

Zinc Supplementation in Adult Mechanically Ventilated Trauma Patients is Associated with Decreased Occurrence of Ventilator-associated Pneumonia: A Secondary Analysis of a Prospective, Observational Study

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Abstract

Background: Ventilator-associated pneumonia (VAP) is a type of lung infection that typically affects critically ill patients undergoing mechanical ventilation (MV) in the Intensive Care Unit (ICU). The aim of this analysis is to determine potential association between zinc supplementation with the occurrence of VAP in adult mechanically ventilated trauma patients. **Subjects and Methods:** This secondary analysis of a prospective observational study was carried out over a period of 1 year in ICUs of one teaching hospital in Iran. A total of 186 adults mechanically ventilated trauma patients, who required at least 48 h of MV and received zinc sulfate supplement ($n = 82$) or not ($n = 104$) during their ICU stay, were monitored for the occurrence of VAP until their discharge from the ICU or death. **Results:** Forty-one of 186 patients developed VAP, 29.09 days after admission (95% confidence interval [CI]: 26.27–31.9). The overall incidence of VAP was 18.82 cases per 1000 days of intubation (95% CI: 13.86–25.57). Patients who received zinc sulfate supplement have smaller hazard of progression to VAP than others (hazard ratio: 0.318 [95% CI: 0.138–0.732]; $P < 0.0001$). **Conclusion:** The findings show that zinc supplementation may be associated with a significant reduction in the occurrence of VAP in adult mechanically ventilated trauma patients. Further well-designed randomized clinical trials to confirm the efficacy of this potential preventive modality are warranted.

Key words: Intensive Care Units, supplementation, ventilator-associated pneumonia, zinc sulfate

INTRODUCTION

Ventilator-associated pneumonia (VAP) is an important complication in patients who need mechanical ventilation (MV).^[1] VAP is the most common infection among patients undergoing MV and has been associated with increased mortality (approaching 50%), morbidity, duration of MV, and length of Intensive Care Unit (ICU) stay. Despite advances in preventive strategies, such as the implementation of VAP bundle and Centers for Disease Control and Prevention recommendations in critical care, the mortality and morbidity rate still requires substantial improvement.^[1,2]

It is believed that critical illness stress-induced immune suppression plays an important role in the development of hospital infections.^[3] Insufficient zinc levels have been

suggested to play a role in stress-induced lymphopenia, and consequent immune suppression. Zinc is a crucial mineral for many biological functions in humans.^[3,4] A number of studies have been performed in children and elderly, clearly demonstrated the beneficial impact of zinc supplementation on immune function and the prevention of pulmonary infections;^[5-7] however, the association between zinc supplementation

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and occurrence of VAP remains unknown. In addition, an inverse correlation between serum zinc concentrations and Sequential Organ Failure Assessment (SOFA) scores has been demonstrated in critically ill patients. It is believed that critical illness can lead to a decline in serum zinc concentrations.^[8]

Substantial benefits that exist in VAP prevention in critically ill patients^[9] and also the paucity of information in the literature about the association of zinc supplementation and VAP development encouraged us to do this secondary analysis of a prospective observational study. We aimed for the first time to assess the association of zinc supplementation and the development of VAP in critically ill trauma patients undergoing MV admitted to ICU.

SUBJECTS AND METHODS

Study design

This is a secondary analysis of a prospective, observational study conducted in three general ICUs of a 1000-bed medical center in Sari, Northern Iran, which serves as a regional referral center for trauma patients. Approval of the institutional review board and informed consent from the patient family were obtained for this prospective study between September 22, 2012, and September 23, 2013, to determine the incidence, risk factors, and outcome of VAP in the ICUs.

Patients and follow-up

All traumatic patients aged >18 years without pneumonia at ICU admission, who required at least 48 h of MV were included. Patients who were undergoing MV before admission to ICU or those who died within 48 h of starting MV were excluded. A group of attending physicians and nurses prospectively collected data on all patients who undergoing MV. They take relevant data from medical documents, bedside flow sheets. Moreover, the clinical pulmonary infection score (CPIS) was calculated for diagnosis of VAP. Patients were assessed every day (at morning; every 24 h) during the study period. Patients were followed until ICU discharge or death. Only the first episode of VAP was evaluated in this study. All the patients undergoing MV routinely received stress ulcer prophylaxis (ranitidine, 50 mg intravenous [IV] three times a day) and IV antibiotic prophylaxis for 24–36 h. Administered antibiotic prophylaxis was based on hospital routine, including cefalotin (1 g, divided into four doses a day) for mechanically ventilated adult trauma patients.

In our ICUs, some intensivist prescribes zinc supplement for the mechanically ventilated trauma patients on a routine basis, while the others do not this. In patients who received the zinc supplements in the period of our study, the dose of zinc sulfate supplement was between 60 and 90 mg/day (supranutritional dose) and received it through nasogastric tube.

Data collection and baseline data

Baseline demographic data (sex, age, body mass index [BMI], date of admission to the ICU), primary diagnosis, underlying illness, type of tracheal intubation (elective/emergency),

number of re-intubation, history of hypertension (HTN), chronic obstructive pulmonary disease (COPD), diabetes mellitus (DM), limitation in positional changes, enteral nutrition (gavage feeding), gastric residual volume, ICU and hospital length of stay, intubation duration, number of transportation out of ICU, Glasgow coma scale (GCS; with ventilatory support and with or without sedation), duration of MV and using of zinc sulfate orally were collected for all patients.

Ventilator-associated pneumonia diagnosis

The diagnosis of VAP was according to original CPIS after at least 48 h of initiation of MV. CPIS developed in 1991 and is including a new chest X-ray infiltrate persistent for 48 h or more plus a body temperature more than 38.58°C or <35.08°C, changes in white blood cell count as a leukocyte count of more than 10,000 (cells/mm³) or <3000 (cells/mm³), worsening hypoxia (arterial oxygenation/fraction inspired oxygen ratio ≤ 240) without acute respiratory distress syndrome, a purulent tracheal secretions and microorganisms isolated from at least one of the following samples: Bronchoalveolar lavage (BAL; $\geq 10,000$ CFU/ml), endotracheal aspirate (ETA; $\geq 100,000$ CFU/ml), or sputum.^[10,11] Semi-quantitative ETA or BAL samples of suspected cases of VAP were collected from ICU patients in this study.^[12] The CPIS scores range from 0 to 12 and scores higher than 6 indicate VAP. Validity and reliability of the Persian version of the CPIS score are confirmed, and it is used widely in research studies to appraise suspected VAP in several studies.^[13,14]

Data analysis

After data collection and initial data analysis, we observed a significant trend toward a higher incidence of VAP, developing over the course of MV in patients who did not receive zinc sulfate supplement. To estimate if there was an independent association between zinc sulfate supplement and development of VAP, we performed a second analysis. Cumulative survival curve was calculated using the Kaplan–Meier method and was compared by use of log-rank tests. All statistically marginally significant prognostic factors which identified by univariate analysis ($P < 0.1$) were entered into a Cox proportion hazards regression model with forward stepwise (Likelihood ratio) to identify independent predictors of VAP event. For all analyses, P values were two-sided, and $P < 0.05$ was considered statistically significant. All statistical analyses and graphics were performed using SPSS software package (version 16.0, SPSS Inc., Chicago, IL, USA) and STATA version 10 (StataCorp, College Station, TX, USA).

RESULTS

During the study, 186 patients required MV for more than 48 h; of these, 82 patients received zinc supplementation and 104 patients did not receive. Basic and clinical characteristics of patients who received zinc sulfate or not are shown in Table 1. As shown in Table 1, there was no significant difference in terms of gender, age, BMI, COPD, limitation in positional changes, tracheal intubation, and GCS between

patients who received zinc sulfate and patients who did not receive it. However, there were significant differences in terms of HTN and gavage feeding between groups [Table 1].

Among all 186 patients who assessed during the study, VAP developed in 41 patients, corresponding to 18.82 (95% confidence interval [CI]: 13.86–25.57) VAP cases per 1000 days of intubation (10.9 [95% CI: 32.16–38.09] and 30.7 [95% CI: 15.18–21.01] VAP cases per 1000 days of intubation in patients who received zinc sulfate and patients who did not received it, respectively).

The mean age was 47.81 years (± 21.7), mean duration of admission; ICU stay and intubation were 17.16 days (± 13.34), 16.2 days (± 13.19), and 11.71 days (± 7.56) respectively. The vast majority of our patients were males with 30–65 years old

Table 1: Basic and clinical characteristics of patients according to zinc sulfate receiving state			
Variables	Zinc supplementation		P
	Yes (n=82), n (%)	No (n=104), n (%)	
Gender			
Female	32 (39)	32 (30.8)	0.2
Male	50 (61)	72 (69.2)	
Age (year)			
<30	20 (24.4)	22 (21.2)	0.7
30-65	42 (51.2)	52 (50)	
>65	20 (24.4)	30 (28.8)	
BMI (kg/m ²)			
<18.5	4 (5.6)	6 (6.4)	0.7
18.5-22.99	18 (25)	22 (23.4)	
23-27.49	42 (58.3)	50 (53.2)	
>27.5	8 (11.1)	16 (17)	
HTN			
Yes	10 (12.2)	4 (3.8)	0.03
No	72 (87.8)	100 (96.2)	
COPD			
Yes	8 (9.8)	6 (5.8)	0.3
No	74 (90.2)	98 (94.2)	
DM			
Yes	10 (12.2)	22 (21.2)	0.1
No	72 (87.8)	82 (78.8)	
Patients with limitation in positional changes			
Yes	32 (39)	52 (50)	0.1
No	50 (61)	52 (50)	
Tracheal intubation			
Elective	20 (23.8)	30 (28.8)	0.1
Emergency	64 (76.2)	74 (71.2)	
GCS score			
≤7	40 (48.8)	50 (48.1)	0.5
>7	42 (51.2)	54 (51.9)	
Gavage feeding			
Yes	56 (68.3)	46 (44.2)	0.01
No	26 (31.7)	58 (55.8)	

BMI: Body mass index; HTN: Hypertension; COPD: Chronic obstructive pulmonary disease; GCS: Glasgow coma scale; DM: Diabetes mellitus

and overweight [Table 2]. The median time from hospitalization to VAP was 29.09 days (95% CI: 26.27–31.9) and these time according to patient characteristics are shown in Table 2.

Median time from hospitalization to VAP development was higher in female, middle age year's old, nondiabetic, with no limitation in positional changes, high GCS and zinc sulfate prescribed patients. Cox proportion hazards regression model revealed that after adjusting of other variables, patients who received zinc supplement have smaller hazard of progression to VAP than others (hazard ratio: 0.318 [95% CI: 0.138–0.732]; $P < 0.0001$) [Table 3]. This assumption of the Cox PH model was evaluated with the Schoenfeld residuals method, and we saw that the plot of the residuals were horizontal and close to 0. ICU mortality rates in patients who received zinc sulfate and patients who did not received it, were 26.8% and 32.6%, respectively (odd ratio [OR]: 0.7; 95% CI: 0.39–1.42; $P = 0.3$).

However, Table 3 shows that patients with limitation in positional changes versus patients with no limitation (3.68; 95% CI: 1.78–7.6; $P < 0.0001$), diabetic patients (versus nondiabetic) (11.14; 95% CI: 5.23–23.73; $P < 0.0001$), aging patients versus lesser than 30-year-old patients (2.86; 95% CI: 1.18–2.08; $P = 0.005$), thin (7.4; 95% CI: 1.35–40.64; $P = 0.021$), and overweight (2.48; 95% CI: 1.145–5.374; $P = 0.021$) patients versus normal weight patients have higher hazard of progression to VAP.

A survival curve of 186 patients with different characteristics of zinc sulfate supplement prescription was shown in Figure 1.

DISCUSSION

A major finding of this secondary analysis was that the patients who received zinc sulfate supplement had significantly lower incidence of VAP compared with the other patients who did not receive this supplement. This study also demonstrated that the limitation in positional changes, DM, age, and overweight are also as risk factors for the development of VAP.

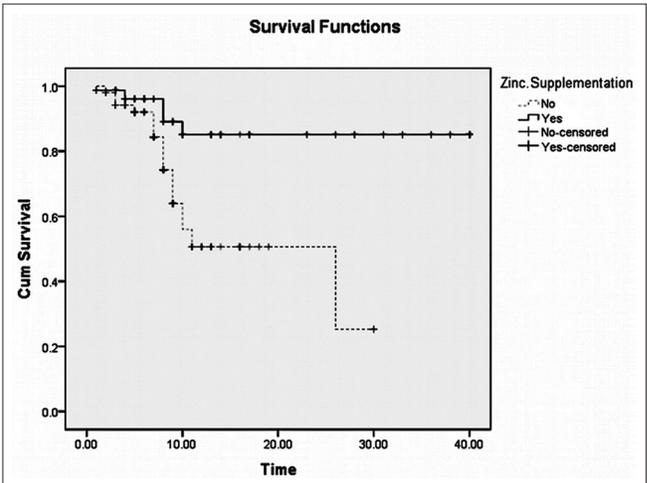


Figure 1: Survival curves of 186 patients with different state of zinc sulfate supplement prescription.

Table 2: Median (95% confidence interval) time to the progression of ventilator-associated pneumonia (Kaplan-Meier method) in Intensive Care Unit patients according to the possible prognostic factors

Variables	n (%)	Median (95% CI)	P [†]
Gender			
Female	64 (34.4)	36.28 (33.09-39.46)	<0.0001
Male	122 (65.6)	24.86 (21.09-28.63)	
Age (year)			
<30	42 (22.6)	23.83 (17.56-30.11)	0.002
30-65	94 (50.5)	34.3 (31.26-37.33)	
>65	50 (26.9)	22.73 (16.79-28.66)	
BMI (kg/m ²)			
<18.5	32 (17.2)	20.5 (8.25-32.75)	0.47
18.5-22.99	40 (21.5)	30.13 (24.42-35.85)	
23-27.49	92 (49.5)	27.11 (23.04-31.17)	
>27.5	22 (11.8)	13.22 (10.97-15.48)	
HTN			
Yes	14 (7.5)	32.25 (22.95-41.55)	0.43
No	172 (92.5)	28.85 (25.91-41.55)	
COPD			
Yes	14 (7.5)	26.44 (16.1-36.8)	0.94
No	172 (92.5)	29.22 (26.27-32.16)	
DM			
Yes	32 (17.2)	9.34 (7.4-11.29)	<0.0001
No	154 (82.8)	34.32 (31.81-36.83)	
Patients with limitation in positional changes			
Yes	84 (45.2)	25.4 (20.75-30.1)	0.03
No	102 (54.8)	31.74 (28.38-35.11)	
Tracheal intubation			
Elective	138 (74.2)	31.95 (27.1-36.84)	0.18
Emergency	48 (25.8)	28.1 (24.72-31.46)	
GCS			
≤7	90 (48.4)	27.54 (23.53-31.55)	0.03
>7	96 (51.6)	31.37 (27.44-35.3)	
Gavage feeding			
Yes	102 (54.8)	29.42 (26.24-32.59)	0.69
No	84 (45.2)	18 (15.7-20.83)	
Zinc sulfate			
Yes	82 (44.1)	35.13 (32.16-38.09)	<0.0001
No	104 (55.9)	18.1 (15.18-21.01)	

[†]Log-rank test; P<0.05 be considered significant level. BMI: body mass index; HTN: Hypertension; COPD: Chronic obstructive pulmonary disease; DM: diabetes mellitus; GCS: Glasgow coma scale; CI: Confidence interval

Recently, Wilkinson *et al.*, in a preclinical study showed that excessive dysfunctional neutrophils are recruited to the lungs of VAP patients, and active proteolytic enzymes are secreted into the alveolar space.^[15] Data have indicated that expression of matrix metalloproteinases (MMPs), which are a large family of zinc-dependent endopeptidases, significantly increased in BAL fluid in VAP patients. These zinc-dependent endopeptidases are capable of degrading all kinds of extracellular matrix proteins.^[16] MMPs are also thought to play a major role on cell behaviors such as cell proliferation, migration, differentiation,

angiogenesis, apoptosis, host defense, and pathogenesis of different types of pneumonia, such as VAP.^[16,17]

To the best of our knowledge, there is no trial which evaluates the effects of zinc supplementation on the occurrence of VAP in critically ill patients. Data across many studies have provided evidence of the effectiveness of zinc in preventing pneumonia in children and elderly, worldwide.^[18,19] Srinivasan *et al.* showed that, although zinc adjuvant therapy reduces mortality in severe childhood pneumonia, it had no significant effect in the treatment of severe pneumonia.^[20] In a Cochrane review stated that zinc supplementation in children aged two to 59 months is associated with a drop in the incidence and prevalence of pneumonia, and eventually children's death.^[21]

It has been demonstrated that normal serum zinc level in nursing home elderly is associated with reduced incidence and duration of pneumonia and diminished utilize and duration of treatment with antimicrobial agents. The authors concluded that using zinc to conserve normal serum zinc level might help decrease pneumonia incidence in the elderly.^[18] A review study indicated that zinc deficiency is a new risk factor for pneumonia in the elderly. This study showed that low zinc level deteriorates immune system and fighting to pathogens, and not only is associated with increased incidence and length of pneumonia, and duration of antibiotic therapy, but also associated with augmented mortality in the elderly.^[19]

An inadequate store of zinc is a major cause of mortality in the critical care and can also impair immunity and increase susceptibility to infectious diseases.^[22-24] T cell dysfunction, delayed antibody response to T cell-dependent antigens, dysregulation of apoptosis and redistribution of zinc to the liver in response to proinflammatory cytokines are potential mechanisms of immune dysfunction following zinc deficiency.^[25,26] We speculate that zinc might affect the risk of VAP through improvement in T and B cell-mediated function in critical intubated patients.^[24,26]

Inflammation is closely related to infection in critically ill patients in the ICU.^[27] Zinc supplementation is effective in diminishing inflammatory cytokines such as interleukin-6 (IL-6), tumor necrosis factor- α and IL-1 β in elderly subjects.^[19,24,28,29] Zinc supplementation may reduce risk of VAP by inhibition of inflammatory response and consequently lead to improvement of immune system function in these patients.^[30] It is known that host zinc deficiency is linked to increased susceptibility to bacterial infection. In a study demonstrated that the innate immune system may use zinc as an antimicrobial agent.^[31] Zinc metabolic status correlated with inflammation and the severity of illness in critically ill patients; so plasma zinc concentrations reduce to below normal level in these patients.^[32,33] This important matter maybe consider as another mechanism of zinc supplementation in VAP risk reduction.

In agreement with several previous studies, this study showed that the limitation of positional changes,^[34] increase in age,^[35] and also obesity^[36] are as risk factors of developing VAP.

Table 3: Association between prognostic factors and progression to ventilator associated pneumonia in Cox proportion hazards regression multivariate analysis

Factors	Coefficient	SE	Significant	Wald	HR	95% CI for HR
Zinc sulfate supplementation	-1.145	0.425	0.007	7.253	0.318	0.138-0.732
DM	2.41	0.386	<0.0001	38.96	11.14	5.23-23.73
Patients with limitation in positional changes	1.302	0.371	<0.0001	12.32	3.68	1.78-7.6
Age (year)						
≤30	Reference	Reference	Reference	Reference	1	Reference
>65	1.052	0.378	0.005	7.767	2.86	1.18-2.08
BMI (kg/m ²)						
≤18.5	2.001	0.869	0.021	5.298	7.4	1.35-40.64
18.5-22.9	Reference	Reference	Reference	Reference	1	Reference
23-27.49	0.908	0.394	0.021	5.302	2.48	1.145-5.374

P<0.05 is considered significant level. BMI: Body mass index; DM: Diabetes mellitus; SE: Standard error; HR: Hazard ratio; CI: Confidence interval

DM has been associated with alternation of immune response and are often encountered in the critical ill patients.^[37] Although the prevalence of DM in critically ill patients is high,^[38] the effects of DM as a risk factor for VAP in these patients has not been sufficiently assessed.^[37] More studies are still needed to confirm that patients with DM undergoing MV have a higher risk of developing VAP compared to nondiabetic patients in ICU.

This study has several limitations. Although the data in this analysis were prospectively collected, due to the nature of the secondary analysis studies, the available data for the study was not collected to address the particular research question of the present study. Therefore, our results need confirmation, and future studies are needed to investigate the effect of zinc supplementation in the mechanically ventilated ICU patients to specifically focusing on VAP as a primary outcome. As previously stated this study is a secondary analysis and thus was not specifically designed for the research question. Some variables including ICU scoring such as Simplified Acute Physiology Score II and SOFA score were not recorded for the analysis. In addition, semi-quantitative ETA more than BAL have been used for VAP diagnosis in the current study, due to its cost and ease. The duration of zinc sulfate supplementation was not documented in our study. Furthermore, over the study period, serum zinc concentrations were not measured. These issues should be kept in consideration when interpreting the results.

CONCLUSION

It seems that zinc supplementation may be significantly associated with reduced VAP risk in adult mechanically ventilated trauma patients in ICU. The results are intended to create new hypotheses for clarifying zinc's role in the prevention of VAP; although further large-scale cohort and clinical studies are clearly required to confirm this finding.

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Conflicts of interest

There are no conflicts of interest.

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