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Original Research Article

Ventilator-associated pneumonia (VAP) prevention using clarithromycin among ICU-hospitalized patients

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Abstract

Ventilator-Associated Pneumonia (VAP) is a nosocomial infection which may be prevented using interventions such as Clarithromycin (Clrtm) prophylaxis. Then, the aim is to do a clinical trial on the prophylactic effect of this macrolide drug on VAP. Sixteen Intensive Care Unit (ICU) hospitalized patients, randomly were categorized into Clrtm and placebo groups. Twenty-seven patients were received 500 mg Clrtm (intervention group) and 33 were received the placebo (placebo group), both bi-daily for 5 days. We analyzed the occurrence of VAP, mortality rate, duration of mechanical ventilation, length of ICU staying and organ dysfunction via comparison of two groups with statistical methods where the confidence interval was 95%. The average duration of ICU staying was 13.26 days in Clrtm-treated and 8.12 days in placebo-treated groups. APACHE scores were significant between two studied groups only for day 10 and not for days 1 and 5. Ventilator associated pneumonia was confirmed with microbial culture and was also meaningful among survived patients; Clrtm-treated group had lower positive cultures than placebo (p=0.031). Sixteen (59.25%) Clrtm and 23 (69.69%) placebo patients were expired from whom 11 (40.75%) were in Clrtm group and 10 (30.31%) in placebo group which was not statistically significant (p=0.399). Other investigated variables were not statistically different between two groups. Clarithromycin was effective in the reducing the rate and complications of VAP; however, some investigated variables had not significant results probably due to the low sample size of study which was obligatory due to the entity of the clinical trial. Anyway, it is concluded that prophylactic administration of Clrtm, could decrease the length of ICU-staying and VAP.

Keywords: Clarithromycin, ventilator associated pneumonia (VAP), organ dysfunction, intensive care unit, clinical trial

INTRODUCTION

Hospital pneumonia causes about 30% of mortalities due to acquired nosocomial infections (Leu et al., 1989). Ventilator-associated pneumonia (VAP) occurs in some patients under mechanical ventilation and could be early or late depending on the time of manifestation (Pingleton et al., 1992). Early pneumonia bacterial agents mostly included Staphylococcus aureus, Haemophilus influenzae and oxacillin-sensitive pneumonia whereas late VAP pathogens commonly are antibiotic-resistant species such as Staphylococcus aureus, Pseudomonas aeruginosa, Acinetobacter and oxacillin-resistant Enterobacter (Niederman et al., 1990; Kollef et al., 1995; Rello et al., 1993). VAP increases the time of hospitalization and burden of health-care facilities and services in addition to the mortality rate (Craven and Steger, 1995; Papazian et al., 1996).

Clinical diagnosis criteria of VAP are not so valuable; these criteria at least resulted to about 30-35% false-negative and 20-25 false-positive results. Furthermore, radiographic findings have low sensitivity and specificity for diagnosis of this type of involvement (Fàbregas et al., 1999; Lefcoe et al., 1994; Wunderink et al., 1992). Then, prophylaxis approach could be vital in the prevention of nosocomial infection in critically ill patients under ventilator respiration whom are hospitalized in the intensive care units (ICUs).

There are discrepant evidences about the antibiotic prophylaxis for prevention of VAP; some evidences confirm the prophylactic usage of antibiotics and another rejects its role and have shown a reverse impact on the prevention of VAP (Kollef, 1993; Craven et al., 1986; Torres et al., 1990; Elatrous et al., 1996; Rello et al., 1996; Kollef et al., 1997).

The mortality rate of VAP due to late pneumonia which is caused by antibiotic-resistant bacteria have been reported to be higher than 10% (Kollef et al., 1995; Fagon et al., 1993; Brewer et al., 1996). Colonization of bacteria, especially acquired from ventilation devices, and aspiration of gastrointestinal secretion's containing enteric bacteria are the main sources of VAP (Craven and Steger, 1995; Tablan et al., 1994).

VAP treatments include supportive and antibiotic therapies. Early actions, such as wide-spectrum antibiotic therapy, for controlling infection have been shown to be effective in reducing the rate of mortality due to probable VAP (Rello et al., 1997; Luna et al., 1997; Kollef and Ward, 1998).

VAP prevention programs should be concordant with the new effective strategies and cost-effective methods, according to the clinical experiences and related investigations (Tablan et al., 1994; Boyce et al., 1985; Joiner et al., 1996; Kelleghan et al., 1993; Gaynes and Solomon, 1996).

There are two main approaches for prevention of VAP which are based on the drug application and other options. In this regard, drug application is essentially focused on the antibiotics (Brewer et al., 1996). However, antibiotic resistance is a problem that maybe resolved by replacement with more effective options (Brewer et al., 1996; Goldmann et al., 1996; Johanson et al., 1972; Garrouste-Orgeas et al., 1997; Kollef et al., 1997).

Prophylactic usage of antibiotics has its complexities and limitations; low response to aerosol form of antibiotics (Tablan et al., 1994) and antibiotic resistance provoked with oral or injection administration route (Gastinne et al., 1992; Sirvent et al., 1997) make limitations for this type of prophylaxis.

Clrtm belongs to the macrolide family of drugs which has anti-inflammatory effects and specifically blocks cytokines synthesis by mononuclear cells, in vitro. Investigations have proposed Clrtm as a VAP prophylactic agent; increased survival period in patients who were expired and therapeutic effect in survived patients have been evidences of its probable effectiveness (Giamarellos-Bourboulis et al., 2008). Anyway, evidences are not enough for application of Clrtm in clinical settings as a routine prophylactic agent. Then, the aim of current study has been to evaluate the effectiveness of Clrtm in the reduction of VAP incidence in critically ill patients.

MATERIALS AND METHODS

Patients, ethical statement, inclusion and exclusion criteria

In this randomized clinical trial (RCT) study, we have made intervention on patients whom were hospitalized in the intensive care unit (ICU) and under mechanical ventilation. As all investigated patients were critically ill, their family members declared their approval with the study by fulfilling the consent forms. All patients were upper than 18 years and from both sexes. Patients were excluded from the study if they had neutropenia (less than 500 neutrophils/µL), positive immunoassay result of human immunodeficiency virus (HIV), and corticosteroid-therapy with doses higher than 1 mg/kg and for a therapeutic period higher than 1 month, any sign of pneumonia or any probable diagnosis of respiratory infection according to chest X-ray findings.

Patient's randomization and study setting

This study was done in Shahid-Sadoughi hospital in Yazd city, at the center of Iran. Patient's randomization was done using randomize generator software. Concealment method was used for randomization and the 3rd number in patient's list was allocated to Clrtm or placebo group. Demographic data for each patient was gathered using a checklist. There were 27 patients in the Clrtm group and 33 patients in placebo group.

Intervention

Clrtm was prepared from Kimdaru Company (Iran) and placebo had similar appearance. ICU nurses were blind about the drug contents and therapeutic packages were in unique packs.

The dose of Clrtm was 500 mg bi-daily for five days treatment period; normal saline solution was used as placebo and administered same as Clrtm, again for 5 days treatment. Nurses were blinded about the physician's prescription and the drugs, Clrtm or normal saline, were taken to nurses for injection as similar ampules without any mark and sign about the content.

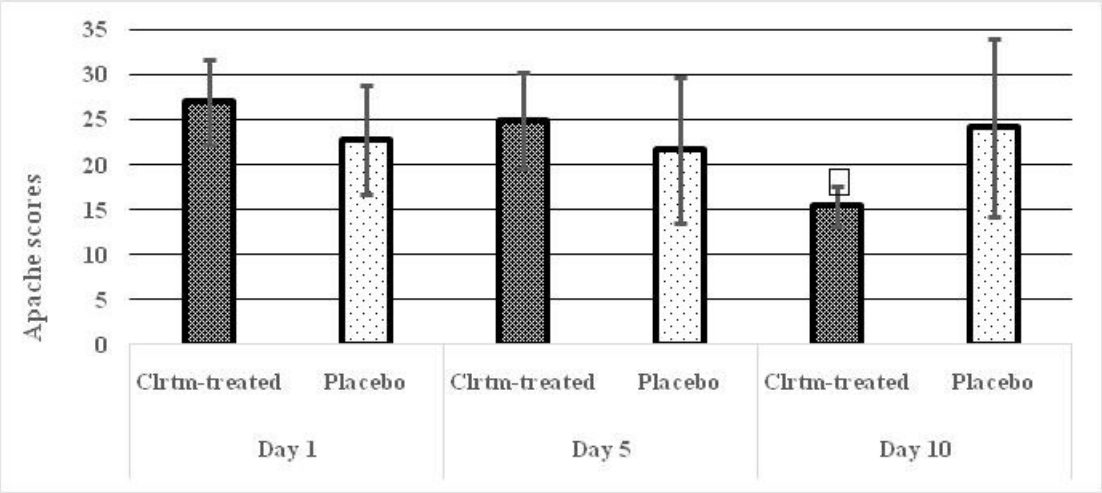

Figure 1. APACHE scores comparison among days 1, 5 and 10 after starting treatment with Clrtm (Clrtm-treated) for intervention group and placebo for placebo patients; There were not any significant result for day 1 (P=0.15) and day 5 (P=0.213); however, a significant reduction is obvious when comparing Clrtm group with placebo category in day 10 (P=0.042). Significant compared with placebo at day 10.

Clinical and paraclinical evaluations

Investigator physician had daily visit and checking from patients and recorded the data. Vital signs, test results, blood gas and the ratio of oxygen partial pressure to fraction of inspired oxygen (PaO_2/FiO_2 ratio), anti-microbial drug prescriptions, vasopressors, hydrocortisone, insulin, tracheobronchial secretions (TBS) appearance and chest X-ray findings were recorded. APACHE scores for days 1, 5 and 10 were calculated and recorded. Patients in the Clrtm group were not different from placebo patients when comparing APACHE score averages at the beginning of the study (P-value>0.05); the investigated population was homogenous. TBS cultures were done on days 1, 5 and 10 after sampling from intubated airway which was connected into a negative-pressure system. The TBS samples were cultured on eosin methylene blue (EMB), blood agar medium for aerobic and chocolate agar for anaerobic cultures. The culture mediums were kept in 37 degree centigrade for 48 hours. Cultures were considered positive if a pathogen were growth with a colony count higher than 1×10^5 colony forming unit per milliliter (CFU/mL). Patient's status was rechecked daily if him/her hospitalization was continued or followed for 28 days post-discharging from hospital.

Statistical analysis

Chi-square and two independent samples t-test were used for statistical analysis using SPSS ver.23 software. At least 95% confidence interval was considered for obtaining significant results.

RESULTS

Descriptive statistics and APACHE scores

In total, 60 ICU-hospitalized patients were included in the study; 27 patients were received Clrtm and 33 were under placebo treatment. Before starting treatment process the APACHE-scores which is representative of disease severity, were not significantly different between Clrtm-treated and placebo-treated patients (P> 0.05).
APACHE scores were not meaningfully different again at the days 1 and 5 after starting interventions using Clrtm or placebo (P= 0.15 and 0.213, respectively). However, Clrtm-treated patients had significantly lower APACHE scores at day 10 than placebo-treated patients (P= 0.042) (Figure 1).

Microbial culture results

Microbiological evaluations showed that Clrtm-treated patients had lower culture positive results than placebo-treated patients (P=0.013); however, 48.48% of placebo-treated and 18.15% of Clrtm-treated patients had unknown culture result because of expiration prior to microbial culture evaluation (Table 1).

Comparison of hospitalization days in ICU ward

Patients receiving placebo were remained in ICU ward for shorter period than Clrtm-treated patients (P= 0.022; Figure 2). However, there was not any significant result between survived patients in both compared groups (P=

Table 1. Comparison of microbial culture result of Clrtm and placebo treated patients hospitalized in ICU ward and under mechanical ventilation

Culture Result Ventilator-associated pneumonia (VAP)	Placebo N(%)	Clrtm-treated N(%)
Positive pneumonia	9 (27.20%)	8 (29.62%)
Negative pneumonia	8 (24.32%)	14 (51.85%)
P-value	0.031	
Unknown	16 (48.48%)	5 (18.51%)

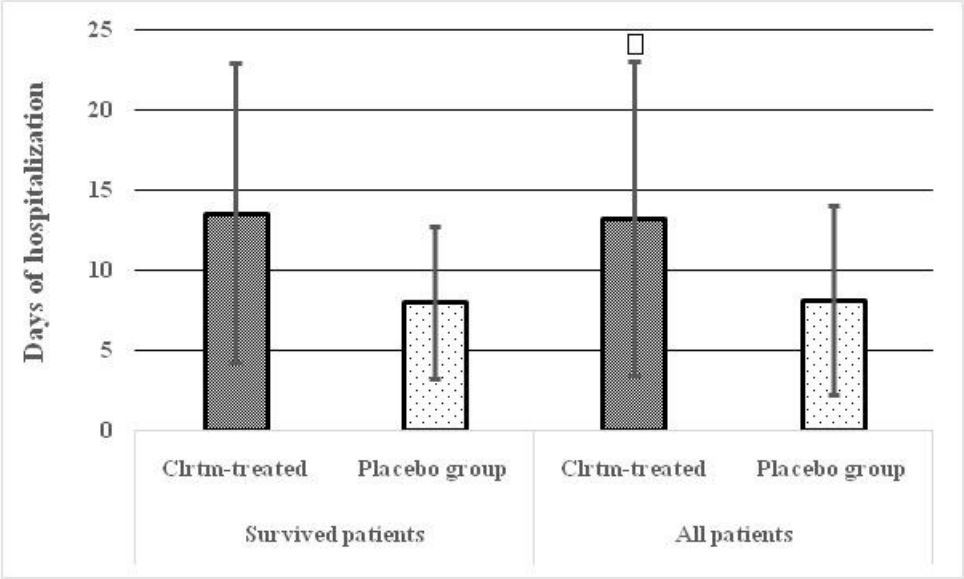

Figure 2. Comparison of hospitalization days between Clrtm-treated and placebo-treated groups. As it is shown, by a star mark, comparison of hospitalization days has significant result when comparing all patients (survived plus died persons), but not for survived individuals.

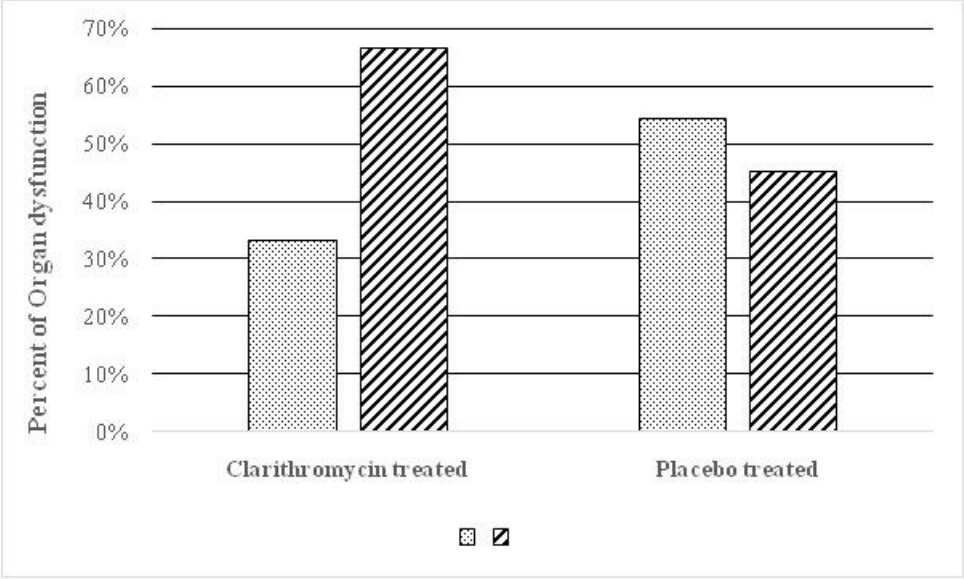

Figure 3. Comparison of organ dysfunction incidence between Clrtm-treated and placebo-treated patients. There was any meaningful result statistically between two investigated groups.

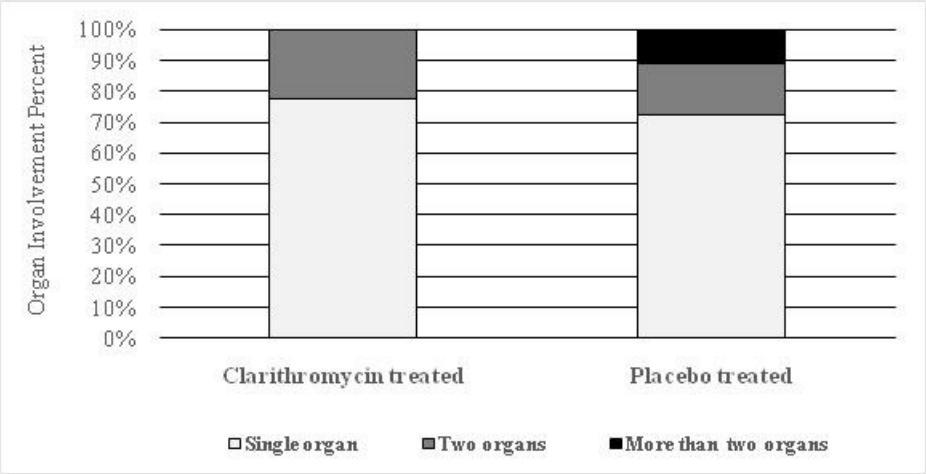

Figure 4. Percentage of organs involved in VAP patients; most patients had single involvement; not any patient in Clrtm-treated group had more than two involved organs.

0.103; Figure 2 and columns of survived patients).

Organ dysfunction

The incidence of organ dysfunction was not significantly different between Clrtm-treated and placebo-treated patients (P= 0.100) but as figure 3 shows patients under Clrtm treatment had better status than placebo-treated individuals. Furthermore, the count of involved organs, were not different between Clrtm-treated and placebo-treated patients (P= 0.57; Figure 4). In Clrtm-treated patients 18 individuals and in placebo-treated patients 15 persons had not any evidence of organ involvement. Seven patients in Clrtm-treated patients and 13 placebo-treated patients had single organ's involvement whereas 2 patients in Clrtm and 3 in placebo group had two involved organs. However, 2 patients in placebo-treated group had more than two involved organs. Figure 4 depicts the percentages of organ involvements recorded in each group of treatments.

Clarithromycin did not reduced the mortality percent of VAP patients

The rate of mortality was 59.25% (16 individuals; 11 persons were survived) and 69.69% (23 individuals; 10 persons were survived) in Clrtm-treated and placebo-treated patients (P= 0.399), respectively. Then, Clrtm had not a clear effect on the death prevention of VAP patients.

DISCUSSION

Ventilator-associate pneumonia is one of the most frequent cause of death in ICU wards. This status increases the time period of ventilation and ICU-hospitalization (Diaz et al., 2010). Investigations have shown that about 60% of mortalities due to nosocomial infections caused by hospital-acquired pneumonia, especially when using mechanical ventilator for critically-ill patients (Gross et al., 1980).

In the present study, we have seen that APACHE scores were different between two groups of intervention; and Clrtm-treated patients had better status than placebo group after 10 days. The survival days were higher in Clrtm-treated patients. Organ dysfunction and organ-involvement rates were lower in Clrtm-treated patients but with insignificant results, statistically. Culture-negative results were significantly higher in Clrtm-treated patients compared placebo-treated (51.85% vs 24.32%, respectively). Then, in total, it could be said that Clrtm has a preventive effect against ventilator associated pneumonia infection in critically-ill patients. We think that insignificant results in our study could be because of low sample size. However, our results were promising for larger-sample size studies. Anyway, performing clinical trial studies on the critically-ill patients who were hospitalized in ICU wards, most of them were not cautious and were under intense cares has its special limitations for increasing the study sample size.

Reports with high sample size that have evaluated the prophylactic prescription of antibiotics, have shown that the mortality rate could be reduced up to 20% and the rate of respiratory infections decreases up to 65% (D'amico et al., 1998). Although our results were not significant, however, reduced mortality rate also was seen in Clrtm-treated than placebo-treated patients. This finding could be promising for next studies especially if a bigger VAP population to be evaluated. In addition, other risk factors threating ICU hospitalized patients may have a role in mortality rates obtained in our study.

A multivariate analysis have shown that prophylactic administration of antibiotics has been effective with an

odd's ratio equal to 3.1 for postponing VAP (Kollef, 1993). Another study (Palmer et al., 1998) and a randomized clinical trial on the prophylactic administration of Cefuroxime following 24 hour after intubation also representing evidences about the effectiveness of antibiotics in postponing early VAP (Sirvent et al., 1997). In addition, Palmed and coworkers have shown that aminoglycosides reduce the volume of tracheostomy secretions and eradication of Gram-negative bacteria from tracheostomy tube samples (Palmer et al., 1998).

In the present study, we have seen that Clrtm-treated patients had more negative microbial cultures than placebo-treated patients and this result was statistically significant (Table 1).

Clrtm intra venous administration for 3 days has been associated with faster VAP remediation and mechanical ventilator weaning, postponing patient's expiration due to sepsis and multi-organ dysfunction (Giamarellos-Bourboulis et al., 2008).

In our study, hospitalization period in ICU and mechanical ventilation were longer in Clrtm-treated than placebo-treated patients, probably due to better survival after Clrtm administration. Fortunately, the incidence rate of organ dysfunction were lower in Clrtm-treated patients; an evidence of protective effect of Clrtm on the organ function.

CONCLUSION

In total, Clarithromycin was effective against VAP and is recommended to be used in the clinical settings and for ICU hospitalized patients. Presented study is wrathful because of its clinical trial format. However, we suggest more investigations with higher sample size and different dosages of Clarithromycin.

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