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Original Article

Efficacy of sulbactam for the treatment of *Acinetobacter baumannii* complex infection: A systematic review and meta-analysis

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ABSTRACT

Meta-analyses that ignore the full programme of clinical trials may lead to a misleading interpretation. We did a comprehensive meta-analysis to explore the efficacy of sulbactam for the treatment of *Acinetobacter baumannii* complex infection. We searched electronic databases, including Pubmed and Embase up to April 24, 2016, to identify relevant published trials. Clinical trial registries were likewise searched to identify completed unpublished studies. Primary outcomes of interest were the clinical and microbiological efficacy and in-hospital mortality. Effect model was based on heterogeneity across studies. Altogether 12 observational trials, comprising about 1500 patients, were included. Compared with control group, the clinical response (OR 1.16, 95% CI 0.77–1.75), bacteriological response (OR 1.71, 95% CI 0.89–3.29) and in-hospital mortality (OR 0.76, 95% CI 0.57–1.01) of sulbactam-based therapy group achieved similar therapeutic in *A. baumannii* complex infection. Subgroup analysis showed the clinical response (OR 1.66, 95% CI 1.11–2.48) of *A. baumannii* complex infection favored high-dose sulbactam group. In conclusion, our findings suggested that the overall therapy effect of sulbactam was no more superior than alternative therapeutics. However, when taking consideration of the dose factor, we found that high dosage regimen of sulbactam showed an obvious advantage in the treatment of *A. baumannii* complex infection.

1. Introduction

Acinetobacter baumannii possesses an impressive armamentarium of resistance mechanisms, leading to the prevalence of multidrug-resistant (MDR), extremely drug-resistant (XDR), even pandrug-resistant (PDR) *A. baumannii* [1]. In addition, infections with MDR *A. baumannii* are associated with increased mortality, morbidity, length and cost of hospital stay. Class agents used to treat MDR *A. baumannii* have become invalid and new antibiotics available might have become targets for bacterial mechanisms of resistance. Recent meta-analyses suggested that colistin may be as efficacious and safe as standard antibiotics for the treatment of MDR *A. baumannii* infection [2,3]. The efficacy of a newer antimicrobial agent, tigecycline also yielded controversy [4]. Therefore, evaluation of "old" antimicrobial for efficacy has become an urgent priority.

Sulbactam, a β-lactamase inhibitor, has been co-formulated with ampicillin (SAM) or cefoperazone (SCF) to overcome the destruction of β-lactamase-producing organisms [5]. It is approved by the US Food and Drug Administration (FDA) for skin and soft tissue infection, intra-abdominal infection and gynaecological infection. Meanwhile, sulbactam itself has high affinity for penicillin binding proteins (PBPs), in particular types 1a and 2. As a result, it exhibits intrinsic *in vitro* activity against *Acinetobacter* spp., including carbapenem-resistant strains [6].

Many studies have assessed *in vitro* activity of sulbactam against resistant organism and its clinical efficacy [5–7]. A previous effort to assess the efficacy of sulbactam in the treatment of *A. baumannii* infection by pooling the results of existing trails was done by Chu et al. [8], but was limited to four published observational cohort studies. Their findings indicated that sulbactam-based therapy may be similarly efficacious to alternative antimicrobial therapies for

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the treatment of *A. baumannii* infection. However, meta-analyses that ignore the full programme of clinical trials could reach a narrow and misleading interpretation [9]. Therefore, we aimed to assess the efficacy of sulbactam, compared with other antimicrobial agents, for treatment of *A. baumannii* complex infection by updating the meta-analysis conducted by Chu et al. with more comprehensive search. This report follows PRISMA (Preferred Reporting Items for Systematic reviews and Meta-Analysis) statement [10].

2. Materials and methods

2.1. Search strategy and selection criteria

We searched electronic databases, including Pubmed and Embase from their inception until April 24, 2016, to identify relevant published trials, with the main search terms "*baumannii*" and "sulbactam". To identify relevant completed trials that were unpublished, we searched the relevant website (https://clinicaltrials.gov). Furthermore, the reference lists of reports identified by this search strategy were also searched to select relevant articles [8,11,12]. No language restrictions were used.

Two investigators (HC, CL) independently made a choice on trials considered eligible for inclusion if they were randomized control trials (RCTs) or observational cohort trials with comparison of the clinical efficacy of sulbactam, eradication of pathogen and in-hospital mortality, against other antimicrobial agents for treatment of *A. baumannii* complex infection. We excluded experimental trials in animals, trials focusing on pharmacokinetic or pharmacodynamic variables, *in vitro* activity of sulbactam, series with <10 infected patients in group, no available data and unpublished studies that were incomplete.

2.2. Data extraction and quality assessment

Two investigators (HC, CL) independently extracted the relevant data and evaluated the quality of studies. The controversy will be discussed. The following variables were collected from each study: first author; year of publication; country; study period; study design; baseline characteristics of the study population, including sample size, age, sex, site of infection, severity of illness [Acute Physiology and Chronic Health Evaluation (APACHE) scores]; dose of sulbactam administered; co-administration of other antibiotics; treatment duration; type of organisms; outcomes, concluding clinical response, microbiological response, in-hospital mortality. If the data could not be extracted from trials, the investigators would contact with the first author for retrieval of missing data.

The primary outcome of interest was the clinical response, which was defined as cure/success (resolution of symptoms and signs of infection at the end of therapy) or clinically significant improvement of patients (partial resolution of symptoms and signs of infection by end of therapy) [13]. The secondary outcome of interest were mortality and microbiological response defined as eradication of organisms or suppression of organisms [13].

The Newcastle-Ottawa Scale (NOS) score was determined to assess the quality of observational non-randomized control trials included in the meta-analysis [14]. Trials with a NOS score <3 were classified as poor quality and were excluded from this meta-analysis.

2.3. Statistical analysis

The meta-analysis was performed by Review Manager v5.3 and STATA v12.0 software. Pooled odds ratios (ORs) and 95% confidence intervals (CIs) were calculated using either fixed effects model (Mantel-Haenszel method) or random effects model (DerSimonian and Laird's method) according to between-study heterogeneity results. The heterogeneity across studies was assessed using the χ^2 based Q statistics and I^2 test, and was defined as low ($I^2 = 25\%–49\%$), moderate ($I^2 = 50\%–75\%$) and high ($I^2 \geq 75\%$) [15]. In case of substantial inconsistency, a L'Abbe plot was employed to graphically identify the potential sources of heterogeneity in meta-analysis [16]. Subgroup analyses were conducted by type of infection, study design and antimicrobial agents. Subgroup analysis based on the dosage regimens of sulbactam that was defined as low (sulbactam, 3 g/day), moderate (sulbactam, 6 g/day) and high (sulbactam $\geq$ 9 g/day) [17], was also performed. A funnel plot or Arcsine Thompson test were used to evaluate the possible publication bias. Peters and Harbord test was adopted if the heterogeneity was insignificant. Otherwise, Arcsine transformation test was used [18].

3. Results

3.1. Flow of included studies

A total of 1435 studies from the two databases plus 10 additional studies from other sources were identified. 50 full-text articles met the inclusion criteria according to information in the title and abstract and were assessed for eligibility. After that, 38 studies were excluded for no control regimens, no available data and series with <10 infected patients in group. Finally, a total of 12 studies were included in meta-analysis [13,19–29]. The detailed search process and study selection are provided in Fig. 1.

3.2. Study characteristics

Finally, 12 studies (1472 patients) were included in this meta-analysis. Including, one prospective cohort study and eleven retrospective cohort studies. Six trials compared the efficacy of SAM or SCF with carbapenem or colistin. Four trials compared the efficacy of sulbactam combination with colistin against colistin-based therapy. Two trials compared the efficacy of sulbactam plus carbapenem with cephalosporins, penicillins, fluoroquinolones, aminoglycosides and tigecycline. Ten trials provided the APACHE II scores of patients. The mean APACHE II scores were 26.66 for the sulbactam group and 26.8 for the control group. The other two studies did not provide the APACHE II scores. The median quality score of the twelve published studies was 8 (range 6–9) and eleven trials had a high score of 9. Most of these patients were associated with bloodstream infection (BSI) and pneumonia infected MDR *A. baumannii*, XDR *A. baumannii* or PDR *A. baumannii*. The characteristics of the studies included in this analysis are shown in Table 1.

3.3. Clinical response

As is shown in Fig. 2, twelve studies (1472 patients) compared the clinical response of sulbactam group with the control group. No significant statistical difference was observed across these studies (OR 1.16, 95% CI 0.77–1.75). Of note, substantial heterogeneity was presented among the studies ($\chi^2 = 29.64$, $p = 0.002$, $I^2 = 63\%$). There were at least 8 studies deviated from the line in the L'Abbe plot. Therefore, random-effects model was used in this analysis.

3.4. Microbiological response

As is shown in Fig. 2, of the eight studies (1049 patients) that reported the microbiological response compared sulbactam-based therapy group with the control group. Substantial heterogeneity was observed among these studies ($\chi^2 = 22.53$, $p = 0.002$, $I^2 = 69\%$). Although the microbiological response rate favored sulbactam-