

Effectiveness of Preoperative Zinc Lozenges for Reduction of Post Operative Sore Throat in Patients Receiving General Anesthesia - A Prospective Randomized Placebo-Controlled Study

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Received: 19-06-2023 / Revised: 18-07-2023 / Accepted: 20-08-2023

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Conflict of interest: Nil

Abstract:

Background: Post operative sore throat (POST) is a very common complication among patients undergoing general anesthesia. Though not very serious but it can significantly reduce patient satisfaction and delay in discharge after day care surgery and reduce turn over. Several methods had been used in the past to reduce its incidence. A novel approach is use of zinc lozenges preoperatively utilizing its anti-inflammatory properties to reduce the incidence of POST.

Methods: This study was designed as randomized placebo-controlled trial with hundred and eight patients, divided into two groups, each containing fifty-four patients. One group received 75 mg zinc lozenges and other group received placebo. Each patient was assessed for development of POST on a 4-point scale (0-3) at different time interval. Primary objective was to determine severity of POST at 4 hours after surgery. We also determined incidence and severity of POST at 0 minutes, 30 minutes, 6 hour and 24 hour after surgery

Result: 3.7% of patients in zinc group developed POST, compared to 48.14% in placebo group ($P < 0.001$) in 4 hour. Overall incidence of POST was 13% in zinc group with a reduction of 52% from placebo group (64.8%). During initial hours zinc reduced incidence of mild POST, but at 4 hours reduction of severe POST occurred. At 24-hour reduction of POST was not significant.

Conclusion: Preoperative oral administration of 75mg zinc lozenges reduces the incidence of POST during initial postoperative hours (up to 6 hour), with significant reduction of mild POST during first 30 minutes and severe POST in 4 hour time point.

Keywords: Zinc lozenges, Post Operative Sore Throat, Endotracheal intubation.

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Introduction

Endotracheal intubation is an important component of general anesthesia. Postoperative sore throat (POST) is the second most prevalent complaint among patients receiving general anesthesia with endotracheal intubation, second only to nausea and vomiting. [1] Though it is considered a minor event, but it can significantly change the patient satisfaction score and delay in discharge from hospital, especially after day care surgery, which is considered very important now a days for rapid turnover & effective utilization of resources. [2] Reported incidence of POST is quite high in post operative patients ranging from 10% to 58% depending on the endotracheal tube cuff design. [3] Several methods have been used for the reduction of POST, like using smaller size endotracheal tube, designing cuff which is having less contact area with tracheal mucosa, maintaining intracuff pres-

sure, lignocaine gargle or sprays, preoperative oral magnesium lozenges, prophylactic topical magnesium application etc. Magnesium is used here for its anti-inflammatory & anti-nociceptive properties. [4]

Zinc is micronutrient metal which has various activities including growth promotion, tissue repair and anti-inflammatory properties. [5] Recently resurgence in the use of oral zinc occurred during COVID-19 pandemic, utilizing its anti-inflammatory properties on respiratory tract mucosa. [6] Zinc has long been used in varying dose strength (75-600 mg/day) for 2-3 weeks for the treatment of post chemotherapy induced oral mucosal inflammation & to relieve oral pain, for common cold and for healing of venous ulcer without any side effect. [7,8]

Farhang B *et al* first reported a novel use of zinc lozenges for prevention of POST in 2018. [9] Which was followed by only one more study with dispersible zinc tablet at this point of time. [10] Both the studies used 40 mg zinc. In our study we used single dose of Zinc 75 mg, with an assumption that it will cause more reduction of incidence of POST, without causing any adverse effect. We choose lozenges form because of its better effects on oropharyngeal mucosa.

We hypothesized that oral administration of 75mg zinc lozenges 30 minutes before intubation will reduce incidence of POST for 24 Hour after surgery, where POST was caused by endotracheal intubation, because of Zinc's properties on tissue repair and anti-inflammatory action.

Materials & Methods:

This study was carried out after getting approval by the Institutional Ethical Board and registration with CTRI (CTRI/2023/03/05110, Registered on: 28/03/2023). Study was designed as a prospective, randomized, double-blinded placebo controlled trial. Randomization was achieved by using a computer-generated random number table and sealed envelope method to receive either zinc sulphate lozenges or a placebo which was similar in appearance and taste containing vegan, inert microcrystalline cellulose (corn starch), free of sugar or dyes. Investigator, patient & anaesthesiologists were kept blinded about group allocation.

This study was conducted on hundred-eight patients of either sex between age group of 18-60, with American Society of Anaesthesiologists Physical Status (ASA-PS) I & II, posted for elective surgeries requiring endotracheal intubation, with expected surgical duration of one to six hours. Minimum duration of one hour surgery was chosen to ensure enough irritation of airway mucosa to cause POST. During pre anesthetic check-up we interviewed hundred and twenty patients and 108 patients who meet the inclusion criteria and gave consent were enrolled for the study. They were divided into two groups containing 54 each (one group received Zinc & the other received placebo).

Patients with head & neck surgeries, history of preoperative sore throat, history of difficult intubation, Malampatti Grade more than II, known allergy to zinc were excluded from the study.

After taking written informed consent with all the risks explained, in the preoperative room each patient was provided with a sealed coded envelope containing either zinc sulphate (containing 75 mg of elemental zinc) or placebo (as described above) and instructed to dissolve the lozenges orally by sucking completely 30 minutes preoperatively. No sedation was given in preoperative room. Then

patients were transferred to operating room and standard American Society of Anaesthesiologists monitors were applied. General Anaesthesia was induced and muscle relaxant given and endotracheal intubation done by a single anaesthetist with more than five years' experience for all cases (to exclude confounding variable of experience). 7 mm cuffed endotracheal tube for females and 8 mm cuffed tube for males were given. Initial intracuff pressure was measured and maintained at 20-24 cm of H₂O throughout the procedure. O₂ and N₂O with inhalational agent used for all procedure. Duration of laryngoscopy, number of attempts, Cormack-Lehane Laryngoscopic view, presence of oropharyngeal bleeding were all recorded. All patients received 1 gm Paracetamol. Dexamethasone use & total fentanyl dose recorded. During extubation bucking (coughing on endotracheal tube) recorded. At the end of surgery patient extubated and shifted to post anaesthesia care unit (PACU). Total duration of anaesthesia & duration of operation recorded. Immediately on arrival at PACU each patient was assessed for the presence of POST (0 Hour), using a standardized scale. Severity of POST was graded on a 4 point scale (0 to 3) [3]. 0= No POST (no sore or scratchy throat and no evidence of hoarseness), 1= Mild POST (minimal or scratchy throat, patient tell only on questionnaire & no hoarseness), 2=Moderate POST (moderate scratchy throat, which patient complaints on their own and/or some hoarseness), 3=Severe POST (severe scratchy throat and hoarseness) and evaluated at 0 Hour, 30 minutes, 4 Hour, 6 Hour & 24 Hour.

Primary outcome of our study was the incidence of POST at 4 Hour, as the onset of anti-inflammatory action of zinc lozenges is between 30 minutes to 4-6 hours. [5] Any side effects like nausea, vomiting, metallic taste, diarrhoea noted during each evaluation.

Data were analysed using Statistical Package for Social Sciences (SPSS) version 29 (International Business Machines SPSS Statistics Inc., Chicago, Illinois, USA) Mac software program. Descriptive analysis for patient demographics and intraoperative events was carried out by mean and standard deviation for quantitative variables, frequency and proportion for categorical variables. Continuous variables analysed using Man-Whitney U test and categorical variables analysed using Chi-square/Fisher's Exact test. During the 24 hour evaluation period Incidence of POST between two groups compared using the Chi-square test/Fisher's Exact Test. A P value of <0.0125 was considered statistically significant after doing Holm-Bonferroni correction (0.05/4=0.125) to reduce family wise Type I error. For analysing severity of POST over time in between groups P<0.008 (0.05/6) was considered significant. From previous

studies. [3,11] we took the incidence of POST to be 52.2%. Using power analysis, sample size calculation revealed that 54 patients per group would be required to detect a 50% reduction in the incidence of POST, with $\alpha = .05$ and $\beta = .20$ for 2-tailed statistical analysis.

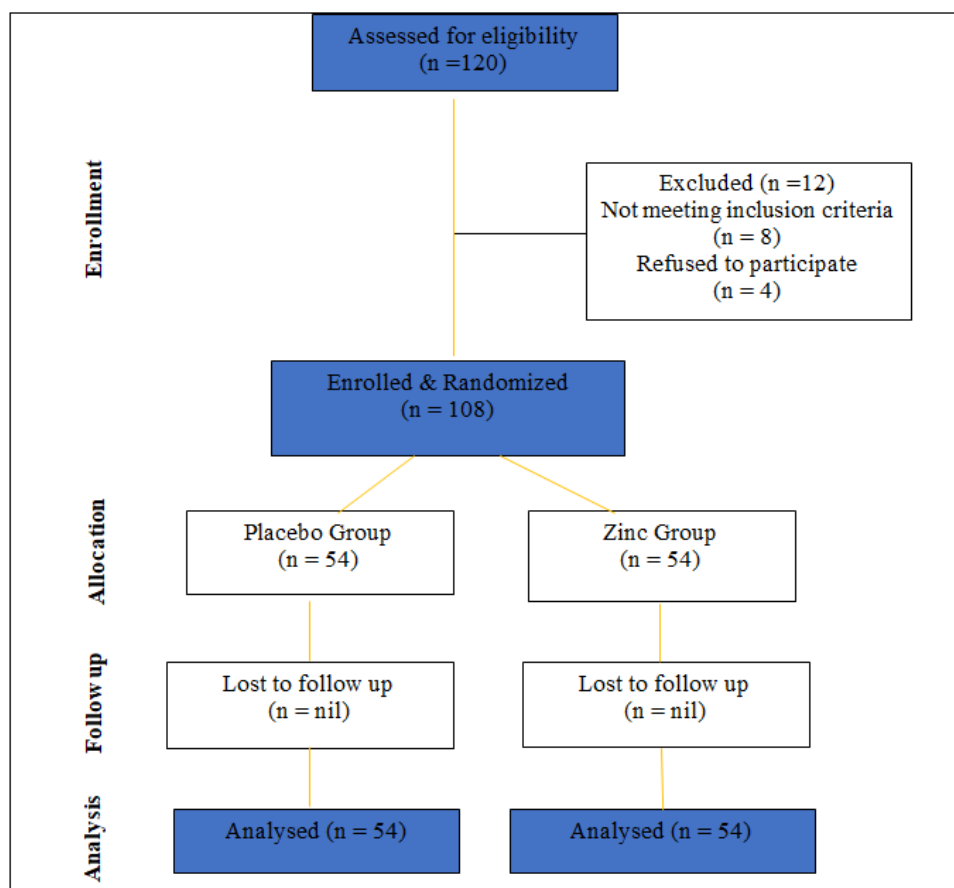
Results

Demographic and intraoperative variables compared in Table 1 & 2 respectively shows there were no significant differences between the groups ($P \leq 0.05$). Overall incidence of POST was significantly lower in zinc group (13%) compared to placebo (63.8%) with $P=0.0000000326$ (Figure 1)

Incidence of POST between the groups compared at different time interval shown in Table 3 & Figure 2. At time 0 zinc group had nil incidence of POST, whereas in placebo it was 27.7% (as value in one

group is 0 so OR can't be calculated) with p-value 0.001. At 30 minutes incidence of POST in zinc group was 1.8%, compared to 29.6% in placebo group, with OR 22.316 (95% CI 2.836, 175.579). At 4 hour incidence of POST in Zinc group 3.7% compared to 48.14% at placebo group with OR 24.143 (95% CI 5.334-109.268). At time point 24 hour after operation there was not much significant difference between the two groups, with OR 3.250 (CI 0.626-16.884). Maximum reduction of POST occurred in 4 Hour, with no significant effect at 24 hour, indicating cause of POST may be different at 24 hour.

Figure 3 & Table 4 shows comparison of severity of POST at different time point. Maximum reduction of incidence of severe POST occurred at 4 hour with nil incidence in zinc group and 22% incidence of severe POST in placebo group with $P=0.000238$,



Consort flow diagram

Table 1. Comparison of demographic variables

Group	Zinc	Placebo	P- value
Mean age (year)	45.83 ± 11.543	44.00 ± 11.813	0.395
Weight (Kg)	65.44 ± 8.711	65.37 ± 9.060	0.485
Gender(M/F)	22/32 (40.7%/59.3%)	31/23 (57.4%/42.6%)	0.123
Malampatti Grade(I/II)	32/22 (59.3%/40.7%)	24/30 (44.4%/55.6%)	0.177
ASA-PS classification(I/II)	30/24 (56%/44%)	35/29 (65%/35%)	0.432
Hypertension	19(35%)	23(43%)	0.554

Diabetes	17(31%)	19(35%)	0.838
GERD	15(27%)	12(21%)	0.657
Smoking	20(37%)	17(31%)	0.685

ASA-PS- American Society of Anaesthesiology- Physical Status,
GERD- Gastro Oesophageal Reflux Disorder

Table 2. Comparison of intraoperative events

Group	Zinc	Placebo	P- value
Mean duration of anaesthesia (Min)	82.7□14.36	79.28□13.143	0.103
Mean duration of surgery (Min)	71.2□12.129	68.98□11.549	0.269
Duration of laryngoscopy(seconds)	23.61□4.668	24.5□4.563	0.217
CL grading(I/II/III)	35/10/9	33/12/9	0.887
Dexamethasone	30(55.5%)	39(72.2%)	0.108
Mean fentanyl dose	107.78□11.27	105.74□11.09	0.430
Traumatic laryngoscopy	3((0.05%)	5(0.09%)	0.716
Initial cuff pressure	21.3□1.075	21.09□0.853	0.430
NG tube	6(11%)	8(15%)	0.776
Bucking/coughing on extubation	21(39%)	24(44%)	0.696

CL grading- Cormack Lehane Grading
NG tube- Naso Gastric tube

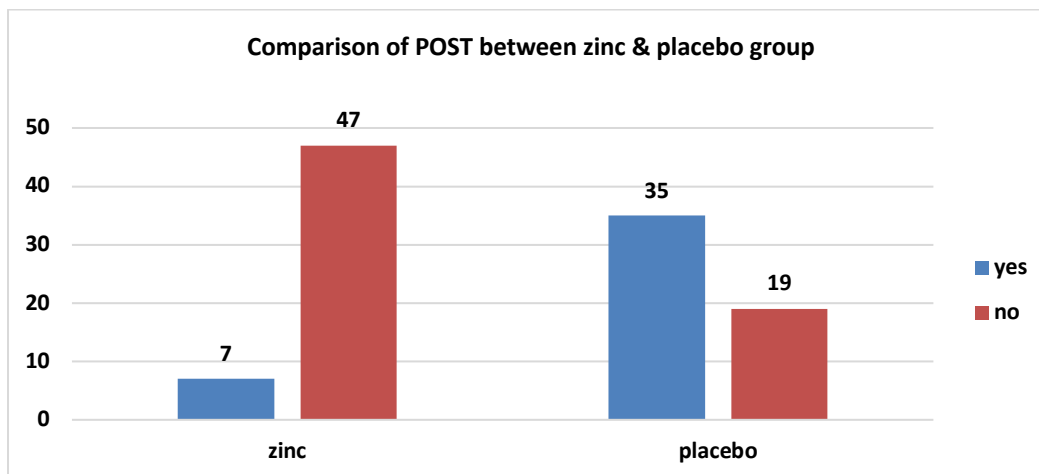


Figure 1. Comparison of overall incidence of Post

In zinc group it was 7(13%) and in control group it was 35(64.8%). Odds of developing POST in placebo group was 12.368 (95% CI 4.685, 32.653) with P-0.0000000326. Incidence of POST and placebo treatment were significantly associated on chi-

square test , with test statistics value $\chi^2 = 30.545$ with df 1 and a strong strength of Phi Φ 0.532

POST- Post Operative Sore Throat, df- degree of freedom , CI- confidence interval

Table 3. Incidence of POST at different time interval

	Group		P- value	OR	CI
	Zinc(n=54)	Placebo(n=54)			
0 minutes	0	15(27.7%)	0.0000299†	NA	NA
30 minutes	1(1.8%)	16(29.6%)	0.000739†	22.316	2.836,175.579
4 Hour	2(3.7%)	26(48.14%)	0.000000136†	24.143	5.334,109.268
6 Hour	3(5.5%)	16(29.6%)	0.001†	7.158	1.946,26.335
24 Hour	2(3.7%)	6(11.1%)	0.142	3.250	0.626,16.884

OR- Odds Ratio, CI- Confidence Interval

†-Significant P-value was set at 0.0125 after using Holm-Bonferroni correction (0.05/4) to reduce chances of familywise Type I error.

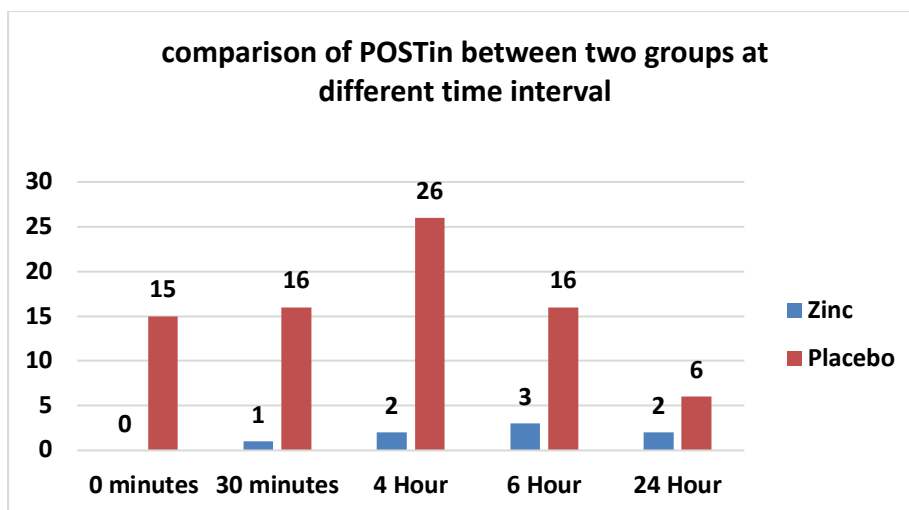


Figure 2. Incidence of POST at different time interval

At time 0 zinc group had incidence of 0, whereas in placebo it was 27.7%, as value in one group is 0 so OR can't be calculated with p- value 0.001. At 30 minutes incidence of POST in zinc group is 1.8%, compared to 29.6% in placebo group, with OR 22.316 (95% CI 2.836, 175.579). At 4 hour incidence of POST in Zinc group 3.7% compared to 48.14% at placebo group with OR 24.143(95%

CI 5.334, 109.268). At time point 24 hour after operation there was not much significant difference between the two groups, with OR 3.250(CI 0.626, 16.884), showing maximum reduction POST in 4 Hour, with no significant effect at 24 hour, indicating cause of POST may be different at 24 hour.

Table 4. Comparison of severity of POST at different time point

Time interval	Mild POST	Moderate POST	Severe POST
0 Hr			
Zinc (n=55)	0	0	0
Placebo (n=55)	7(12.7%)	6(11%)	0
P- value	0.0009 [†]	0.022	NS
Odds ratio with 95% Confidence Interval	NA	NA	NA
30 minutes			
Zinc(n=55)	1(1.8%)	0	0
Placebo(n=55)	10(18.5%)	6(11%)	0
P-value	0.004 [†]	0.013	NS
Odds ratio with 95% Confidence Interval	10.0 (1.326-75.438)	NA	NA
4 Hour			
Zinc(n=55)	1(1.8%)	1(1.8%)	0
Placebo(n=55)	8(14.8%)	6(11%)	12(22.2%)
P-value	0.0148	0.0506	0.000238 [†]
Odds ratio with 95% Confidence Interval	8.0 (1.036-61.793)	6.0 (0.747-48.177)	NA
6 Hr			
Zinc(n=55)	0	2(3.6%)	1(1.85%)
Placebo(n=55)	4(7.3%)	10(18.5%)	2(3.7%)
P-value	0.059	0.014	0.5
Odds ratio with 95% Confidence Interval	NA	5.0 (1.149-21.759)	2.0 (0.187-21.408)
24 Hr			
Zinc(n=55)	3(5.5%)	0	0
Placebo(n=55)	2(3.7%)	4(7.4%)	0
P-value	0.5	0.059	NS
Odds ratio with 95% Confidence Interval	1.529 (0.245-9.538)	NA	NA

[†] - P-value significant. Significant P-value was set at 0.008 after using Holm-Bonferroni correction (0.05/6) to reduce chances of familywise Type I error.

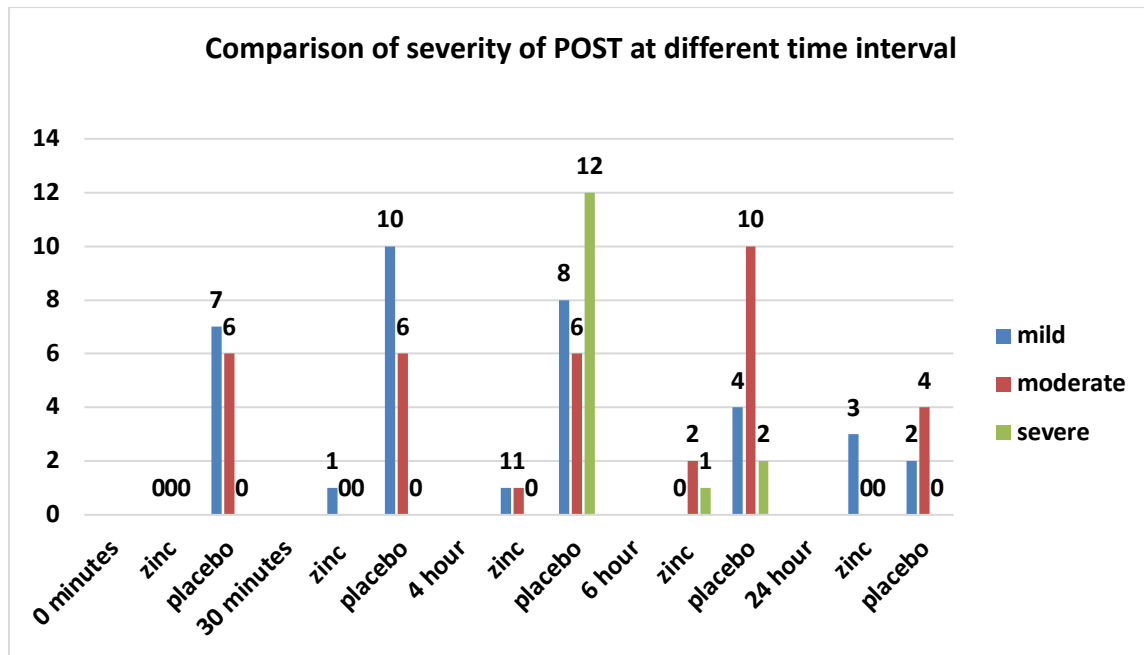


Figure 3. Comparison of severity of POST in two groups at different time points

Discussion

It was known that pharyngeal, laryngeal, or tracheal irritation leading to inflammation may be the cause for POST, but POST may occur even in the absence of tracheal intubation. [12,13] Multiple factors are involved for development of POST like gender (Female preponderance), endotracheal tube and cuff design, size and cuff pressure, duration of intubation, trauma during laryngoscopy etc. [14,15] So it is difficult to determine whether POST is occurring because of aseptic inflammation of airway mucosa or localized trauma leading to congestion and oedema of airway. Steroids, nonsteroidal anti-inflammatory drugs and opioids have beneficial effect in reducing incidence of POST. [13]

In a previous study, Thomas *et al.* showed that intravenous dexamethasone reduced POST significantly. [16] A Kuriyama *et al.* showed compared to lignocaine, corticosteroids applied to tracheal tubes were associated with reduced incidence of postoperative sore throat. [17] In another study, Chang *et al.* showed preoperative benzydamine hydrochloride gargles significantly reduced the incidence of POST after tracheal intubation using double lumen tube. [18] Hale Borazan *et al.* studied the effects of oral magnesium preoperatively on the incidence of POST and found a significant reduction of the incidence of POST. [4]

Farhang B *et al.* used 40 mg of oral zinc preoperatively to reduce the incidence of POST. He showed 58% reduction in incidence of POST in zinc group (18% incidence in zinc group vs. 43% in placebo group with P=0.003).

All of these studies suggested that the reduction in the incidence and severity of POST was related with anti-inflammatory effects of the drugs administered.

Zinc is an essential mineral which is a part of many enzyme systems that are necessary for cell proliferation during cell repair, especially in superficial layers of tissues. Therefore, it is required for wound healing of the skin, connective tissue, and intestinal lining, particularly epithelial tissue. The primary mechanisms of action are thought to be related to its anti-inflammatory and antioxidant functions. Zinc reduces inflammatory cytokines, such as interleukin-1 β , interleukin-8, interleukin-6, and tumour necrosis factor in a dose-dependent manner. [19]

Overall incidence of POST in our study was 13% in zinc group and 64.8% in control group with 52% reduction. There is more reduction of incidence of POST compared to study conducted by Farhang B *et al.* In our study zinc group had significantly lower incidence of POST up to 6 hours, but after that in 24 hour the difference was not significant. We found zinc was most significantly beneficial in reducing POST in 4 hour time point with an incidence of 3.7%, compared to 48.14% in placebo group with almost 44% reduction. Zinc reduced incidence of only mild POST during the initial hours (up to 30 minutes). At 4 hours though it reduced overall incidence and severity of POST, but reduction of mild & moderate POST was not significant which was contrary to the study conducted by Farhang B *et al.*, who found significant reduction of mild and moderate POST, but not severe POST. From 6 hours onwards its efficacy reduced, which may be because of

termination of action of single dose and different aetiology involved in causing POST after 6 hours.

Conclusion

In conclusion a single dose of 75 mg oral zinc 30 minutes preoperatively can significantly reduce the incidence of POST in the first 4 hour after intubation.

Though we found more reduction of incidence of POST using 75 mg Zinc, compared to 40 mg used in a previous study, a comparative trial will be required to determine whether this difference is really significant, and what will be the optimum dose of zinc tablet for significant reduction of POST with a larger sample size.

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