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Original Article

Association of macrolides with overall mortality and cardiac death among patients with various infections: A meta-analysis

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ABSTRACT

Background: A large body of evidences suggested that macrolide therapy could improve the survival of patients with various infections. While in the same time, macrolides are known to increase fatal arrhythmogenic risks and cause cardiac death. To assess the risks and benefits of macrolide therapy, we systematically reviewed all studies of macrolide use, cardiac death and mortality among patients with various infections.

Methods: We searched Pubmed, Embase and Cochrane library and reviewed reference lists from 1980 through April 2015. Studies were included if they compared macrolides to other antibiotics in adults with various infections. The outcome measures were the overall mortality and the risk of cardiac death.

Results: Overall, macrolide use was associated with a statistically significant mortality reduction compared with nonmacrolide use (OR: 0.65, 95% CI: 0.46–0.92). There was no difference in the risk of cardiac death between macrolide and nonmacrolide regimes (OR: 1.43, 95% CI: 0.86–2.40). In subgroup analyses, macrolide use was found to be associated with the decreased risk of mortality in a population of older individuals (age > 48 years, OR: 0.69; 95% CI: 0.66–0.72). While in a general population of young and middle-aged adults, the use of macrolide-based regimens could not decrease the risk of death from any cause (age < 48 years, OR: 0.42; 95% CI: 0.02–11.01). As for cardiac death, macrolide use was found to be associated with increased risk of cardiac death in a population of older individuals (age > 48 years, OR: 1.99; 95% CI: 1.53–2.59).

Conclusion: Despite the potential cardiotoxic effects, there is a net benefit associated with macrolide use in older patients with various infections and macrolide use except roxithromycin was found to be associated with increased risk of cardiac death in a population of adults aged > 48 years.

1. Introduction

Macrolides, such as erythromycin and azithromycin, are commonly prescribed for outpatient treatment of respiratory infections, urinary tract infections and sexually transmitted diseases [1]. Recently, accumulating evidences suggested that these macrolide antibiotics can increase the risk of serious ventricular arrhythmias including torsades de pointes, and are associated with an increased risk of sudden cardiac deaths [2]. The Food and Drug Administration's Adverse Event Reporting System included at least 20 reports of torsades de pointes associated with azithromycin, erythromycin and clarithromycin, thus it issued public safety notification warning of proarrhythmic risks with macrolides [3]. Despite the risk of potentially fatal rhythms, use of macrolide antibiotics in community acquired pneumonia has been consistent with improved short-term mortality in observational studies [4,5]. Retrospective cohort study comparing older patients hospitalized with pneumonia prescribed with azithromycin therapy and patients receiving other guideline-concordant antibiotic therapy suggested a lower risk of 90-day mortality and a smaller increased risk of myocardial infarction, which showed a net benefit associated with macrolide use [6]. On one hand, a large body of evidences suggested that short term mortality is reduced in patients receiving macrolides for severe infections such as community acquired pneumonia. While on the other hand, macrolides themselves were found to increase the risk of severe arrhythmia and cardiac death during the treatment of the exactly same infections. Thus risks and benefits of macrolide therapies should be considered when making prescription decisions. To assess the risks and benefits of macrolide therapy, we systematically reviewed all studies of macrolide use, cardiac death and mortality among patients hospitalized with various infections.

2. Methods

2.1. Literature search and study selection

Relevant studies were identified by searching Medline, Pubmed, Cochrane library and Embase published until May 2015. Search

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criteria used were related to macrolide treatment, the risk of cardiac deaths and mortality. Specifically the following search items were used: macrolides, azithromycin, clarithromycin, roxithromycin, death, mortality. There were no language limitations for the initial search. Randomized controlled trials (RCTs), cohort studies and case–control studies were included.

2.2. Study selection

Human studies were included if they met the following criteria: (1) the study design was a case–control or cohort study; (2) the study investigated the association between the macrolide treatment and the risk of cardiac death/all-cause death.

2.3. Quality assessment

Two reviewers (Xiang Li and Min Wang) independently assessed the study quality using the criteria described in the Newcastle–Ottawa scale. A "score system" was developed and the total scores ranged from 0 (worst) to 9 (best) for case–control or cohort study.

2.4. Data extraction

Titles and abstracts of the articles were screened by two reviewers independently. Included articles for full text screening were compared during a consensus meeting. In case of disagreement, a third reviewer was consulted for the decision on inclusion or exclusion for full-text evaluation. Articles that did not contribute to the answer of our research questions after full text evaluation were excluded. After consensus the remaining articles were included for critical appraisal and assessed by two reviewers independently.

2.5. Data analysis and statistical methods

The significance of the combined OR was determined by the Z-test, in which $P < 0.05$ was considered significant. The χ^2-based Q statistical test was used for the assessment of the between-study heterogeneity, which was considered significant for $P < 0.1$. In analyses, if the heterogeneity was low (<50%), then we used a fixed-effect model, or else applied the random-effect model. Software of Review Manager 5 was used to perform the meta-analyses (available from Cochrane).

3. Result

3.1. Study selection

Fig. 1 shows the selective process after the search: of the 10 included articles in this systemic review, 4 reported the association between macrolide treatment and the risk of cardiac death [7–10], 7 reported the association between the macrolide treatment and the risk of crude mortality [6,11–15]. Patients in the included studies were prescribed with macrolide antibiotics and met the eligibility criteria on the date on which the prescription was filled. These criteria were as follows: eligible members were 18 to 74 years of age, had no life-threatening noncardiovascular illness, and had not been hospitalized in the prior 30 days. The persons in the control group had to satisfy the eligibility criteria on the day that the control period began and were prescribed other antibiotics rather than macrolides.

3.2. Characteristics of the studies

The characteristics of the included articles were reported in Table 1.

3.3. Assessment of methodological quality

Table 2 showed the quality scores of the included studies. Two studies [6,15] contained mild cohort selection bias because the exposed cohorts were not well representative (The researchers used data from the Veteran Administration health care system administrative and clinical databases). Two studies [11,13] had moderate comparability because they didn't fully adjust some confounding factors such as the severity of community acquired pneumonia.

3.4. The association between the macrolide treatment and the risk of overall mortality

A total of 7 studies included in our analysis reported the association between macrolide treatment and overall mortality. When compared with recipients in nonmacrolide containing regimens, only one study showed an increased risk of all-cause death in patients treated with macrolide antibiotics [7]. Another six studies demonstrated that use of macrolides is associated with improved survival after various infections [5,6,11–13]. Meta-analysis of these seven studies on macrolide therapy and all-cause mortality resulted in a pooled OR of 0.58, 95% confidence interval [CI]: 0.40–0.82, indicating that macrolide use was associated with a significant reduction in mortality as compared with nonmacrolides in patients hospitalized with various infections (Fig. 2A). There was considerable heterogeneity ($I^2 = 96\%$). We then assessed the source of heterogeneity by age and examined two subgroups according to the average age of patients involved in our analysis: subgroup 1 (age > 48 years) and subgroup 2 (age < 48 years). Among these studies, one study conducted by Brown RB et al. [13] didn't report the age of enrolled patients, thus it was not included in any subgroup. A total of four studies were included in the subgroup 1 and the remaining two studies were included in the subgroup 2. As a result, macrolide use was found to be associated with decreased mortality risks in a population of older individuals (age > 48 years, OR: 0.69; 95% CI: 0.66–0.72, $I^2 = 46\%$, P = 0.14) (Fig. 2B). While in a general population of young and middle-aged adults, the use of macrolide-based regimens could not decrease the risk of death from any cause (age < 48 years, OR: 0.42; 95% CI: 0.02–11.01, $I^2 = 97\%$, $P < 0.00001$) (Fig. 2C).

3.5. The association between the macrolide treatment and the risk of cardiac death

Comparing macrolide-based regimens with nonmacrolide use, no significant association with cardiac death was observed (OR: 1.43; 95% CI: 0.86–2.40) (Fig. 3A). Heterogeneity in this analysis was high ($I^2 = 87\%$). Since age was found to contribute to substantial heterogeneity in previous analysis, we then assessed the source of heterogeneity by age as well. Among the four observational studies included in our analysis, only one study reported the association between the macrolide treatment and the risk of cardiac death in younger and middle-aged patients (average age, 40 years) [9]. Another 3 studies reported the risk of cardiac death associated with macrolide use among patients at high baseline risk (age > 48 years). Besides, type of macrolides might also play a key role in affecting the rate of cardiac death. Among 3 included studies (age > 48 years), roxithromycin treatment was not associated with an increased risk of cardiac death, while other macrolides such as clarithromycin and azithromycin treatment could increase the potential risk of cardiac death. Therefore we investigated the risk of cardiac death associated with the use of clarithromycin and azithromycin. As a result, macrolide use (roxithromycin excluded) was found to be associated with increased risk of cardiac death in a population of older individuals (age > 48 years, OR: 1.99; 95% CI: 1.53–2.59, $I^2 = 37\%$, P = 0.20) (Fig. 3B).