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COMPARATIVE STUDY ON EFFECTIVENESS OF ZINC LOZENGES AND MAGNESIUM LOZENGES ON POSTOPERATIVE SORE THROAT

Anaesthesiology

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ABSTRACT

Post-operative sore throat (POST) is a common complication of endotracheal intubation and it hampers the positive feedback of ambulatory surgery in spite of so many measures. Aim of this study was to compare the effectiveness of Zinc and Magnesium Lozenges on POST. **Material And Methods:** prospective, randomized, double blinded placebo controlled study, enrolling 90 adult patients of either sex, aged 18-60 of American Society of Anaesthesiologist physical status I-II, scheduled for surgeries of less than 4hours duration, were randomly allocated to Group Z (n=30) receiving Zinc Lozenges (40mg elemental Zinc), Group M (n=30) receiving Magnesium lozenges (100mg magnesium ion) and Group C (n=30) receive candy 30 minutes prior to surgery. The incidence and severity of POST was assessed for incidence and severity (4-point scale, 0–3) of postoperative sore throat at 0,2,4,8,12 and 24 hours postoperatively. **Results:** Total incidence of sore throat in the study was 56.66%. Highest incidence was observed in the second hour. Statistically significant difference was seen when group M and group Z was compared with group C ($p<0.05$). On comparing group Z and group M, the incidence of POST was reduced in group M and it was statistically significant at 2, 4, 8, 12 and 24 hours postoperatively ($p<0.05$). Cough and hoarseness were also reduced in group M. **Conclusion:** The study concluded that magnesium lozenges and zinc lozenges decreased the incidence of POST, and magnesium lozenges was better than zinc lozenges in reducing incidence and severity of POST.

KEYWORDS

Endotracheal Intubation, Postoperative Sore Throat, Lozenges, Zinc, Magnesium.

INTRODUCTION:

Postoperative sore throat (POST) is rated as one of the most common adverse effect in postoperative period in patients undergoing surgery under general anaesthesia with an incidence of 21-65%.[1,2] Incidence of POST is the highest after endotracheal intubation (45.4%), whereas the incidence was low with laryngeal mask airway (17.5%) and with face mask(3.3%).[3,4,5] A recent study comparing POST showed incidence between males and females 32% and 37% respectively, though the risk factors for both the sex were different.[6] Although the current treatments are not exactly effective the management of preventing POST is still advised because it promotes the patient's satisfaction and affects the activities postoperatively and after discharge from the hospital.[3] Over the years, several pharmacological and non-pharmacological remedies were used, with varying degree of success.[7-14]

Zinc is a micronutrient that is involved in the diverse physiological properties like tissue repair, immune modulation, growth, anti-oxidant and anti-inflammatory properties.[15,16] Zinc has been used topically for the prevention of oral mucositis, xerostomia and pain associated with chemotherapy.[17] Oral lozenges have been effective in reducing incidence and severity of POST.[13]

Magnesium has antinociceptive effects and are primarily due to the inhibition of calcium entry into the cells and blockade of NMDA receptors.[18] NMDA receptors have a role in nociception and inflammation and are found in peripheral nerves and central nervous system and it is possible that inflammation stimulates peripheral NMDA receptors.[19] Magnesium sulphate gargles are found to be more effective than ketamine gargles.[20] Magnesium nebulisation was also used for the prevention of postoperative sore throat. [21] Magnesium lozenges has been shown to reduce the severity and incidence of POST.[14]

Lozenge form was taken up for study because of the potentially better local effect in oropharyngeal mucosa in addition to systemic effect compared to pill or capsule form. Lozenges also have better patient compliance.

We hypothesized that administration of oral magnesium lozenges will be more effective when given 30 minutes prior to surgery in reducing POST because of its anti-inflammatory and antinociceptive properties as compared to zinc. To evaluate this, we analyzed the effect of zinc and magnesium lozenges on the severity and incidence of POST, cough, and hoarseness of voice after tracheal intubation in patients undergoing general anaesthesia.

Material and methods

This study was designed as prospective, randomized, double blinded placebo controlled study and taken up following approval by the institutional ethical committee (Government Medical College, Amritsar, Punjab, India, ECC/TH-032 dated: 16/05/2019), and written informed consent was taken (which included the risks, benefits and explanation of process) to participate in the study. Randomization was done using a computer generated random number table and sealed enveloped method and patients received zinc, magnesium or placebo. The code was maintained until the study was complete.

The study was carried out prospectively on 90 patients in age group of 18 to 60 years of either sex of American Society of Anesthesiologists (ASA) grade I & II undergoing surgery under general anaesthesia with tracheal intubation and lasting for more than 1 hour and less than 4 hours. Non cooperating or unwilling patients, patients with ASA grade more than II, smokers, patients with recent history of sore throat or upper respiratory tract infection, pregnant patients and patients with allergic history to zinc or magnesium were excluded from the study.

Sample size was calculated on the basis of previous studies[13,14] and taking into account the parameters like incidence of sore throat, side effects etc. keeping in view at most 5% risk, with minimum 85% power and 5% significance level (significant at 95% confidence interval) ($\alpha=0.5$, $\beta=0.5$) for comparison of quantitative and continuous data, a minimum of 30 patients in each group with a total minimum of 90 patients either male or female were included.

Group Z (n=30):
Received zinc lozenges in the form of zinc sulfate (40mg elemental zinc)

Group M (n=30):
Received magnesium lozenges in the form of magnesium citrate (100mg magnesium ion per dose)

Group C (n=30):
Received candy and was the control group.

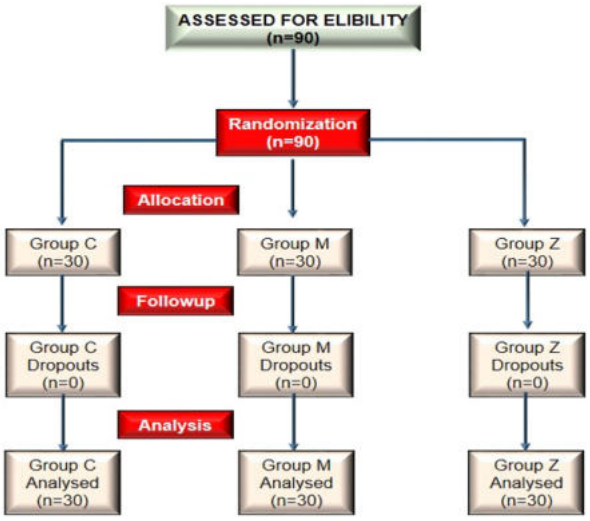

Figure 1: Consort Diagram

The patients were instructed to completely dissolve the lozenges 30 minutes prior to surgery and to maintain head end elevated for at least 30 minutes post ingestion of lozenges. Patients didn't receive any sedative medication while dissolving the lozenges.

Patients were then transferred to the operating room where standard monitors were attached. Patients of all three groups received the same and standardized medications for induction and analgesia peri-operatively. Patients belonging to all the groups received Inj. Glycopyrrolate (0.01mg/kg) IV, and Inj. midazolam (0.02mg/kg) IV as premedication before the induction of anaesthesia.

Intravenous line using 18 /20 G cannula was secured in the operating room and an IV infusion of ringer lactate started. After attaching all the monitors (NIBP, pulse rate, respiratory rate, ECG, SpO_2), the baseline readings were noted.

Intra operatively electrocardiography (ECG), non-invasive blood pressure (NIBP), pulse oximetry (SpO_2), End tidal CO_2($EtCO_2$) were monitored at every 5 minutes till 30 minutes and cuff pressure monitoring at 15 minutes interval till completion of surgery.

The induction regimen was standardized for all groups as follows: after 3 minutes of pre-oxygenation, inj. propofol 2.0mg/kg and inj. fentanyl 2 micro gm/kg was given IV immediately afterwards, we facilitated intubation by giving succinylcholine 2mg/kg and laryngoscopy done after 60-90 seconds using Macintosh laryngoscope blade size 3 or 4 (depending on the patient). Then the patient was intubated with endotracheal tube of internal diameter of 7/7.5/8 mm as per the patient. Experienced anaesthesiologist with minimum three years of experience performed the intubation in all the patients and the duration of laryngoscopy as well as the number of attempts was noted. Patients who required more than two attempts were excluded from the study. The endotracheal tube cuff was then inflated until there is no air leakage heard on auscultation at a peak airway pressure of 20 cm of H_2O, which will be further checked intraoperatively at an interval of every 15 minutes.

Heart rate (HR) and Blood pressure were recorded pre-operatively and thereafter every 5 minutes throughout the surgery. General anaesthesia was maintained with 50% oxygen in 50% nitrous oxide, isoflurane 1.2 MAC and atracurium 0.1mg/kg maintenance dose. IV ondansetron 4 mg was given 15 minutes prior to the end of surgery. On completion of surgery, with the patient adequately anaesthetized, special care was taken while suctioning the posterior pharynx using only a blunt and gentle suction catheter under direct vision to avoid any kind of trauma to tissues and to confirm clearance of secretions. FiO_2 was increased to 100%, 5 minutes prior to extubation.

Once the spontaneous ventilation returned, the neuromuscular block was reversed with IV neostigmine (50 µg/kg) and glycopyrrolate (10 µg/kg).

Extubation was done after the return of spontaneous ventilation and when the patient started following commands and were transferred to post anaesthesia care unit (PACU). Patient was evaluated for presence and severity of sore throat on reaching the PACU (0 hour) using a standardized scale. The severity of POST was graded on a 4 point scale ranging from 0 to 3; score 0 being no sore throat; 1, mild sore throat (complaints only on questioning); 2, moderate sore throat (complains of sore throat on patients own); 3, severe sore throat (will be having hoarseness of voice and throat pain). The evaluation was repeated at 2, 4, 8, 12, 24 hours postoperatively. The primary outcome of our study was incidence of POST 2 hours after surgery. The secondary outcome included the incidence and severity of postoperative sore throat at 0, 4, 8, 12 and 24 hours after surgery and to evaluate any side effects such as cough, hoarseness, nausea, vomiting, gastric irritation and dry mouth. Postoperative pain was evaluated using VAS (visual analogue scale (0-10), at 2hours, 4hours, 6 hours, 8hours, 12hours, and 24hours after the surgery. The patients was familiarized with the concept of visual analogue scale for pain assessment with 0= no pain and 10= worst possible pain during pre-anesthetic check-up.[22] For patients with a VAS score more than 4, rescue analgesia was given in the form of intravenous paracetamol 1 gram.

STATISTICALANALYSIS

Raw data was recorded in a Microsoft excel spread sheet and analysed using Statistical Package for Social Sciences (SPSS version 24.00 Armonk, NY: IBM Corp.). The continuous variables were expressed as mean with standard deviation (mean±SD). All categorical variables were expressed as number and percentage. Categorical variables were analysed using chi-square test. Normally distributed continuous variables were analyzed using independent sample t-test. The p value was determined finally to evaluate the levels of significance. The p value of >0.05 was considered non-significant, p value of 0.01 to 0.05 was considered to be significant and p value < 0.001 was considered as highly significant. The results were then analyzed and compared to the previous studies.

RESULTS

90 patients were enrolled in the present study in three different groups. No patients were lost in follow-up and excluded from analysis. All the three groups were comparable in terms of demographic parameters (Table 1).

Table 1: Demographic parameters

Parameters	Group C	Group M	Group Z	p value
Age (years)	41.57± 10.14	39.30± 14.03	43.23±14.20	0.33
Sex (female/male)	23/7	26/4	24/6	0.819
Weight (kilogram)	68.63±5.86	68.00±7.18	66.63±6.67	0.350
ASA (I/II)	23/7	26/4	29/1	0.070
Duration of surgery	62.17±9.53	61.33±17.47	61.50±16.56	0.667
Duration of laryngoscopy	9.07±0.58	9.00±0.37	9.00±0.45	0.310

The overall incidence of POST was 56.66% (51/90) (TABLE 2). In group C the incidence of POST was 80% (24/30). In group M the incidence of POST was 40% (12/30). In group Z the incidence of POST was 50% (15/30) (Table 2).

Table 2: incidence of POST at different time intervals

Time interval	Group C		Group M		Group Z		p-value		
	No.	%	No.	%	No.	%	C/M	M/Z	C/Z
0 hour	22	73.33	6	20.00	12	40.00	0.001**	0.145	0.020*
2 hours	24	80.00	12	40.00	15	50.00	0.000**	0.008*	0.049*
4 hours	24	80.00	8	26.67	15	50.00	0.001**	0.032*	0.045*
8 hours	20	66.67	8	26.67	14	46.67	0.002*	0.031*	0.037*
12 hours	18	60.00	5	16.67	12	40.00	0.001**	0.045*	0.121
24 hours	16	53.33	2	6.67	9	30.00	0.001**	0.020*	0.067

Significant* ($p<0.05$), Highly significant** ($p<0.001$), Non significant ($p>0.05$)

At 2 hours (PRIMARY OUTCOME) postoperatively, the total incidence of postoperative sore throat was 56.66%. Statistically

significant difference was seen when group M (p- 0.001) and group Z (p-0.049) was compared with group C.

Incidence of POST was statistically significant at 0 hours, 2 hours, 4 hours and 8 hours in group Z and group M when compared to group C. Incidence of POST in group M was also statistically significant at intervals 12 and 24 hours when compared with group C.

On comparing group Z and group M, the incidence of POST was reduced in group M and the observation was statistically significant at 2, 4, 8, 12 and 24 hours postoperatively ($p<0.05$).

Overall we observed that, POST was significantly reduced in zinc and magnesium group when compared to control group and also the maximum decrease was seen with magnesium.

The intensity of sore throat was assessed in three groups using Visual analog scale (VAS) .VAS was measured post operatively for sore throat at 2, 4, 6, 8, 12 and 24 hours. Statistically significant decrease in VAS score was seen with group M and group Z when compared to group C ($p<0.05$) during all the time intervals. On comparing group M with group Z, VAS score was, 1.30 in group M and 2.93 at group Z at 2 hours ($p =0.005$), 1.27 in group M and 2.57 in group Z at 4 hours ($p=0.001$), 0.73 in group M and 2.13 in group Z at 6 hours (0.02), 0.67 in group M and 1.73 in group Z at 8 hours ($p=0.03$), 0.67 in group M and 1.40 in group Z at 12 hours ($p=0.04$), 0.43 in group M and 0.93 in group Z at 24 hours ($p=0.04$). VAS score was reduced in group M and it was statistically significant throughout all the time intervals. Patients with VAS score >4 received rescue analgesia with paracetamol 1gm IV (figure 2).

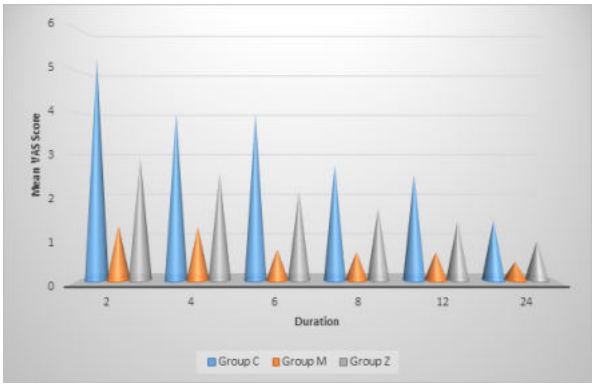

Figure 2: Mean VAS score at different time intervals

There was definitive decrease in the incidence of cough in group M and group Z 0, 2 and 4 hours as compared to the control group. The incidence of cough was least with magnesium group followed by zinc group and it was highest in the control group. Statistically significant difference was observed in group M when compared to group C at 0 hour ($p=0.03$) and 2 hours ($p=0.035$), and also in group Z when compared to control group at 2hours (0.035). There was no incidence of cough in any of the groups 4 hours after extubation (figure 3).

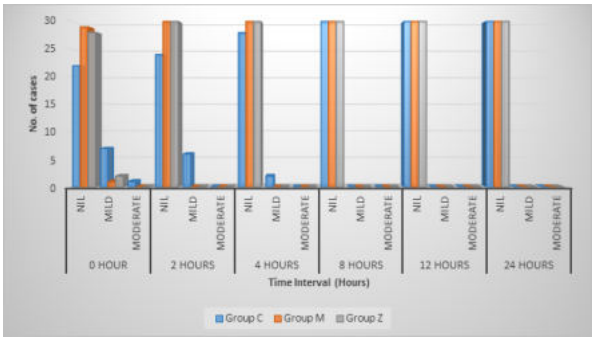

Figure 3: Incidence of cough postoperatively

Incidence of hoarseness decreased in Group Z and M at 0,2,4,8,12,24 hours after surgery. The maximum decrease in hoarseness was observed in group M, followed by group Z. Statistically significant difference was observed in group M in comparison with control group (group C) at 0, 2, 4 and 8 hours, and also in group Z when compared to control group at 2 and 4 hours($p<0.05$). There was no incidence of hoarseness 12 hours after surgery in any of the three groups. (figure 4)

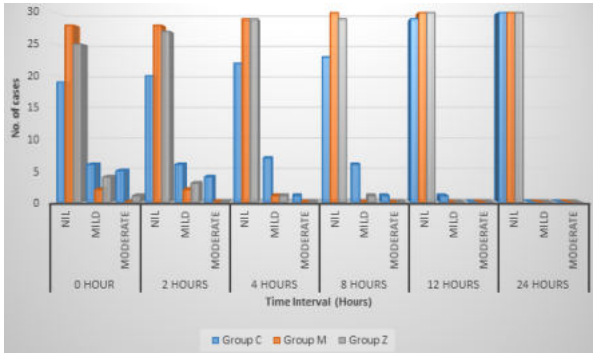

Figure 4: incidence of hoarseness of voice

No patients reported side effects like nausea, vomiting, headache, gastric irritation, diarrhea during the study.

DISCUSSION

Postoperative sore throat is a commonly reported complaint in patients receiving general anaesthesia. Although a minor complaint, postoperative sore throat many a times contributes to postoperative morbidity and patient dissatisfaction. [3] The underlying cause of postoperative sore throat is related to the local irritation, inflammation and edema associated with airway instrumentation which also leads to the reduction in the mucosal blood flow in tracheal mucosa leading to ischemic damage. Postoperative sore throat is attributed to several perioperative conditions like large size of tracheal tube, increased duration of surgery and intraoperative tube movement. Over the years several pharmacological and non-pharmacological remedies have been tried with variable success.

Zinc is involved in various physiologic processes like growth, immune system modulation tissue repair and it also acts as an anti-inflammatory agent and anti-oxidant.[15,16] Zinc is very effective in the prevention of oral mucositis and xerostomia and moreover zinc lozenge shows a significant reduction in the use of analgesics for oral pain.[17] It has been used in the treatment of sore throat associated with upper respiratory tract infections in the past. Oral lozenges is effective in reducing the incidence and severity of POST.[13]

NMDA receptors have a role in nociception and inflammation and are found in peripheral nerves and central nervous system (CNS).[19] Magnesium is a NMDA receptor antagonist and magnesium lozenges have been shown to improve postoperative sore throat. [14] Magnesium sulphate gargles and nebulisation were also used for the prevention of postoperative sore throat.[20,21]

All the groups were compared with respect to intraoperative and postoperative hemodynamic parameters, duration and number of attempts of laryngoscopy and it was observed to be statistically non-significant. This was consistent with observation by Sarkar et al.[8]

Cuff pressure of the ETT was recorded for the entire surgery period and the mean value was between 19-20 cm H_2O in all the patients in all three groups and it was statistically non-significant ($p>0.05$) Increase in the cuff pressure is seen as a risk factor for POST Loeser et al in his study suggested that the major cause of POST was due to tracheal mucosal damage secondary to cuff-trachea contact.[1]

We observed that the overall incidence of POST in our study was 56.66% (51/90) and the maximum incidence was observed at 2 hours postoperatively. Incidence of sore throat at 2 hours was taken as the primary outcome as the patients are mostly awake and alert after surgery during this time and so they are more cooperative to participate in the study. In previous studies incidence of sore throat was 21-65% in patients receiving GA with tracheal intubation.[1,2] There was a statistically significant reduction in the incidence of POST in Group Z and M as compared to the control group (group C). All the groups exhibited decreased incidence of POST at 8 hrs, 12 hrs and 24 hours. Maximum decrease at 24 hrs was seen with magnesium group as compared to the zinc group. This observation was consistent with studies by Farhang et al and Borazan et al.[13,14]

The maximum decrease in incidence was observed in magnesium group, followed by zinc and control group, this was in line with the observation made by Teymourian H et al, who in his studies showed that incidence and severity of POST was reduced with magnesium by any route.[20]

We also observed in our study, the decreased incidence of cough in zinc and magnesium group, with overall incidence of less than 5%, which is in agreement with Narinder P et al[9] and Sarkar et al[8] which had also showed reduced incidence of cough in magnesium and zinc respectively as compared to control groups at 2 hours and 4 hours postoperatively.

Incidence of hoarseness was also decreased in all our study groups and decreased with time, which is in agreement with Sarkar et al [8] and Chattopadhyay et al.[11]

There were no side effects like nausea, vomiting, headache, gastric irritation, diarrhea observed in any of the patients. This can be attributed to the better local action of lozenge form and minimal systemic absorption leading to fewer side effects.

LIMITATIONS OF STUDY

A drawback of our study was the absence of the measurements of plasma drug levels. So we cannot rule out the contribution of the systemic effect of drugs in our results, though not expected to be much. Data concerning pharmacokinetic effects of magnesium and zinc lozenge are limited; therefore the exact administration time and dosage is difficult to pointout. Also in our study the dose of lozenge was empirical based on previous studies which didn't have any pilot data. Also in our study, we had more number of females enrolled, so that could have contributed to the increased incidence of sore throat, as POST is known to occur more in female patients as compared to males. Though results of our study were conclusive but we feel that larger sample size would have been more beneficial and would have added more strength to our findings. Also dose range studies can be done using different doses and possibility of giving lozenges in the post-operative period, also instead of giving one single dose pre operatively and can serve as future guideline.

CONCLUSION

From our study, we concluded that, pre-operative administration of zinc and magnesium lozenges is a simple and effective method to reduce incidence of postoperative sore throat in patients undergoing tracheal intubation under general anaesthesia. Magnesium lozenges were more effective than zinc lozenges in preventing incidence and severity of postoperative sore throat from immediate post extubation period (0hours) to 24 hours. Magnesium lozenges were effective in reducing cough in the postoperative period than zinc lozenges till 2 hours and hoarseness till 8 hours. No side effects were observed with any of the drugs used.

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