

Effect of Ondansetron on Prevention of Ventilator Associated Pneumonia in Intensive Care Unit Patients in Kashani Hospital in 2013

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ABSTRACT

Introduction: Ventilator Associated Pneumonia (VAP) is the second most common infection with high mortality (24-50%). Ondansetron is a reliable and safe drug and it is currently used in the prevention of nausea and vomiting and has no side effects.

Aim: The aim of the present study was to examine the effect of ondansetron on prevention of VAP in Intensive Care Unit (ICU) patients.

Materials and Methods: The present study was a randomized clinical trial study (IRCT201406156480N6), carried out at Kashani Hospital, Iran, in 2013 on 80 patients aged from 15-65 years. The patients were randomly allocated to two groups: Case group (n=40) and Control group (n=40). The patients in first group were injected with 4 mg ondansetron, twice daily for five days. The patients of other group were injected with distilled water as placebo. The presence of VAP was assessed in the two groups.

The collected data were analysed by SPSS software through Fisher-exact test.

Results: Eleven (13.8%) patients were diagnosed with VAP. Among them, 9 (81.8%) patients were male and 2 (18.2%) patients were female. The incidence of VAP in Case group was 5 (12.5%) patients and in Control group was 6 (15%) patients ($p>0.05$). Results showed that VAP in Case group was less prevalent than that in the Control group, but this difference was not significant.

Conclusion: The study did not find an association between ondansetron administration and reduction in VAP incidence; vomiting alone may not be leading to VAP, instead silent micro aspirations may be the cause of it. None of the factor such as age, sex, weight, smoking, drug addiction was found significantly related to VAP. Only variable found related was comorbidity.

Keywords: Inflammation of the lung, Nosocomial infections, Pulmonary diseases, Respiratory tract diseases

INTRODUCTION

Hospital Associated Pneumonia (HAP) is the parenchymal infection of the lung that is not present while referring to the hospital and start after a minimum of 48 hours of hospitalization [1]. The incidence of HAP is between 30-60% and it is the second most common infection after urinary tract infections in the United States of America [2].

While, VAP is a subset of HAP including all patients supported by mechanical ventilation at the time of infection, VAP occurs almost exclusively in the ICU and represents about 86% of all HAP occurring in ICU [3].

Most of the patients are under mechanical ventilation only for a short time period and half of all the cases of VAP occur during the first four days after placement of an endotracheal tube. The risk of VAP is highest, early in the course of hospital stay, and is estimated to be 3% per day during the first 5 days of ventilation, 2% per day during days 5 to 10 of ventilation, and 1% per day after that [4].

Mortality due to nosocomial pneumonia is around 24% to 50% and if the infection is associated with other risk factors, its mortality is increased to 76% [3,5]. Its highest occurrence is observed in patients with bacteraemia, patients infected with high-risk pathogens (e.g., *Pseudomonas aeruginosa*) and occur in patients admitted to the ICU [4].

A study carried out by Yavagal DR et al., investigated the role of the metoclopramide in the prevention of HAP, in 305 ICU patients who received enteral nutrition, it was concluded that metoclopramide does not have any role in reducing HAP [6].

In another study, Paul AK et al., studied the effects of metoclopramide and ranitidine in the prevention of aspiration, it was shown that metoclopramide and ranitidine combination regimen was much

better and more effective than either of them alone to reduce the risk factors associated with aspiration of gastric contents [7].

A study carried out by Ranjbar H et al., on 80 patients admitted to the ICU, evaluated the effect of chlorhexidine gluconate mouthwash in the prevention of VAP. Selective rinsing of the oral cavity with chlorhexidine gluconate mouthwash, twice a day did not show any significant difference in preventing VAP as compared to normal saline solution, but it can reduce the incidence of late-onset pneumonia and is effective in patients with more severe condition [8].

In a study carried out by van der Maarel-Wierink CD et al., in elderly and disabled patients, it was confirmed that oral hygiene including toothbrushing after every meal and oral cleaning every day and professional health care every week is the best way to reduce aspiration pneumonia [9].

A study by Kelly SD investigated the usefulness of subglottic secretion drainage technology as a method of preventing VAP, it was suggested that subglottic secretion drainage is a cost-effective preventive method [10].

A study by Shiohara Y et al., in Japan checked the influence of Angiotensin Converting Enzyme (ACE) inhibitor drugs in preventing pneumonia in patients with a history of stroke, the results of meta-analysis of five studies on 8693 Asian patients was examined. It was concluded that ACE inhibitor drugs, in comparison with other anti-hypertensive drugs or placebo were more effective in reducing the risk of pneumonia in patients with history of stroke [11].

In a study by Cohen IT et al., the acceptability and efficacy of ondansetron was assessed, the results of the study showed that the incidence of vomiting was significantly less in the ondansetron group [12]. In a study by Salvucci AA et al., the effect of ondansetron in the treatment of nausea and vomiting was examined and it was

shown to be safe and an effective drug in the treatment of nausea and vomiting [13].

The main cause of VAP is considered to be, regurgitation of digestive secretions into trachea; therefore, we decided to do this research with the aim of probable reduction in the incidence of VAP. In this study, the effect of ondansetron on prevention of VAP in ICU hospitalized patients was examined.

MATERIALS AND METHODS

The present study was a randomized clinical trial, with IRCT code: 201406156480N6, carried out in Kashani hospital from September 21st 2012 to December 20th, 2013 on patients aged between 15 and 65 years. Ethics Committee of Shahrekord University of Medical Sciences approved the study. The participants provided the written consent in their native language (Persian) prior to the study. The patients were randomly divided and allocated equally into two groups i.e., Case and Control groups (n=40).

Inclusion criteria: Patients admitted to ICU and on mechanical ventilation, aged between 15 and 65 years, hospitalised for more than 48 hours in ICU and have consented to participate in the study.

Exclusion criteria: Those patients who had suspected or were proved to have lung disease prior to mechanical ventilation were not included in the study.

Case group patients were injected with 4 mg ondansetron (2 ml) twice daily for five days and Control group patients were injected with distilled water as placebo, every 12 hours for five days [14]. The presence of VAP was assessed in two groups based on the clinical, laboratory and radiologic criteria. The injection was administered by a specialist nurse. Patients were examined daily for five days by an anesthesiologist and the CDC criteria was used for the diagnosis of pneumonia [15].

Sample size formula:

$$N = \frac{\{P1(1-P1)\} + \{P2(1-P2)\} \times (Z \cdot 1-\alpha/2 + Z \cdot 1-\beta)^2}{(0.25)^2}$$

$$N = \frac{(0.25 \times 0.86) + (0.5 \times 0.5) \times 10.5}{(0.25)^2}$$

$$N=39.6 = 40$$

Patient information was entered in a questionnaire designed for this purpose [Appendix-1].

The collected data were analysed by SPSS software through Fisher exact test.

Diagnoses were done based on CDC criteria defined by Center for Disease prevention and control [15] that included:

For any patient, at least one of the following:

1. Fever (>38.0°C or >100.4°F)
2. Leukopenia (≤ 4000 WBC/mm³) or leukocytosis (>12,000 WBC/mm³)
3. For adults >70 years old, altered mental status with no other recognized cause.

And at least two of the following:

1. New onset of purulent sputum or change in character of sputum, or increased
2. Respiratory secretions, or increased suctioning requirements
3. New onset or worsening cough, or dyspnoea, or tachypnoea
4. Rales or bronchial breath sounds
5. Worsening gas exchange (e.g., O₂ desaturations (e.g., PaO₂/FiO₂ <240), increased oxygen requirements, or increased ventilator demand).

Diagnosis was also based on radiographic symptoms: new and persistent or progressive and persistent infiltrate, consolidation or

cavitation (which must be present in atleast two consecutive chest radiographs).

Diagnosis based on microbiological criteria:

At least one of the following:

1. Organism identified from blood
2. Organism identified from pleural fluid
3. Positive quantitative culture from minimally-contaminated LRT specimen {e.g., Bronchoalveolar Lavage (BAL) or Protected Specimen Brushing (PSB)}
4. $\geq 5\%$ BAL-obtained cells contain intracellular bacteria on direct microscopic exam (e.g., Gram's stain)
5. Positive quantitative culture of lung tissue [15].

RESULTS

The results of this study showed that 11 (13.8%) of the patients suffered from pneumonia, of which 5 (12.5%) patients were from Case group and 6 (15%) patients were from Control group. The difference was not statistically significant ($\chi^2 = 0.105$, DF=1,

Variables	Have Pneumonia n (%)	Does not have Pneumonia n (%)	p-value
Number	11(13.8%)	69(86.2%)	NS
Age (Mean±SD)	50.73±6.50	43.45±16.22	NS
Weight	73.54±15.54	85.11±9.40	NS
Sex			
Male	9(15.3%)	50(84.7)	NS
Female	2(9.5%)	19(90.5)	
History of smoking			
Yes	2(10)	18(90)	NS
No	9(15)	51(85.1)	
History of drug addiction			
Yes	1(7.7)	12(92.3)	NS
No	10(14.9)	57(85.1)	
History of comorbidity with pneumonia			
Yes	6(3.33)	12(66.7)	<0.05
No	5(8.1)	57(91.2)	

[Table/Fig-1]: The association between demographic characteristics, history of smoking, history of drug addiction, history of comorbidity with pneumonia and without pneumonia.

Fisher exact test

NS: Not significant, p>0.05

p<0.05 was considered to be significant

p-value=0.745). Patients aged between 15 and 65 years were included in the study.

In the group that had history of comorbidities, 6 (3.33%) patients were suffering from VAP and in group that had no history of comorbidities, 5 (8.1%) patients were suffering from pneumonia. It showed that there was a significant relationship between comorbidity and VAP (p<0.05) [Table/Fig-1].

A total of 5 (45.4 %) of those who had pneumonia were among those who were hospitalized due to head trauma plus major trauma.

DISCUSSION

Pneumonia is one of the common complication that occurs while using mechanical ventilation devices. This condition causes increased mortality and the economics of VAP include increased ICU length of stay (from 4 to 13 days) and an increased health care cost. Aspiration is the most common cause of bacterial pneumonia, such that the mortality rate in patients with aspiration of gastric contents was reported to be 30-60% [16].

Nowadays, ondansetron as antiemetic drug is taken into consideration, and several studies have examined its effectiveness and had positive view on its quality in controlling vomiting [12]. Since

vomiting is one of the risk factors of aspiration, in this study, the role of ondansetron in the prevention of VAP was examined.

In some studies, role of metoclopramide in the prevention of aspiration and hospital pneumonia were studied but no similar research has been done on the direct impact of Ondansetron in the prevention of VAP [6].

Each of the factors i.e., age, sex, weight, smoking history, history of drug addiction, cause of hospitalisation and systemic disease were separately studied as was done in a similar study [7].

Nausea and vomiting may have broad causes which include side effects of medications, systemic disorders or infections, vestibular dysfunction, central nervous system infection or increased pressure, peritonitis, hepatic or biliary disorders, radiation or chemotherapy and gastrointestinal obstruction and motility disorders. Vomiting performance of ondansetron is limited to attributable vagal stimulation (stimulation of the gastrointestinal mucosa) and it poorly controls the other drivers of vomiting.

In a study by Farhat K et al., it was observed that the prophylactic use of ondansetron is more effective than metoclopramide, with lesser side effects, in preventing Post Operative Nausea Vomiting (PONV) in adult females undergoing laproscopic cholecystectomy [17].

In the study by Chio DK et al., combination of ramosetron and ondansetron was used [18]. In the study by Ekinci, ondansetron in combination with tropitzone and dopidole was used [19]. So, probably a combination of ondansetron with such medications is effective in reducing PONV. In some studies, combination of antibiotic and sucralfite has also been used for gastric cleaning and prevention of pneumonia aspiration [20,21]. One of the most important difference in the incidence of VAP between these studies was difference in methods to control infection and prevention of VAP in ICU.

Differences in diagnostic methods used in studies play a role in the frequency of VAP. It seems that studies examined incidence of VAP based mostly on clinical methods and reported higher prevalence as compared to studies using laboratory methods, especially PSB and BAL.

None of the factor such as age, gender, smoking or drug addiction did reflect a statistically significant difference. Although, in few studies higher age is reported as one of the factor associated with VAP and increased mortality among patients on mechanical ventilation [22,23]. Also, there is no single point of view about the effects of age on the incidence of pneumonia; some studies have reported, age over 70 years as one of the risk factors for developing hospital pneumonia [24].

Also, there is no single point of view regarding the effect of gender on the incidence of VAP. Some studies have reported males and some other have reported females to be at risk factor for developing VAP [24,25]. The results of the present study showed that there was no significant difference between the two sexes and the incidence of VAP.

The results of the present study showed that smoking history in patients receiving mechanical ventilation was not associated with the incidence of VAP and this result is consistent with those of a study conducted in 2005 in which it was observed that there was no relationship between smoking history and pneumonia associated with ventilators [26].

The results of the present study showed that the incidence of VAP is more common in people with a history of underlying disease or comorbidity which is consistent with the results of a study conducted by da Silva JM Jr et al., [27].

The mechanically ventilated patients need Nasogastric Tube (NGT) for feeding, NGT causes incomplete closing of the lower oesophageal sphincter and consequently secretions come up and

thus, by silent aspiration may cause VAP. Thus, if we can replace NGT by another method like jejunostomy and conduct the study again, it is likely to achieve new results.

LIMITATION

In this study, no significant relationship between ondansetron and incidence of VAP was observed. The number of subjects was likely not enough to determine this relationship. Further research is required with different research projects to determine the efficacy of ondansetron on VAP. Also, according to the drug half-life (4 to 9 hours), perhaps if the drug was injected with the higher dose the efficacy would have been more.

CONCLUSION

Ondansetron alone may have no effect on VAP and vomiting alone does not lead to VAP, instead silent aspiration causes it. None of factors such as age, sex, weight, smoking, drug addiction was shown to be effective in VAP. Instead comorbidity was shown to be influential in VAP.

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APPENDIX -1

Checklist for Effect of Ondansetron on prevention of Ventilator associated pneumonia in Intensive care unit patients in Kashani hospital in 2013

Full name:

Sex:

Age:

Weight:

Cause of hospitalization:

ICU No.:

History of systemic disease:

Have: Do not have:

History of smoking:

Have: Do not have:

History of addiction:

Have: Do not have:

Ondansetron:

Receive: Do not receive:

Pneumonia:

Positive: Negative:

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