Ceftriaxone combination therapy versus respiratory fluoroquinolone monotherapy for community-acquired pneumonia: A meta-analysis

Ying-Qi Zhang, MD a,b, Shui-Lan Zou, MD b, Hua Zhao, MD a, Ming-Ming Zhang, MD a, Cai-Li Han, MD a

a Department of Emergency Medicine, The First Hospital of Hebei Medical University, 89 Donggang Road, Shijiazhuang, Hebei Province, China. 

b Department of General Internal Medicine, Aviation General Hospital of China Medical University, 3 Beiyuan Road, Beijing 100012, China

ABSTRACT

Background: The goal of this study was to investigate whether ceftriaxone combination therapy is associated with better clinical outcomes than respiratory fluoroquinolone monotherapy for adults with community-acquired pneumonia (CAP). We conducted a meta-analysis of published studies.

Methods: Using the PubMed, EMBASE, and Cochrane Library databases, we performed a literature search of available randomized controlled trials (RCTs) published as original articles before September 2017.

Results: Nine RCTs, involving 1520 patients, were included in the meta-analysis. The pooled relative risks (RRs) for the efficacy of ceftriaxone combination therapy versus respiratory fluoroquinolones monotherapy were 0.96 (95% CI: 0.92–1.01), based on clinically evaluable populations, and 0.93 (95% CI: 0.88–0.99) based on intention-to-treat (ITT) populations. No statistically significant differences were observed in microbiological treatment success (pooled RR = 0.99, 95% CI: 0.95–1.01), although drug-related adverse events were significantly lower with ceftriaxone combination therapy than with respiratory fluoroquinolones monotherapy (pooled RR = 1.27, 95% CI: 1.04–1.55).

Conclusions: Current evidence showed that the efficacy of ceftriaxone combination therapy was similar to respiratory fluoroquinolone monotherapy for hospitalized CAP patients, and was associated with lower drug-related adverse events.

1. Introduction

Community-acquired pneumonia (CAP) is one of the leading causes of death and hospitalization for all age groups throughout the world [1,2]. Short-term mortality (in-hospital and 30-day mortality) for hospitalized patients with CAP ranges from 4.0% to 18.0% [3]. It is likewise the most frequent cause of community-acquired infections admitted to intensive care units (ICU) [4], and mortality can reach 50% for patients in the ICU [5]. The most common cause of CAP is Streptococcus pneumoniae [6–8]. However, it is a challenge to treat CAP due to increased incidence of antibiotic resistance [9,10] and the occurrence of other atypical pathogens (Mycoplasma pneumoniae, Chlamydophila pneumoniae, and Legionella species). The treatment of CAP requires antibiotics, and inappropriate use of them in the community and hospitals has contributed to resistance. Thus, antibiotic therapy for CAP should be focused on the most efficient and effective antibiotic regimens.

Patients’ outcomes from CAP depend on timely diagnosis and treatment, involving appropriate antimicrobial therapy directed at the most common possible respiratory pathogens. Beta-lactam-based therapy for CAP covers the most common possible pathogens involved in the pathogenesis of CAP and acts as one of the first-line standard treatments. It was suggested that patients be administered third-generation cephalosporin, such as cefotaxime or ceftriaxone, for high-severity CAP [11]. Ceftriaxone is a broad-spectrum antibiotic, most commonly used in the emergency department, particularly for patients with community-acquired pneumonia [12]. Fluoroquinolones have also been considered a possible regimen for CAP because of their effectiveness as a single agent [13], low spontaneous mutation rate for resistance, and cost-saving potential [14]. However, previous studies were not consistent and did not assess which was the better choice for CAP. We aimed to compare the efficacy, drug-related adverse events, and microbiological responses to ceftriaxone combination therapy with respiratory fluoroquinolone monotherapy for the treatment of CAP and conducted a meta-analysis of randomized controlled trials.

2. Methods

2.1. Search strategy

A systematic search was performed in the PubMed, EMBASE, and Cochrane Central Register of Controlled Trials (Cochrane Library Issue 1 of 9, 2017) databases to find studies published before September 2017.
2017. Because several quinolones have been withdrawn from clinical use since the conduct of the trials, we used the keywords “levoﬂoxacin”, “moxifloxacin”, “ceftroxime” in combination with “community acquired pneumonia” and “CAP” to search the literature. There was no limitation on language or date of publication. We reviewed the reference lists of included articles for additional studies.

2.2. Selection criteria

Studies were included in the meta-analysis if they fulfilled the following criteria: (1) randomized controlled trials (RCTs) of adults aged >18 years with community acquired pneumonia (CAP); (2) comparison of the clinical efﬁcacy and/or safety of ceftriaxone combination therapy versus respiratory ﬂuoroquinolone monotherapy; (3) trials with blinded or unblinded design were included.

2.3. Data extraction and risk of bias

Data on study characteristics, treatment success, microbiological treatment success, and drug-related adverse events (AEs) were abstracted onto a standardized form by 2 authors independently and discrepancies were resolved by consensus in consultation with a third reviewer. The risk of bias for included studies was assessed by the Cochrane Collaboration’s tool for evaluating study bias [15].

2.4. Analyzed outcomes

Treatment success was deﬁned as primary outcome at the test-of-cure (TOC) visit based on clinically evaluable and ITT populations. The secondary outcomes included drug-related adverse events (AEs) and microbiological treatment success. Treatment success was deﬁned as “clinical cure”, which was the disappearance of all signs and symptoms related to infection.

2.5. Statistical analysis

The statistical heterogeneity among studies was tested with the Q statistic, and inconsistency was quantiﬁed with the I² statistic [16]. For the Q statistic, statistical signiﬁcance was set at P < 0.1. When heterogeneity was detected, the random-effects model was used [17]. Analyses were performed with STATA 14.0 (StataCorp, College Station, TX, USA) and RevMan 5.3 (Cochrane Collaboration, Copenhagen, Denmark).

3. Results

3.1. Study characteristics and risk of bias

Six hundred sixty-eight potentially relevant articles were identiﬁed using the pre-deﬁned search criteria by a primary computerized literature search. After screening titles and abstracts and reviewing the full-text articles, nine RCTs [18–27] were included (Fig. 1). Of these studies, six were in English, two were in Chinese, and one was in Spanish. The majority of participants included in the studies were the patients with moderate and/or severe CAP. The length of treatment was 7–14 days in most studies. The main characteristics of the studies that were included in the meta-analysis are summarized in Tables 1. The risk of bias summary for included studies is listed in Fig. 2.

3.2. Treatment success

All included trials reported the treatment success for clinically evaluable populations at the test-of-cure (TOC) visit. In Fig. 3, the analysis of all the studies revealed that there was no difference in treatment success between ceftriaxone combination therapy and respiratory ﬂuoroquinolone monotherapy (pooled RR = 0.96, 95% CI: 0.92–1.01) based on clinically evaluable populations. Only ﬁve trials provided data about treatment success for ITT populations at the TOC visit. Ceftriaxone combination therapy was slightly more effective than respiratory ﬂuoroquinolone monotherapy (pooled RR = 0.93, 95% CI: 0.88–0.99) based on ITT populations, as shown in Fig. 4.

3.3. Drug-related adverse effects

Data on drug-related AEs in the clinically evaluable populations were reported for six trials. The most common AEs were gastrointestinal disturbances, including diarrhea, vomiting, and other GI complaints. Fig. 5 shows that ceftriaxone combination therapy was associated with fewer adverse events (pooled RR = 1.27, 95% CI: 1.04–1.55).

3.4. Microbiological treatment success

Four of the nine relevant RCTs provided microbiological treatment success outcomes. No signiﬁcant difference was observed between a ceftriaxone combination regimen and respiratory ﬂuoroquinolone monotherapy (pooled RR = 0.99, 95% CI: 0.90–1.09), as shown in Fig. 6.

4. Discussion

To our knowledge, no meta-analysis comparing respiratory ﬂuoroquinolone monotherapy to ceftriaxone combination therapy for community-acquired pneumonia has been published. A total of 1520 patients in 9 independent studies were identiﬁed in this meta-analysis. The results of this meta-analysis indicated that ceftriaxone combination therapy was similar to respiratory ﬂuoroquinolone monotherapy, and the drug-related AEs were fewer in the ceftriaxone combination therapy regimen.

A meta-analysis conducted by Vardakas et al. [28] reported that respiratory ﬂuoroquinolones were associated with higher clinical efﬁcacy than combination therapy was. Similarly, a cohort from Querol-Ribelles JM et al. [29] also reported that levofloxacin was superior to the combination of ceftriaxone and clarithromycin in the treatment of community-acquired pneumonia that requires hospitalization. Furthermore, Fan H et al. [30] reported that in the treatment success rates, no signiﬁcant differences were found between the respiratory ﬂuoroquinolone monotherapy and the β-lactams plus macrolides combination therapy based on the data of intention-to-treat (ITT) and per-protocol (PP) analyses. Our meta-analysis demonstrated that the efﬁcacy of ceftriaxone combination therapy was similar to respiratory ﬂuoroquinolone monotherapy for hospitalized CAP patients, with higher treatment success rates based on ITT populations.

In the included studies, in which drug-related adverse events were mentioned, the most common AEs for ceftriaxone were gastrointestinal disorders, such as diarrhea and vomiting; other AEs were phlebitis, nausea, rash, and so on. Macrolides were the most common combination drug regimen with ceftriaxone; six studies (azithromycin in three articles, clarithromycin in two articles, and erythromycin in two articles) used it. It was reported that Clostridium difﬁcile infection, enterocolitis, central nervous system (CNS) effects, and digestive effects are common drug-related AEs in patients taking macrolide antibiotics [31]. For the compared regimens, ﬂuoroquinolones can cause a range of serious drug-related adverse events. The drug-related adverse events that were reported in the included studies were gastrointestinal disorder (nausea, vomiting, diarrhea), rash, urticarial, phlebitis, dizziness, insomnia, paroniria, seizures, and headache. In addition, the Food and Drug Administration (FDA) recently advised restricting ﬂuoroquinolone antibiotic use for its potential side effects [32]. All in all, there were fewer drug-related adverse events in CAP patients taking ceftriaxone combination therapy in our meta-analysis, which may make it a better choice for treating CAP.

The results of this meta-analysis indicated that there was no statistical difference between the two antibiotic regimens in microbiological treatment success. However, another meta-analysis reported that...
Table 1

<table>
<thead>
<tr>
<th>Study</th>
<th>Year</th>
<th>Type of study</th>
<th>Included population</th>
<th>Drug regimen</th>
<th>Enrolled population</th>
<th>Intention to treat</th>
</tr>
</thead>
<tbody>
<tr>
<td>Frank</td>
<td>2002</td>
<td>Multicenter, randomized, open-label study</td>
<td>Patients ≥18 years old with a primary diagnosis of CAP</td>
<td>i.v. azithromycin 0.5 g OD + i.v. ceftriaxone 1 g OD</td>
<td>236</td>
<td>121 vs. 115</td>
</tr>
<tr>
<td>Erard</td>
<td>2004</td>
<td>Randomized, open-label, controlled pilot observational study</td>
<td>Patients ≥18 years old admitted for the treatment of CAP</td>
<td>i.v. ceftriaxone 2 g OD ± i.v/p.o. clarithromycin 1 g OD</td>
<td>129</td>
<td>37 vs. 79</td>
</tr>
<tr>
<td>Fogarty</td>
<td>2004</td>
<td>Randomized, open-label, comparative, study</td>
<td>Patients ≥18 years old with signs and symptoms of CAP</td>
<td>i.v/i.m. ceftriaxone sodium 1–2 g OD + i.v. erythromycin 0.5–1 g/6 h</td>
<td>269</td>
<td>137 vs. 132</td>
</tr>
<tr>
<td>Zervos</td>
<td>2004</td>
<td>Multicenter randomized, open-label study</td>
<td>Patients ≥18 years old with a clinical diagnosis of CAP</td>
<td>i.v. ceftriaxone 1 g OD + i.v. azithromycin 0.5 g OD</td>
<td>219</td>
<td>112 vs. 107</td>
</tr>
<tr>
<td>Welte</td>
<td>2005</td>
<td>Multicenter, randomized, controlled, nonblinded study</td>
<td>Patients ≥18 years old with a primary diagnosis of CAP</td>
<td>i.v. ceftriaxone 2 g OD ± i.v. erythromycin 1 g OD</td>
<td>397</td>
<td>197 vs. 200</td>
</tr>
<tr>
<td>Yang</td>
<td>2009</td>
<td>Randomized study</td>
<td>Elderly patients with moderate to severe CAP</td>
<td>i.v. ceftriaxone sodium 2 g OD + i.v. azithromycin 0.5 g OD</td>
<td>100</td>
<td>50 vs. 50</td>
</tr>
<tr>
<td>Liu</td>
<td>2010</td>
<td>Randomized, controlled clinical study</td>
<td>Patients ≥18 years old with a primary diagnosis of CAP</td>
<td>i.v. ceftriaxone sodium 2 g OD + i.v. azithromycin 0.5 g OD</td>
<td>58</td>
<td>30 vs. 28</td>
</tr>
<tr>
<td>Lee</td>
<td>2012</td>
<td>Randomized, open-label study</td>
<td>Patients admitted to a hospital for CAP treatment</td>
<td>i.v. ceftriaxone 2 g OD ± p.o. clarithromycin 0.5 g OD</td>
<td>40</td>
<td>20 vs. 20</td>
</tr>
<tr>
<td>López-Véjar</td>
<td>2013</td>
<td>Randomized, open-label, controlled study</td>
<td>Patients ≥18 years old with CAP with a severity index of pneumonia ≥ III</td>
<td>i.v./p.o. levoflaxacin 0.75 g OD</td>
<td>72</td>
<td>36 vs. 36</td>
</tr>
</tbody>
</table>

i.v.: intravenous, OD: once daily, b.i.d.: twice daily, p.o.: oral.

moxifloxacin had a favorable microbiological treatment success rate compared with β-lactam-based regimens [14]. It seemed that for microbiological treatment success, ceftriaxone combination therapy was not superior to respiratory fluoroquinolones monotherapy.

Several potential limitations of this meta-analysis should be noted. First, the included studies in this meta-analysis were open-label trials. Consequently, the relatively low quality of the included trials may affect our findings. Second, our meta-analysis was based on a small number of studies, and the results in this paper may also be affected. Third, one RCT [25] assessed the efficacy and safety in the elderly and one RCT [24] included only patients with mycoplasma pneumonia, making these results also less applicable to the general population.

The findings of this meta-analysis suggest that ceftriaxone combination therapy was as efficacious as respiratory fluoroquinolones monotherapy, but the drug-related AEs were lower in the ceftriaxone combination therapy regimen. Given the limitation of quantity and quality of these included studies, more high-quality RCTs are required to explore the conclusion further.

**Conflicts of interest**

The authors declare no conflicts of interest.

**Acknowledgments**

This work was supported by grants from the Medical Science Research Program of the Health and Family Planning Commission [Grant number 20160210] and Provincial Science and Technology Social
Fig. 3. Forest plots of treatment success, comparing respiratory ceftriaxone combination therapy with fluoroquinolone monotherapy for the treatment of CAP, based on the clinically evaluable population.

Fig. 4. Forest plots of treatment success, comparing respiratory ceftriaxone combination therapy with fluoroquinolones monotherapy for the treatment of CAP, based on the ITT population.

**Fig. 5.** Forest plots of drug-related adverse effects comparing ceftriaxone combination therapy with respiratory fluoroquinolone monotherapy.

<table>
<thead>
<tr>
<th>Study (year)</th>
<th>RR (95% CI)</th>
<th>Weight (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Frank (2002)</td>
<td>1.99 (1.08, 3.00)</td>
<td>10.64</td>
</tr>
<tr>
<td>Erard (2004)</td>
<td>0.30 (0.02, 5.68)</td>
<td>1.81</td>
</tr>
<tr>
<td>Fogarty (2004)</td>
<td>1.16 (0.79, 1.71)</td>
<td>27.75</td>
</tr>
<tr>
<td>Welte (2005)</td>
<td>1.19 (0.91, 1.55)</td>
<td>51.68</td>
</tr>
<tr>
<td>Liu (2010)</td>
<td>1.87 (0.83, 5.52)</td>
<td>3.32</td>
</tr>
<tr>
<td>Lee (2012)</td>
<td>1.17 (0.46, 2.88)</td>
<td>4.81</td>
</tr>
<tr>
<td>Overall (I² = 0.0%, P = .553)</td>
<td>1.27 (1.04, 1.55)</td>
<td>100.00</td>
</tr>
</tbody>
</table>

**Fig. 6.** Forest plots of microbiological treatment success comparing ceftriaxone combination therapy with respiratory fluoroquinolone monotherapy.

<table>
<thead>
<tr>
<th>Study (year)</th>
<th>RR (95% CI)</th>
<th>Weight (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Frank (2002)</td>
<td>1.03 (0.81, 1.17)</td>
<td>27.40</td>
</tr>
<tr>
<td>Fogarty (2004)</td>
<td>0.93 (0.82, 1.06)</td>
<td>52.04</td>
</tr>
<tr>
<td>Zervos (2004)</td>
<td>1.22 (0.77, 1.50)</td>
<td>10.98</td>
</tr>
<tr>
<td>Lee (2012)</td>
<td>Excluded</td>
<td>0.00</td>
</tr>
<tr>
<td>Overall (I² = 0.0%, P = .378)</td>
<td>0.99 (0.90, 1.09)</td>
<td>100.00</td>
</tr>
</tbody>
</table>
Benefit Program [Grant number 15277710D] in Hebei Province. The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

References

[22] Welte T, Petermann W, Schuurman D, Bauer T, Reimitz P, Group MS. Treatment of sequential intravenous or oral moxifloxacin was associated with faster clinical improvement than was standard therapy for hospitalized patients with community-acquired pneumonia who received initial parenteral therapy. Clin Infect Dis 2005;41:1697–705.