

Preoperative oral zinc tablet decreases incidence of postoperative sore throat

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ABSTRACT

Background and Aims: Postoperative sore throat (POST) is very frequently reported after endotracheal intubation. Zinc lozenge has been shown to reduce POST. The aim of this study was to evaluate the effect of dispersible zinc tablet on POST. **Methods:** Eighty-eight patients undergoing surgery with endotracheal intubation were randomly allocated into two groups, to either receive dispersible zinc tablet 40 mg (zinc group) or placebo tablet (control group), 30 min preoperatively. Assessment for incidence and severity was performed for POST, on a 4-point scale (0–3) at 0, 30 min, 2, 4, and 24 h postoperatively. The primary outcome was incidence of POST at 4 h postoperatively. Secondary outcome was severity of POST at the 5 evaluation time points postoperatively. Mann–Whitney *U* test, Fisher's exact, and Chi-square test were used as applicable. **Results:** At 4 h, there was a significantly lower incidence of POST in zinc group (6.8%) than the control group (31.8%) with a *P* value of 0.003. Three patients in placebo group complained of severe POST compared to none in the zinc group. The severity of POST was significantly lower in Zinc group than Placebo group at 0 min (*P* = 0.003), 30 min (*P* = 0.002), 2 h (*P* < 0.001), and 4 h (*P* = 0.001). **Conclusion:** Preoperative administration of 40 mg dispersible zinc tablet effectively reduces the incidence and severity of POST in the immediate postoperative period.

Key words: Zinc, postoperative sore throat, tracheal intubation, dispersible tablet

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INTRODUCTION

Postoperative sore throat (POST) is a common complaint in patients receiving general anaesthesia.^[1,2] Although symptoms often ameliorate without any treatment, prophylactic management improves patient satisfaction and impacts discharge from hospital. Over the years, several pharmacological and nonpharmacological remedies have been tried, with varying degree of success.^[3-9] A recently published meta-analysis recommends the prophylactic use of topical magnesium to prevent POST owing to its anti-inflammatory properties.^[10]

Zinc is a micronutrient with anti-inflammatory and antioxidant properties which promotes growth, tissue repair and modulates immune system.^[11-14] As a topical agent zinc has been used for prevention of oral mucositis in patients receiving high dose chemotherapy.^[15] Oral zinc lozenge has been shown to reduce the incidence and severity of POST.^[9]

We hypothesized administration of oral zinc in form of dispersible tablet will reduce the incidence of POST due to its inherent anti-inflammatory and tissue healing properties. To test the hypothesis, this study was designed to investigate the efficacy of oral zinc sulfate given 30 min preoperatively in reducing POST till 24 h after surgery, where POST was caused by endotracheal intubation. At the time this study was designed, no literature pertaining to the effects of zinc on POST in Indian population was available. The dispersible tablet form of zinc was preferred due to its easy availability in our

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country and comparatively better local effect on oropharyngeal mucosa.

MATERIALS AND METHODS

Following approval by the institutional ethics committee (dated: 07/01/2019; approval number IEC/NBMC/2018-19/22) and registration with CTRI (CTRI/2019/03/018065), written informed consent was obtained from all patients for participation. This study was designed as a prospective, randomized, double-blinded placebo control trial. Randomization was achieved by using a computer-generated random number table and sealed envelope method to receive either dispersible zinc tablet or a placebo. The code was maintained until the study was completed.

Eighty-eight patients of either sex, between 18 and 60 years of age, with American Society of Anaesthesiologists Physical Status (ASA-PS) I and II, posted for low to moderate risk surgeries of duration greater than 1 h and less than 6-h duration completed the study. This specific surgical duration was chosen to ensure that the patient was intubated long enough to cause irritation of oropharyngeal mucosa. Smokers, pregnant patients, patients with a recent history of sore throat or upper respiratory tract infection, Malampatti grade (MPG) greater than II and patients with allergy to zinc were excluded from the study. Traumatic or more than one attempt at intubation also lead to exclusion from the study.

After written informed consent was received in the preoperative visit, a sealed and coded envelope with either zinc or placebo tablets was given to the patient, with instruction to dissolve the tablet in mouth by sucking on it 30 min prior to surgery. The zinc group received two dispersible zinc sulfate tablets (equivalent to 40 mg elemental zinc) of same commercially available brand and the control group received two placebo tablets with no active ingredient but were indistinguishable in appearance and taste from the one containing zinc. The investigators and the patients were blinded about the content of the envelope and the code was maintained until the completion of the study.

Preoperatively any sedative medication was withheld till the patient was sucking on the provided dispersible tablet, other premedication included injection ranitidine (50 mg iv), inj. ondansetron (4 mg iv). In the operating room routine monitors such as ECG,

noninvasive blood pressure and pulse oximeter were attached. After 3 min of preoxygenation, anaesthetic induction was commenced with intravenous fentanyl (2 µg/kg) and propofol 2 mg/kg followed by orotracheal intubation facilitated by atracurium 0.5 mg/kg. An anaesthesiologist (with more than 5 year of experience) performed all the laryngoscopies in both groups using 3 or 4 Macintosh metal blades to insert endotracheal tubes with an inner diameter of 8 mm and 7 mm for male and female patients, respectively. The laryngoscopic view of glottis was classified using Cormack–Lehane classification as follows: grade 1—full glottic view, grade 2—only posterior extremity of glottis visible, grade 3—only epiglottis visible, and grade 4—no recognizable structure visible without laryngeal manipulation. Duration of laryngoscopy (time from opening mouth to the placement of the endotracheal tube) and the intubation time (the interval between the insertion of the laryngoscope blade into the mouth to the inflation of the endotracheal tube cuff) was recorded by the same anaesthetic technician in all patients. Anaesthesia was maintained with 2% sevoflurane in 60% N₂O and 40% O₂ mixture, intermittent fentanyl and atracurium at 0.15 mg/kg was used when required. The cuff pressure of the endotracheal tube was adjusted every 30 min, using a handheld pressure gauge and maintained between 20 and 22 cm of H₂O to limit nitrous oxide related increase in the cuff pressure. The use of steroids and anti-inflammatory drugs was recorded.

During emergence from anaesthesia, any coughing or bucking was duly noted. The presence of traumatic intubation in form of blood in the oropharynx was visually confirmed and such cases were excluded from the study. Upon completion of the surgery, the patients were extubated following careful suctioning of the oropharynx and were transferred to the Post Anaesthesia Care Unit (PACU). On arrival at PACU, immediate evaluation for presence and severity sore throat was done (time = 0), using a standardized scale. The severity of POST was graded on a 4-point scale ranging from 0 to 3; 0 being no sore throat, 1 being mild discomfort (complaints only upon questioning), 2 being moderate sore throat (complaints of his/her own), and 3 being severe sore throat (change in voice, hoarseness and throat pain). The evaluation was repeated at 30 min, 2, 4, and 24 h. The primary outcome of this study was the incidence of POST at 4 h, based on the assumption that the onset of anti-inflammatory action by dispersible zinc tablet may range from 30 min to 4–6 h based on limited

available data from previous studies.^[8,9,11,14] Any side effects such as nausea, vomiting, metallic taste, and diarrhea were also noted.

All analyses were performed using Statistical Package for the Social Sciences (SPSS) software program, version 23.0 (SPSS, Chicago, Illinois). All categorical variables were expressed as number and percentage, whereas the continuous variables were expressed as mean \pm standard deviation.

During the 24 h evaluation period in PACU, the incidence of POST between groups was compared using the Chi-square test. The *P* value for the primary outcome (incidence of POST at 4 h) and secondary analysis (incidence of POST at 0, 30 min, 2 h, and 24 h) was set at 0.01 (0.05/5; Bonferroni correction). The analysis for secondary outcomes, that is, severity of POST at 0, 30 min, 2, 4, and 24 h was done using Mann–Whitney *U* test with Bonferroni correction and a value of $P < 0.01$ was considered significant (0.05/5 = 0.01). Patient demographics and intraoperative variables were analyzed with the Mann–Whitney *U* test for continuous variables and Fisher's exact or Chi-square tests for categorical variables.

From previous studies,^[16,17] the incidence of POST was presumed to be 65%, setting the power of study at 80% and alpha error at 0.05, 36 patients in each group will be required to detect a 50% reduction in the incidence of POST. Considering a drop out ratio of 20%, 44 patients in each group were included, making the total sample size 88.

RESULTS

One hundred patients were considered for the study [Figure 1]. A total of 96 patients who gave consent were enrolled and were randomly allocated, 48 to zinc group and 48 to the placebo group. Three patients who received zinc tablet and two patients who received placebo tablet, did not find the tablet palatable and spit it out. One patient in zinc group and two patients in placebo group required more than one attempt at intubation and were excluded from the study. Data from 88 patients were available for analysis: 44 from zinc group and 44 from placebo group.

Both groups were found be comparable in regards of demographic and intraoperative variables [Tables 1 and 2]. The overall incidence of POST in Zinc group was 20.5%

and Placebo group was 45.5% ($P = 0.01$), resulting in greater than 50% reduction in incidence of POST.

The incidence of POST between two groups at 0, 30 min, 2, 4, and 24 h is shown in Table 3. A statistically significant difference was found between groups in our primary outcome (incidence of POST at 4 h) with a *P* of 0.003 (significance level adjusted by Bonferroni correction to 0.05/5 = 0.01). The incidence of POST between groups was also found to be statistically significant at 0 min ($P = 0.001$), 30 min ($P < 0.001$) and 2 h ($P = 0.002$); however, incidence of POST at 24 h postsurgery was found to be comparable between the two groups with a $P = 0.05$ (significance level adjusted by Bonferroni correction to 0.05/5 = 0.01).

The severity of POST is shown in Tables 4 and 5. The severity of POST was significantly lower in Zinc group than Placebo group at 0 min ($P = 0.003$), 30 min ($P = 0.002$), 2 h ($P < 0.001$) and 4 h ($P = 0.001$). No statistically significant difference was found in severity of POST between groups at 24 h ($P = 0.02$). Three patients in placebo group complained of severe POST compared to

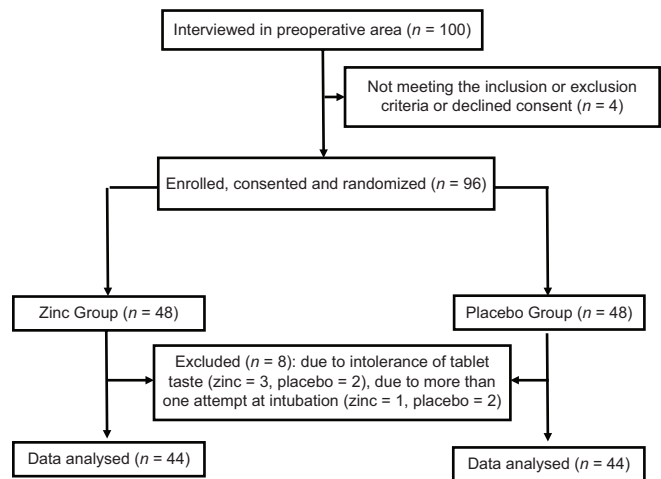


Figure 1: Consort diagram

	Zinc group (n=44)	Placebo group (n=44)	<i>P</i>
Mean age (years)	35.72 \pm 10.4	35.68 \pm 11.50	0.985
Sex (male/female)	22/22 (50%/50%)	27/17 (68.4%/38.6%)	0.283
Weight (kg)	64.74 \pm 11.60	67.73 \pm 11.88	0.237
MP Grade (I/II)	25/19 (56.8%/43.2%)	23/21 (52.3%/47.7%)	0.669
ASA PS (I/II)	34/10 (77.3%/22.7%)	32/12 (72.7%/27.3%)	0.622

MP Grade – Malampatti Grading, ASA PS – American Society of Anesthesiologists Physical Status. Data expressed as number of patients (%) or mean \pm standard deviation. $P < 0.05$ was considered significant. No significant difference was found between the groups

Table 2: Intraoperative events and adverse effects

	Zinc group (n=44)	Placebo group (n=44)	P
Mean duration of laryngoscopy(s)	13.14±3.66	13.09±3.72	0.954
Mean duration of anaesthesia (min)	126.29±27.58	131.68±35.19	0.426
Mean surgery duration (min)	113.41±28.79	118.98±33.31	0.404
CL Grade (I/II/III/IV)	31/12/1/0 (70.5%/27.3%/2.3%/0)	33/10/1/0 (75%/22.7%/2.3%/0)	0.885
Nasogastric tube insertion	19 (43.2%)	17 (38.6%)	0.665
Bucking on ET tube	10 (22.7%)	12 (27.3%)	0.622
NSAID	19 (43.2%)	14 (31.8%)	0.271
Steroid	15 (34.1%)	13 (29.5%)	0.647
PONV	8 (18.2%)	9 (20.5%)	0.787
Diarrhea	1 (2.3%)	2 (4.5%)	0.556

CL Grade – Cormack-Lehane grading, ET tube – Endotracheal tube, NSAID – Nonsteroidal anti-inflammatory drug use, PONV – postoperative nausea and vomiting. Data expressed as number of patients (%) or mean±standard deviation. $P<0.05$ was considered significant. No significant difference was found between the groups

Table 3: Incidence of POST in both groups at different evaluation times

Evaluation time	Zinc group (n=44)	Placebo group (n=44)	P
0 min	1 (2.3%)	12 (27.3%)	0.001*
30 min	2 (4.5%)	15 (34.1%)	<0.001†
2 h	4 (9.1%)	16 (36.4%)	0.002*
4 h‡	3 (6.8%)	14 (31.8%)	0.003*
24 h	7 (15.9%)	15 (34.1%)	0.05 (NS)

NS – Nonsignificant. Data expressed as number of patients (%). $P<0.01$ (Bonferroni correction $0.05/5=0.01$) was considered significant. *Significant. †Highly significant. ‡Primary outcome

none in the zinc group. When comparing overall severity of POST between groups, the incidence of moderate POST was found to be statistically significant. In terms of side effects, no difference in incidences of postoperative nausea, vomiting and diarrhea between the groups was observed.

DISCUSSION

Etiology of POST is multifactorial. Pharyngeal, laryngeal, or tracheal irritation leading to inflammation may be the reason for POST, but it may also occur in absence of tracheal intubation. In the absence of any clearly established single mechanism which leads to POST, treatment with anti-inflammatory agents (e.g., steroids and NSAIDs) to some extent ameliorates the symptoms. Recently magnesium and zinc lozenges have been used to reduce the incidence of POST.^[8,9] Topically applied zinc in the form of a suspension, as well as in the lozenge form, have recently been shown to be as effective as systemic therapy in prevention of mucositis and oral pain associated with chemotherapy.^[15] We used dispersible zinc tablets, because it is easily available in India.

In this study administration of dispersible zinc tablet orally, 30 min before intubation lead to reduced

incidence and severity of POST at 0, 30 min, 2, and 4 h postoperatively. The overall incidence of POST was also lower in Zinc group. Lower incidence of POST in the zinc group is most probably due to prevention of cytokine release, decrease in reactive oxygen species, and a subsequent decrease in cyclooxygenase-2 (COX-2) expression, and prostaglandin-E2 (PGE-2) release.^[18] As there are no studies in context of natural history and duration of POST, it is probable sore throat extending till 24 h and beyond, may have a different mechanism such as direct injury. Also the duration of action of zinc locally is not well established; for upper respiratory therapy it is recommended every 4 h; whereas in oncologic studies mouth washes were given every 6–12 h.^[15,19] The zinc group was not associated with any significant side effects when compared with placebo. The findings of our study with dispersible tablets are very much similar to the previous work by Farhang *et al.*^[9] with zinc lozenges which further validates the potential of zinc in prevention of POST.

Our study has several potential limitations. The sample size is small and the study was not multicentre. Second, the pharmacokinetic data regarding local effects of oral dispersible zinc tablets was not readily available, so the dosage and administration time was empirically based on previous study by Farhang *et al.*^[9] who used zinc lozenges. Third since the tube size was fixed to 7 mm for females and 8 mm for males which may have fit variably among patients of different build and stature.

Further studies are needed with larger sample size to ascertain the exact dosage, timing and frequency of administration. Future studies may also compare lozenges with oral dispersible tablets and zinc with other agents that have been previously used to remedy POST.

Table 4: Severity of POST in both groups at different evaluation times

Evaluation time	Zinc group (n=44)			Placebo group (n=44)			P
	Mild POST	Moderate POST	Severe POST	Mild POST	Moderate POST	Severe POST	
0 min	1 (2.3%)	0	0	9 (20.5%)	2 (4.5%)	0	0.003*
30 min	2 (4.5%)	0	0	11 (25%)	4 (9.1%)	0	0.002*
2 h	4 (9.1%)	0	0	7 (15.9%)	8 (18.2%)	1 (2.3%)	<0.001†
4 h	0	3 (6.8%)	0	2 (4.5%)	9 (20.5%)	3 (6.8%)	0.001*
24 h	7 (15.9%)	0	0	5 (11.4%)	10 (22.7%)	0	0.02 (NS)

NS=nonsignificant, POST=postoperative sore throat Data expressed as number of patients (%) $P < 0.01$ (Bonferroni correction $0.05/5 = 0.01$) was considered significant *Significant. †Highly significant

Table 5: Overall severity of POST in both groups

	Zinc group (n=44)	Placebo group (n=44)	P
Mild POST	6 (13.6%)	6 (13.6%)	1 (NS)
Moderate POST	3 (6.8%)	11 (25%)	0.039*
Severe POST	0	3 (6.8%)	0.241 (NS)

NS=nonsignificant, POST=postoperative sore throat Data expressed as number of patients (%) $P < 0.05$ was considered significant *Significant

CONCLUSION

Prophylactic single dose 40 mg zinc dispersible tablet given 30 min before surgery effectively reduces the incidence and severity of POST in first 4 h after extubation.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form the patient (s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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Nil.

Conflicts of interest

There are no conflicts of interest.

REFERENCES

- Najafi A, Imani F, Makarem J, Khajavi MR, Etezadi F, Habibi S, *et al.* Postoperative sore throat after laryngoscopy with macintosh or glide scope video laryngoscope blade in normal airway patients. *Anesth Pain Med* 2014;4:e15136.
- Lee JY, Sim WS, Kim ES, Lee SM, Kim DK, Na YR, *et al.* Incidence and risk factors of postoperative sore throat after endotracheal intubation in Korean patients. *J Int Med Res* 2017;45:744-52.
- Sumathi PA, Shenoy T, Ambareesha M, Krishna HM. Controlled comparison between betamethasone gel and lidocaine jelly applied over tracheal tube to reduce postoperative postoperative sore throat, cough, and hoarseness of voice. *Br J Anaesth* 2008;100:215-8.
- Ahuja V, Mitra S, Sarna R. Nebulized ketamine decreases incidence and severity of post-operative sore throat. *Indian J Anaesth* 2015;59:37-42.
- Thapa P, Shrestha RR, Shrestha S, Bajracharya GR. Betamethasone gel compared with lidocaine jelly to reduce tracheal tube related postoperative airway symptoms: A randomized controlled trial. *BMC Res Notes* 2017;10:361.
- Rajan S, Tosh P, Paul J, Kumar L. Effect of inhaled budesonide suspension, administered using a metered dose inhaler, on post-operative sore throat, hoarseness of voice and cough. *Indian J Anaesth* 2018;62:66-71.
- Thomas D, Bejoy R, Zabrin N, Beevi S. Preoperative ketamine nebulization attenuate the incidence and severity of postoperative sorethroat: A randomized controlled clinical trial. *Saudi J Anaesth* 2018;12:440-5.
- Borazan H, Kececioglu A, Okesli S, Otelcioglu S. Oral magnesium lozenge reduces postoperative sore throat: A randomized, prospective, placebo-controlled study. *Anesthesiology* 2012;117:512-8.
- Farhang B, Grondin L. The effect of zinc lozenge on postoperative sore throat: A prospective randomized, double-blinded, placebo-controlled study. *Anesth Analg* 2018;126:78-83.
- Singh NP, Makkar JK, Wourms V, Zorrilla-Vaca A, Cappellani RB, Singh PM. Role of topical magnesium in post-operative sore throat: A systematic review and meta-analysis of randomised controlled trials. *Indian J Anaesth* 2019;63:520-9.
- Truong-Tran AQ, Carter J, Ruf'n R, Zalewski PD. New insights into the role of zinc in the respiratory epithelium. *Immunol Cell Biol* 2001;79:170-7.
- Worthington HV, Clarkson JE, Bryan G, Furness S, Glenny AM, Littlewood A, *et al.* Interventions for preventing oral mucositis for patients with cancer receiving treatment. *Cochrane Database Syst Rev* 2010:CD000978. doi: 10.1002/14651858.CD000978.
- Sharir H, Zinger A, Nevo A, Sekler I, Hershinkel M. Zinc released from injured cells is acting via the Zn²⁺-sensing receptor, ZnR, to trigger signaling leading to epithelial repair. *J Biol Chem* 2010;285:26097-106.
- Rostan EF, DeBuys HV, Madey DL, Pinnell SR. Evidence supporting zinc as an important antioxidant for skin. *Int J Dermatol* 2002;41:606-11.
- Hayashi H, Kobayashi R, Suzuki A, Yamada Y, Ishida M, Shakui T, *et al.* Preparation and clinical evaluation of a novel lozenge containing polaprezinc, a Zinc-L-carnosine, for prevention of oral mucositis in patients with hematological cancer who received high-dose chemotherapy. *Med Oncol* 2016;33:91.

16. Loeser EA, Bennett GM, Orr DL, Stanley TH. Reduction of postoperative sore throat with new endotracheal tube cuffs. *Anesthesiology* 1980;52:257-9.
17. Christensen AM, Willemoes-Larsen H, Lundby L, Jakobsen KB. Postoperative throat complaints after tracheal intubation. *Br J Anaesth* 1994;73:786-7.
18. Kim J, Kim S, Jeon S, Hui Z, Kim Y, Im Y, *et al.* Anti-inflammatory effects of zinc in PMA-treated human gingival fibroblast cells. *Med Oral Patol Oral Cir Bucal* 2015;20:e180-7.
19. Arbabi-kalati F, Arbabi-kalati F, Deghatipour M, Ansari Moghadam A. Evaluation of the efficacy of zinc sulfate in the prevention of chemotherapy-induced mucositis: A double-blind randomized clinical trial. *Arch Iran Med* 2012;15:413-7.



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