours. There is a significant difference in the severity of cough in both the groups. However it has been noted that there are conflicting results at 2, 4 and 24 hours, where the severity of sore throat has decreased but there is a statistically non-significant difference in the two groups. Although at 0 hour there is a decreased severity in group B as compared to group C. At 2 hours there is more incidence of cough in group B with 10 patients complaining of mild -scratchy throat and 4 with moderate cough as against only 5 in group C. While at 4 and 24 hours the reports of cough are almost similar. It could be concluded that benzydamine hydrochloride has not been effective in the prevention or reduction of cough post operatively.

Table 9: Incidence of cough.

Incidence of cough		0 hours	2 hours	4 hours	24 hours	p-value
Present (%)	Group C	66	05	04	02	>0.05
	Group B	42	14	02	02	
Absent (%)	Group C	33	95	96	98	
	Group B	58	86	98	98	

Hoarseness of voice

The incidence of hoarseness of voice was more than cough, but less as compared to sore throat (Table 11). The incidence of hoarseness of voice was found to be significantly low in group B at all the times as compared to group C ($p < 0.05$). Both the groups showed an increase in the incidence by 2nd hour post extubation but the incidence was not as high as that of sore throat. At 2nd hour 66% in group C had hoarseness of voice as compared to 37% in group B. However this figure decreased only marginally to 53% in group C as compared to a drastic decrease to 9% in the benzydamine group. At 24 hours post extubation the incidence further decreased to 4% in group C and 0% in group B, hereby concluding that benzydamine is effective in reducing the incidence of hoarseness of voice with complete relief at 24 hours post operatively.

Table 10: Severity of cough in cases and control.

Severity	0 hours		p-value	2 hours		p-value	4 hours		p-value	24 hours		p- value
	Group			Group			Group			Group		
	B	C		B	C		B	C		B	C	
Mild	33	46		10	5		2	4		2	1	
Moderate	8	18	<0.005 **	4	0	<0.05*	0	0	>0.05#	0	0	>0.05#
Severe	1	3		0	0		0	0		0	1	
Total	100	100		100	100		100	100		100	100	

** Highly significant; # Not significant; *Significant.

Table 11: Hoarseness of voice.

Hoarseness of voice		0 hours	2 hours	4 hours	24 hours	p-value
Present (%)	Group C	53	66	53	04	<0.05
	Group B	25	37	09	00	
Absent (%)	Group C	47	34	47	96	
	Group B	75	63	91	100	

Severity of hoarseness of voice can be assessed from Table 12. At all the time intervals i.e. 0, 2, 4 and 24 hours the severity of hoarseness of voice is low in the benzydamine group. The maximum incidence of hoarseness has occurred at 2nd and 4th hour post extubation in group C and B. But the severity is more in group C, with 50% having mild and 3% having moderate hoarseness as compared to group B with only 9% having mild hoarseness. At 24th hour there is no evidence of hoarseness of voice in group B as compared to group C with 4% having mild hoarseness of voice. Thus it has been observed that BH is effective in reducing the severity of hoarseness of voice postoperatively. When asked for, none of the patients complained of any side effects.

Table 12: Severity of hoarseness of voice in cases and control.

Severity	0 hours		p-value	2 hours		p - value	4 hours		p-value	24 hours		p-value
	Group			Group			Group			Group		
	B	**C**		**B**	**C**		**B**	**C**		**B**	**C**	
Mild	15	35	<0.005**	23	41	<0.005**	9	50	<0.005**	0	4	<0.05*
Moderate	9	11		12	23		0	3		0	0	
Severe	1	7		2	2		0	0		0	0	
Total	100	100		100	100		100	100		100	100	

** Highly significant; * Significant.

DISCUSSION

In the present study, the risk factors associated with sore throat were controlled. Both the groups were comparable with respect to- age, gender, duration of surgery, ASA grade, MPC class, types of surgeries (general surgical, gynaecological, orthopaedic), number attempts of laryngoscopy/intubation, endotracheal cuff pressure, tube size, Ryle's tube (present/absent).

Stout DM, Bishop MJ reported that the use of a smaller tracheal tube reduces the incidence of sore throat, presumably because of decreased pressure at the tube-mucosal interface.[6] In present study we have standardized the number of tube and used a 7.0 cuffed (portex) tube for females and 8.5 cuffed (portex) for males in both the groups.

The characteristic of the cuff in the portex tube is high volume low pressure cuff. With respect to the cuff type and design, tube size and tube type, several studies have reported.[7-12] Seegobin et al studied that the tracheal mucosa suffers ischemic changes with the type of cuff and the degree of pressure exerted on the lateral walls of the trachea. Hence a cautious recommendation was made that intracuff pressure should be maintained at <20mmHg

(26 cm H_2O) to prevent ischemia to the tracheal wall.[13] In another study by Seegobin RD the effect on tracheal mucosal blood flow was studied and the recommendations were stated that cuff pressures should not be exceeded beyond 30 cms of H_2O.[14] Hence in our study we found mean pressure values of 20.05±1.226 cms of H_2O in group B and 19.71±1.049 cms of H_2O in group C, which were statistically non-significant with the independent t test. Cuff pressure was within the range of recommended values.

Studies with different drugs to alleviate the incidence of sore throat post operatively have been done. Use of NSAIDs like aspirin gargles or transdermal ketoprofen patch on the anterior part of neck, ketamine gargles, local anaesthetic spray, steroid jelly lubrication of the cuff or steroid sprays over the endotracheal tube cuff have been done for the same. Surprisingly though, Stride PC et al found that the application of topical lignocaine spray on the cuff caused increased sore throat occurrence and had more number of laryngoscopy attempts causing mucosal irritation.[15]

Kati et al found the effectiveness of pre-emptive topical BH in reducing the severity of POST resulting from LMA.[4] Aggrawal et al studied the efficacy of BH and aspirin gargles preoperatively to reduce the severity of POST and concluded that aspirin gargles reduced the incidence of POST for 4 hours whereas benzydamine hydrochloride (BH) gargles reduced POST for 24 hours. POST was more severe in the control group at 0 and 2 hours.[16] The study concluded that the incidence of POST was more frequent in group C compared with group BH at all-time points ($P < 0.05$). A significantly more frequent incidence of POST was observed in group C only at 0 and 2 hours when compared with group AS (aspirin) group ($P<0.05$). No difference in the incidence of POST was observed between the AS and BH groups at any time ($P>0.05$). Aspirin and BH gargles were well tolerated by most patients, except 2 patients in the BH group who complained of numbing of mouth and dysgeusia (distorted sense of taste). Our findings are consistent with the above study except that none of the patients had any complain of numbness, stinging or dysgeusia as we used a diluted solution of 0.15% benzydamine hydrochloride. Studies have shown the occurrence of these side effects were more when the difflam spray (0.15%) was directly sprayed in the mouth for pain relief in post tonsillectomy patients.[17,18]

Hung NK et al have proposed two studies for the effectiveness of BH spray applied on the endotracheal tube cuff, and sprayed over oropharynx just before intubation, in all deviating the incidence and severity of sore throat post operatively. They observed that, highest incidence of POST occurred at 6 hours after extubation.[19] In present study we have recorded the highest incidence at 2 hours post extubation with decrease in the severity after 4th hour, and none of the patients having any complains at 24 hours in the benzydamine study group. In another study Hung et al found that there was no significant correlation between spraying BH over the oropharyngeal cavity or on the ET cuff on the incidence of POST without increased BH related adverse effects.[20] Thus in an attempt to study this drug we decided upon using the oral rinse of BH for gargling. It being a simple technique and patients having knowledge about the technique, it was easy to perform the study. Gargling covers areas like oropharynx, posterior pharyngeal wall, faucial pillars, anterior surface of epiglottis and uvula. Thus most of the areas that could suffer trauma during laryngoscopy and intubation are covered by gargling. However to prevent the hoarseness which is caused by tracheal and vocal cord injuries, we standardized the tube size, endotracheal cuff pressure, inflating agent as room air and duration of surgery (less than 3 hours) in the present study.

A recent study on meta-analysis of randomized controlled trials involving BH for POST performed by Chien-Yu Chen et al.[21] The study reviewed five trials included 824 patients in total. The study proposed that the incidence of POST can be significantly reduced by prophylactic BH topical application to the oral cavity or airway devices. The findings further strengthen the hypothesis proposed in the present study.

CONCLUSION

The use of benzydamine hydrochloride gargles can be helpful in reducing the incidence of POST. There was no evidence of any side effects to the use of this drug in the present study. Thus a simple technique of gargling with benzydamine hydrochloride can help reduce the incidence of post-operative sore throat, emergence phenomenon in the form of coughing and hoarseness of voice.

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