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Original Article

Role of clarithromycin in ventilator-associated pneumonia care bundle in the prevention of ventilator-associated pneumonia

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Abstract

Objective

The purpose of this study was to assess the efficacy of the addition of clarithromycin to the ventilator care bundle to help in the prevention of ventilator-associated pneumonia (VAP).

Patients and methods

Eighty patients of more than 18 years, on a mechanical ventilator for less than 48 h, expected length of stay in the ICU for more than 48 h, with no clinical and radiographic evidence of pneumonia were enrolled in a double-blind comparative study. The patients were randomized to one of the two groups: GROUp A ($n = 40$) where the patients received clarithromycin (through the Ryle over the first 3 days after intubation); group B ($n = 40$) is the control group.

Results

As regards demographic data, length of stay in the ICU, use of vasopressor, prolongation of corrected QT interval Q wave T wave, and incidence of mortality no statistical difference was observed between the two groups, regarding the incidence of VAP in group A was significantly lower than in group B.

Conclusion

Administration of clarithromycin for 3 days reduce the incidence of VAP in mechanically ventilated patients.

Keywords: Clarithromycin, intensive care unit, ventilator-associated pneumonia

Introduction

Ventilator-associated pneumonia (VAP) is the most important nosocomial infection in mechanically ventilated patients and the biggest worry of critical care physicians [1]. Although the incidence of VAP has declined in the developed countries, it continues to be unacceptably high in the developing world, VAP is associated with increased hospital costs, a greater number of days in the ICU, longer duration of mechanical ventilation, and higher mortality.

Crude mortality rates in patients with VAP range from 24 to 50%, increasing to 76% if multiresistant organisms cause infection [2]. The incidence of VAP reported in the literature ranges from 15 to 20%. However, the real incidence of VAP is challenging to be assessed, given the extreme variability of the diagnostic criteria for pneumonia, which often rely on the bronchoscopic procedure.

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As multiple factors contribute to the high risk of VAP, a multistrategy approach is required to prevent such infections.

The Institute of Health Improvement has developed a ventilator care bundle that incorporates several strategies to prevent morbidity associated with the ventilator. Although care-bundle implementation appears to be associated with successful reduction in VAP rates, pathophysiologic aspects of VAP, such as differences between early- and late-VAP episodes, and risk factors that differ between trauma and medical patients, were not considered in the current version of bundles which limit their ability to prevent all episodes of VAP [3]. Macrolides are an old class of antimicrobials with

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an antimicrobial spectrum mainly against Gram-positive cocci and atypical pathogens. However, there is an accumulating body of evidence over the last few years that part of the activity of macrolides is not mediated through their traditional antimicrobial effect. Clarithromycin, a macrolide, is beneficial in some pulmonary conditions, such as cystic fibrosis and diffuse panbronchiolitis [4].

Macrolide antibiotics possess several beneficial, secondary properties that complement their primary antimicrobial activity. In addition to high levels of tissue penetration, which may counteract seemingly macrolide-resistant bacterial pathogens, these agents also possess anti-inflammatory properties, unrelated to their primary antimicrobial activity. Macrolides target cells of both innate and adaptive immune systems, as well as structural cells, and are beneficial in controlling harmful inflammatory responses during acute and chronic bacterial infection [5].

Aim

The main aim of this study was to determine the effectiveness of clarithromycin in the prevention of VAP.

Patients and methods

Ethical committee approval was taken. This study was held from September 2018 to 2019. There were 80 patients who after obtaining written informed consent from first degree relatives of patients were allocated randomly into equal groups (40 patients in each group):

(1) Group A ($n = 40$): received clarithromycin 1 g tablet.
(2) Group B ($n = 40$): control group.

Inclusion criteria

(1) Age greater than 18 years.
(2) Patients on mechanical ventilation for less than 48 h.
(3) Expected length of stay in the ICU greater than 48 h.
(4) No clinical and radiologic evidence of pneumonia.

Exclusion criteria

(1) Age less than 18 years.
(2) Not expected to be in the ICU for greater than 48 h.
(3) Witnessed aspirated patients to exclude chemical pneumonitis.
(4) Evidence of pneumonia.
(5) Patients with prolonged QT interval or with cardiac arrhythmias.

Once the patients had been chosen to be enrolled in this study, the study drug was administered once daily by a nurse blinded to the treatment group. Each dose of clarithromycin (klacid) (1 g tablet) was grounded and administrated to the patient through the Ryle over the first 3 days after intubation (day 1, day 2, and day 3). In both groups, VAP bundle was adopted; it included six components: (head of bed elevation >30°, daily sedation vacation, daily spontaneous breathing trial with assessment for extubation, peptic ulcer prophylaxis, deep vein thrombosis prophylaxis, and topical application of buccal 1% chlorhexidine gel twice daily). Patients who were suspected of having VAP when new, persistent infiltrate was seen on chest radiographies and at least two of the following are observed: a body temperature below 36°C or above 38°C, a white blood cell count lower than 4000/mm^3 or higher than 11 000/mm^3, and macroscopically purulent tracheal aspirate. The tracheal aspirate was classified as purulent or nonpurulent after visual inspection by the clinical treatment team. The definitive diagnosis of VAP was considered only in patients with positive quantitative culture results for bacterial pathogens.

Sputum and blood cultures were performed at VAP diagnosis and 7 days after that.

Data collection

(1) Demographic data including sex and age.
(2) Quantitative sputum cultures and blood culture were performed at day 1, at VAP diagnosis, and the seventh day of follow-up.
(3) Use of vasopressor.
(4) Chest radiography performed immediately after intubation, and every 48 h as routine follow up of ventilated patients. An additional chest radiography was performed according to the clinical condition of the patients.
(5) Length of ICU stay and mortality.
(6) Twelve-lead ECGs were performed with an estimation of corrected QT interval QTc, initial after the start of the VAP care bundle, and every 24 h after that.

Sample size calculation

We estimated the necessary sample size by using G*POWER3.1.7 Institute for Experimental Psychology in Dusseldorf Germany Gustav-Poensgen-Straße 29 40215 Düsseldo program based on the estimated incidence of VAP 47% with assumption to be reduced to 23% in the prophylaxis group with a two-tailed α-level of 0.05 and a power of 80%.

Statistical analysis

Data are expressed as absolute numbers with or without percentages, as means with SD or as medians with ranges. χ^2 test or Fisher's exact test was used to compare proportions, *t*-test or Mann–Whitney *U*-test to compare continuous variables. A probability value of less than 0.05 was considered to show the statistical significance and all reported *P* values are two sided. Statistical analysis will be performed using the SPSS/PC Statistical Package (SPSS Inc., Chicago, Illinois, USA).

Results

In this study, 80 patients, who were fulfilling the inclusion and exclusion criteria for the study, were chosen and arranged into two equal groups:

(1) Group A: included 40 patients who received clarithromycin.
(2) Group B: included 40 patients who served as the control group.

Both groups were compared as regards many variables, including demographic data, ICU stays (days), vasopressor use, the incidence of VAP, estimation of the corrected QT interval, and incidence of mortality.

Regarding demographic data, ICU stays, vasopressor use, statistical studies between both groups showed no significant differences (Table 1).

As regards the incidence of VAP, among the two groups, the diagnosis was established in 10 patients. The incidence of microbiologically confirmed VAP in group A was lower than that of group B (5 vs 20%, respectively, $P = 0.043$).

Seven patients had Gram-negative bacilli and three patients had Gram-positive cocci. The most common species isolated were *Klebsiella pneumoniae* ($n = 2$) and *Acinetobacter baumannii* ($n = 2$) (Fig. 1).

Regarding the estimation of the corrected QT interval, no patient in both groups developed a prolonged QT interval.

Regarding the incidence of mortality, the 28th day mortality rate was 39 (48.7%) patients among our cohort. The mortality incidence in patients in group A was 54% (21 patients). This was not different from the rate of mortality in group B (46%; 18 patients) ($P = 0.42$; Fig. 2).

Discussion

The main finding of the present study was that the addition of clarithromycin was associated with a significant reduction in the incidence of VAP in mechanically ventilated patients.

In this study, the diagnosis of VAP was established in 10 patients. The addition of clarithromycin resulted in a 75% reduction in the risk of occurrence of VAP. Consistent with our findings, Esteban *et al.*[6] tried to evaluate the effect of macrolide administration (clarithromycin and azithromycin) on the prevention of VAP and/or modification of its severity, morbidity, and prognosis in a prospective, double-blind, randomized, placebo-controlled, single-center clinical trial. They randomly allocated 20 patients to receive macrolides and another 20 patients to receive a placebo. They administered the study drugs for 14 consecutive days; then the evaluation of patients was observed for 28 days. They concluded in their study that macrolides appear to be an effective method for the prevention of VAP due to the absence of VAP in the group of patients receiving clarithromycin and the high incidence of VAP in the other group reaching about 71%. They also found that macrolides can help in accelerating the weaning from mechanical ventilation and improve the overall clinical state. The all-cause mortality at day 14 was not altered in their study.

Giamarellos-Bourboulis *et al.*[7] evaluated the effect of clarithromycin in patients diagnosed with VAP. They enrolled 200 patients with VAP into a double-blinded, randomized, multicenter trial; 100 patients received clarithromycin and another 100 patients were treated with placebo.

Intravenous 1 g of clarithromycin was administered once daily for 3 consecutive days. They found that the median time for resolution of VAP was 15.5 and 10.0 days among placebo-treated and clarithromycin-treated patients, respectively. Moreover, the median times for weaning from mechanical ventilation were 22.5 and 16.0 days, respectively ($P = 0.049$).

In this study, the incidence of mortality was comparable among the study groups. These results were in line with Giamarellos-Bourboulis *et al.* [7]; also, Tsaganos *et al.*[8] evaluated the effect of clarithromycin on survival in VAP and sepsis patients, in which 100 were allocated to blind treatment with a placebo and another 100 to intravenous clarithromycin at 1 g daily for 3 consecutive days and then the primary endpoint was 90-day mortality and found that there was statistically significant difference in mortality rate at day 90, at day 28, and in between day 28 and day 90, which indicate that intravenous clarithromycin for 3 consecutive days as an adjunctive treatment in VAP and sepsis developed long-term survival benefit.

Conclusion

Oral clarithromycin, when added to the VAP care bundle, will have a better prevention role of VAP.

Table 1: Showing demographic data, ICU stays, vasopressor use

	Group A ($n=40$)	Group B ($n=40$)	*P*
Age (years)	41.7±18.1	46.3±18.7	0.266
Sex: male	29 (72.5)	21 (52.5)	0.65
ICU stay (days)	18.3±15.2	16.4±18.6	0.525
Vasopressor use: yes	35 (87.5)	36 (90)	0.125

Data are presented as means±SD, frequency (%).

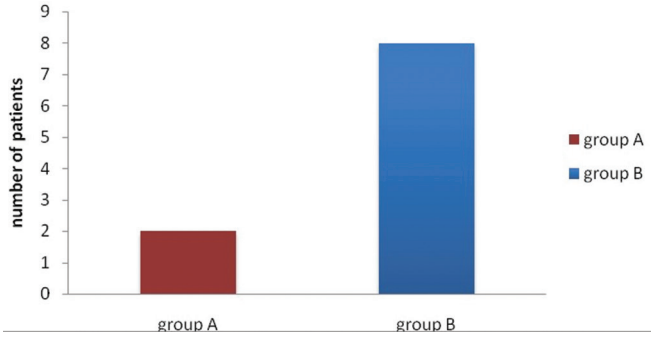

Figure 1: Incidence of ventilator-associated pneumonia.

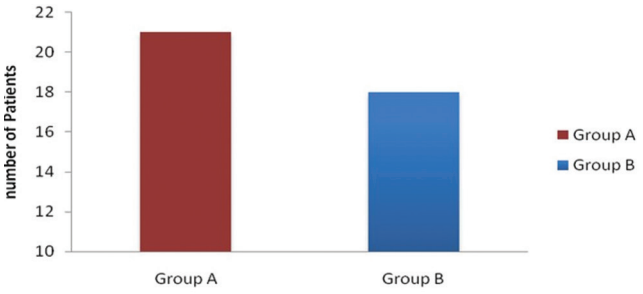

Figure 2: Incidence of mortality.

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Conflicts of interest

There are no conflicts of interest.

References

1. Papazian L, Bregeon F, Thirion X, Gregoire R, Saux P, Denis JP, *et al*. Effect of ventilator-associated pneumonia on mortality and morbidity. American Journal of Respiratory and Critical Care Medicine 1996; 154:91–7.
2. Vincent JL, Bihari DJ, Suter PM, Bruining HA, White J, Nicolas-Chanoin MH, *et al*. The prevalence of nosocomial infection in intensive care units in Europe: results of the European Prevalence of Infection in Intensive Care (EPIC) Study. Jama 1995; 274:639–44.
3. Chastre J, Fagon JY. Ventilator-associated pneumonia. Am J Respir Crit Care Med 2002; 165:867–903.
4. Niederman MS. Gram-negative colonization of the respiratory tract: pathogenesis and clinical consequences. Semin Respir Infect 1990; 5:173–184.
5. Torres A, Ewig S, Lode H, Carlet J. European HAP Working Group. Defining, treating and preventing hospital acquired pneumonia: European perspective. Intensive Care Medicine 2009; 35:9–29.
6. DelPilar Morales EA, Sergenton CS, Salgado MS. Macrolide use as prophylaxis for ventilator-associated pneumonia. Clin Infect Dis 2008; 12:1157–1164.
7. Giamarellos-Bourboulis EJ, Pechere JC, Routsi C, Plachouras D, Kollias S, Raftogiannis M, *et al*. Effect of clarithromycin in patients with sepsis and ventilator-associated pneumonia. Clinical Infectious Diseases 2008; 46:1157–64.
8. Tsaganos T, Raftogiannis M, Pratikaki M, Christodoulou S, Kotanidou A, Papadomichelakis E, *et al*. Clarithromycin leads to long-term survival and cost benefit in ventilator-associated pneumonia and sepsis. Antimicrobial Agents and Chemotherapy 2016; 60:3640–6.