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Full Length Research Paper

Comparing therapeutic and adverse effects of moxifloxacin and levofloxacin in treatment of community acquired pneumonia: A meta-analysis of randomized controlled trials

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The aim of this study was to compare more conclusively the efficacy and safety of moxifloxacin, a new respiratory fluoroquinolone antibiotic with levofloxacin therapy which has been reported to possess good efficacy for community acquired pneumonia (CAP) in hospitalized elderly patient. The entire patients were mild to moderate by CAP. All the trials administered intravenously moxifloxacin (400 mg daily) and intravenously levofloxacin (200- 500 mg daily) for 7-14 days. Clinical response during therapy was between days 3 and 5 after the start of therapy. A meta-analysis of randomized controlled trials (RCTs, identified in CNKI, PubMeD, Embase, Google) were performed. Eight RCTs involving 1310 patients were included in meta- analysis. Two reviewers independently extracted data from published trials that compared fluoroquinolones. A meta-analysis was performed with the clinical outcomes of moxifloxacin and levofloxacin. Moxifloxacin monotherapy was associated with better therapeutic effect [(OR=1.63, 95%CI 1.01-2.63) and similar adverse effect (OR=1.12, 95%CI 0.81-1.55)] compared with levofloxacin therapy for CAP. Moxifloxacin has better therapeutic effects with comparable adverse events compared to levofloxacin.

Key words: Moxifloxacin, levofloxacin, randomized control trial, community acquired pneumonia.

INTRODUCTION

Community acquired pneumonia (CAP) occurs in an estimated 5 to 6 million annually in the United States and results in an estimated 10 million physician visits, about 1.1 million hospitalizations and approximately 60,000 deaths (Niederman et al., 1998).

The outcome of CAP depends on timely diagnosis and treatment involving appropriate antimicrobial therapy directed at the most common and possible respiratory pathogens. Empiric antibiotic therapy in hospitalized CAP patients should consist of a beta-lactam (for example, cefotaxime, ceftriaxone, ampicillin, or for selected patients, ertapenem) plus macrolide regimen or alternatively, respiratory fluoroquinolone (for example, moxifloxacin or levofloxacin) (Mandell et al., 2007). Numerous studies have demonstrated the safety and efficacy of respiratory fluoroquinolones in hospitalized CAP patients (Welte, 2005). Fluoroquinolones lead to earlier hospital discharge, which in some studies has led to cost savings in comparisons to beta-lactam–macrolide regimens or nonstandardized regimens (Bauer et al., 2005). Respiratory fluoroqinolone antibiotic like moxifloxacin and levofloxacin act by inhibiting bacterial topoisomerases II and IV, so they not only posses increased activity against typical, atypical and anaerobic respiratory pathogens, but also have enhanced potential to minimize the emergence of bacterial resistance (Brueggemann et al., 1997; Jones et al., 2001).

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Moxifloxacin has showed greater *in vitro* potency than levofloxacin against pneumococcus and the clinical correlate of this could be more rapid killing of bacteria with a faster time to clinical improvement in CAP patients (Boswell et al., 2002). Moxifloxacin has 90% minimum inhibitory concentration (MIC90) of 0.25 µg/ml *in vitro*. Moxifloxacin 400 mg once daily has a 24 h serum area under the curve (AUC) to MIC90 ratio (AUC/MIC90) of 96. On the other hand, levofloxacin 500 mg once daily has an MIC90 of 1 µg/ml and an AUC/MIC90 ratio of 34, whereas 750 mg daily levofloxacin has an MIC90 of 1 µg /ml and AUC/MIC90 ratio of 64 (Wispelwey, 2005).

Achieving adequate drug concentration at the site of infection is also equally important. In a small study of 47 adult s undergoing diagnostic bronchoscopy, moxifloxacin 400 mg showed equivalent steady- state concentrations in epithelial lining fluid (ELF) and macrophages at <12h compared with levofloxacin 500 mg. In contrast, moxifloxacin achieved significantly higher steady-state concentrations in both ELF and macrophages at 24 h compared to levofloxacin (Bhavnani and Andes, 2005). In other studies, the concentrations of moxifloxacin and levofloxacin in ELF after single or multiple dosing schedules were 20.7 and 10.9 mg/l respectively and in macrophages were 56.7 and 27.7 mg/l, respectively (Capitano et al., 2004).

In the Community-Acquired Pneumonia recovery in the elderly study, a prospective, randomized, double-blind trial, treatment with moxifloxacin 400 mg daily was associated with significantly faster clinical recovery than with 500 mg daily levofloxacin treatment in hospitalized elderly CAP patients, although no such significant difference was seen in clinical cure rates when assessed 5 to 21 days after completion of treatment (Lannini, 2007). A recent retrospective database analysis of hospitalized patients with CAP suggested that initial treatment with intravenous (IV) levofloxacin 750 mg reduced hospital length of stay (LOS) by 0.5 day when compared with initial treatment with IV moxifloxacin 400 mg (Schein et al., 2008).

Several randomized controlled trials (RCTs) and one retrospective study have been performed to compare the efficacy of moxifloxacin with that of levofloxacin (Anzueto et al., 2006; Zhao et al., 2008; Yang et al., 2009; Lin, 2007; Sun and Liu, 2008; Huang et al., 2009; Jiang, 2010; Morganroth et al., 2005). However, no constant result was seen in the above articles. The aim was to compare the therapeutic and the adverse effects of moxifloxacin and levofloxacin in the treatment of CAP.

MATERIALS AND METHODS

Data source

This study was performed using a pre-specified search strategy and study eligibility criteria. An extensive search of CNKI, PubMed, Embase, google was performed to identify relevant RCTs for the meta-analysis. The search was restricted to RCTs. Search term combinations were 'quinolone' and 'community acquired pneumonia'. The language of the research papers was not restricted to English.

Study selection

Two reviewers [BQ Wu, YCP] independently carried out the literature search and examined relevant RCTs for further assessment. Additional case studies were included in the meta-analysis especially if: it was a RCT, it included patients of all ages with CAP. It compared the efficacy and safety of moxifloxacin and levofloxacin for community acquired pneumonia (CAP) and it reported specific data regarding the effectiveness of clinical treatment mortality and adverse reactions. Both double blinded and non blinded trials were included. Abstracts in the proceeding of scientific conferences as well as experimental trials were not included in this meta-analysis.

Qualitative assessment

Evaluation of the methodological quality of the RCTs included in the meta-analysis was performed independently by two reviewers (BQ WU and YCP) using Jaded scoring system (Jadad et al., 1996). A RCTs with a score >2 was considered to be good quality (Khan et al., 1996; Moher et al., 1996).

Data extraction

In the meta-analysis using a predesigned review form, data on study characteristics (methodology, included population, study design, drug tested and publication details), two reviewers (BQ Wu and YCP) independently extracted data from the trials included endpoint data and adverse events during the treatment and post- treatment period were extracted.

Analysis of outcome

The primary efficacy outcomes of this meta-analysis were the success of clinical treatment, 'clinical cure" defined as the disappearance of acute signs and symptoms related to infection with no further requirement of antibiotic therapy for clinically evaluable populations in each study. The primary safety outcome was the patients reporting at least one adverse event.

Data analysis and statistical methods

Statistical analyses were performed with Review manager version (RevMan) 4.3 (cocharane collaboration). The heterogeneity of trial result was determined through the calculation of χ^2 test of heterogeneity and that of I^2 measure of inconsistency. The funnel plot was used to examine the publication bias in the therapeutic effect and adverse effect of moxifloxacin versus levofloxacin in the treatment of CAP. The publication bias was usually caused by lack o f negative literature and lower quality of data. Odds ratio (ORs) and 95% confidence intervals (CIs) were calculated throughout the meta-analysis.

RESULTS

Study selection process

Eight articles were found after the search in CNKI,

Pubmed, Embase and Google involving 1310 patients that fulfilled all the criteria for inclusion in the meta-analysis.

Study characteristics

The main characteristics of the eight included RCTs (type of study design, characteristics of the included population, drugs tested, number of patient, Jadad score and funding source) are presented in Table 1. All of the eight included RCTs were performed exclusively in adult patients with CAP. Seven of the RCTs were assessed to be good in terms of methodology with a Jadad score ≥2; the trial performed by Jiang (2010) was assessed to be of low quality with a jaded score of 1. Treatment schedules were comparable between the included trials with respect to comparing moxifloxacin and levofloxacin therapy for CAP. Patients in the moxifloxacin group received 400 mg once daily (orally or intravenously), while the levofloxacin was given 200 to 750 mg orally or intravenously. Definitions of CAP, Efficacy end points and safety endpoints were also comparable among the included trials. The trials included in the meta-analysis were somewhat heterogeneous in terms of included patients and drug administration route.

Clinical treatment success and mortality

Overall success rates after clinical treatment in the moxifloxacin group [345(91.51%) of 377 patients] were higher than that in the levofloxacin therapy group [331(87.10%) of 380 patients]. In the clinically evaluable population with OR 1.63 and 95%CI (1.01-2.63), thus favouring the moxifloxacin group (Figure 1).

1. The therapeutic effect of moxifloxacin versus levofloxacin in the treatment of CAP. The therapeutic efficiency of moxifloxacin was higher than levofloxacin in the treatment of CAP (Z=1.99, P=0.05) (Figure 1).
2. The test for the susceptibility of data: After removing the article by Jiang with poor Jadad score of one, the results showed that the clinical therapeutic effect of moxifloxacin was not statistically different from levofloxacin (Z=1.91, P=0.06) (Figure 2). If the fixed effect model changed to the random effect model, the therapeutic effect of moxifloxacin was not higher than levofloxacin (Z=1.31, P=0.19) (Figure 3).
3. Funnel plot for publication bias in the therapeutic effect of moxifloxacin versus levofloxacin in the treatment of CAP. The publication bias was usually caused by lack of negative literatures and lower quality of data (Figure 4).

Adverse outcome

The vast majority of adverse events were mild to moderate. The most common adverse events were abnormal liver function tests, diarrhea, nausea, rashes cardiac adverse events etc. for the above two groups as shown in Table 2.

In the total evaluable safety population, 98(17.13%) of 572 patients in moxifloxacin group and 90 (23.74%) of the 579 patients in levofloxacin therapy group experienced at least one adverse event. Moxifloxacin was associated with similar patients experiencing at least one adverse event compared with levofloxacin (OR=1.12, 95% CI 0.81-1.55) (Figure 5).

1. The adverse effect of moxifloxacin versus levofloxacin in the treatment of CAP. The comparison between the adverse effects of moxifloxacin versus levofloxacin in the treatment of CAP had no statistic significance (Z=0.68; *P>0.05*) (Figure 5).
2. The test for susceptibility of data: The result showed that there still was no statstic significance after removing the article by Jiang L with less Jadad score of 1.0 (Z=0.77, *P>0.05*) (Figure 6). If the fixed effect model changed to the random effect model, the adverse effect of moxifloxacin and levofloxacin was still not statistically significant (Figure 7).
3. Funnel plot for publication bias in the adverse effects of moxifloxacin versus levofloxacin in the treatment of CAP. The publication bias was usually caused by lack of negative literatures and lower quality of data (Figure 8).

DISCUSSION

This systematic review with meta-analysis compared the efficacy and safety of moxifloxacin to that of levofloxacin therapy for CAP patients. This meta- analysis indicated that moxifloxacin has higher efficacy rates compared to levofloxacin (Figure 1). The safety analysis regarding the incidence of adverse events proved no difference between the compared treatment armes (Figure 3).

Our analysis of the current published data from the included RCTs which resulted in new finding in addition to the individual findings reported for each trial, indicated that moxifloxacin had a favourable efficacy treatment success rate compared to levofloxacin regimens with a statistical margin (Figure 1) with less adverse events (Figure 5).

Overall clinical treatment success rates in the moxifloxacin group [345(91.51%) of 377 patients] were higher than in the levofloxacin therapy group [331 (87.10%) of 380 patients]. The vast majority of adverse events were mild to moderate. The most common adverse events were abnormal liver function tests, diarrhea, nausea, rashes, cardiac adverse events etc. for the above two groups as shown in Table 2.

In the total evaluable safety population 98 (17.13%) of 572 patients in moxifloxacin group and 90 (15.54%) of the 579 patients in levofloxacin therapy group experienced at least one adverse event. Moxifloxacin was associated with similar patients experiencing at least one adverse event in comparison to levofloxacin arm with OR=1.12

Table 1. Main characteristics of the randomized controlled trials (RCTs) included in the meta-analysis.

Reference	Type of study	Included population	Drug tested		Enrolled patients	Cured patients	Jadad score	Fund
			moxi	levo				
Antonio et al. (2006)	Prospective, double-blind, RCT	Hospitalized, age≥65 years CAP patients	Sequential iv and oral 400 mg once daily	Sequential iv 500 mg and oral 250/500 mg once daily	401	138 vs. 126	4	Bayer industry
Lin Q et al. (2007)	Parallel, open RCT	CAP	iv 400 mg once daily	iv 400 mg once daily	65	30 vs. 28	2	N/A
Sun and Liu (2008)	Open RCT	65-75years old CAP	iv 400 mg once daily	iv 500 mg once daily	80	36 vs. 33	2	N/A
Zhao et al. (2008)	Parallel, block ,open RCT	18-65 years old, OPD or hospitalized <48h CAP	iv 400 mg once daily	iv 200 mg twice daily	92	35 vs. 35	2	N/A
Huang et al. (2009)	Parallel, Open RCT	18-65 years old, OPD CAP without any antibiotic treatment within 48 h	iv 400 mg once daily	iv 300 mg once daily	120	54 vs. 56	3	N/A
Yang et al. (2009)	Parallel, block , open RCT	CAP patients	iv 400 mg once daily	iv 200 mg twice daily	80	33 vs. 35	2	N/A
Jiang, 2010	Parallel, block , open RCT	CAP patients	iv 400 mg once daily	iv 200 mg twice daily	40	19 vs.18	1	N/A
Joel et al. (2005)	Prospective, double-blind, RCT	Age≥65 years CAP patients	Sequential iv and oral 400 mg once daily	Sequential iv and oral 500 mg once daily	432		5	N/A

RCT, randomized control trial; OPD ,out -patient door; N/A ,not associate; iv, intravenous; moxi, moxifloxacin; levo, levofloxacin.

and 95% CI [0.81-1.55] (Figure 5).

However, the present study is the first comparative evaluation of two different fluroquinolones in patients with CAP. The clinical finding led to a significant and rapid clinical improvement and/or resolution in patients undergoing therapy with moxifloxacin over levofloxacin.

Moxifloxacin is a new fluoroquinolone that has enhanced potency against gram positive bacterial pathogens (Bauernfeind, 1997). Compared with levofloxacin, moxifloxacin is 4-8 times more potent against both methicillin-susceptible and resistant isolates of *Staphylococcus aureus* and *Staphylococcus epidermidis*. Resistant subpopulations emerged in 4 strains during therapy with levofloxacin in contrast to moxifloxacin, and this might have important role for treatment of staphylococcal infections. These *in vitro* observations warrant the clinical evaluation of moxifloxacin in the staphylococcal infections treatment (Lister, 2001). Likewise moxifloxacin has showed greater potency *in vitro* than levofloxacin against *Pneumococcus* and this could clinically correlate with more rapid killing of patients (Boswell et al., 2002). Moreover, AUC/MIC ranges were only partly overlapping (moxifloxacin versus levofloxacin) with the simulated AUC/MICs of moxifloxacin and were shifted towards higher values than those of the levofloxacin (Lister and Sanders, 1998) and thereby showing moxifloxacin quite expectedly with greater effects. It is also very important to achieve adequate drug concentration at the site of infection. In a study undergoing diagnostic bronchoscopy, moxifloxacin 400 mg showed equivalent steady- state concentrations in epithelial lining fluid (ELF) and macrophages at <12 h bacteria and a faster time to clinical improvement in CAP compared with levofloxacin 500 mg. In contrast, moxifloxacin achieved significantly higher steady-state concentrations in both ELF and macrophages at 24 h compared to

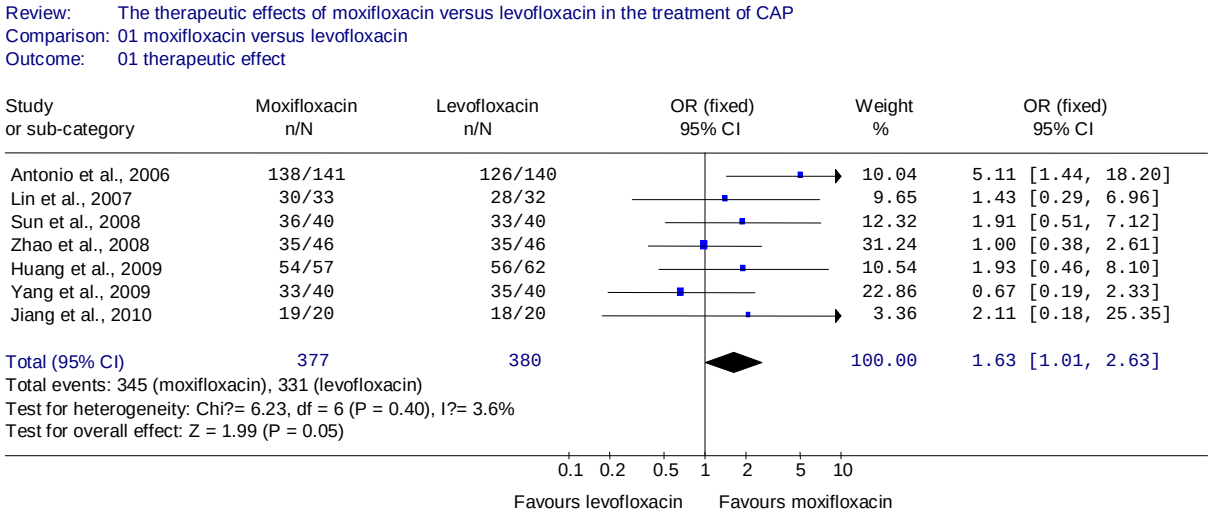

Figure 1. Meta-analysis of therapeutic effect of moxifloxacin versus levofloxacin in the treatment of CAP.

Table 2. The comparison of adverse events between moxifloxacin group and levofloxacin group.

Reference	skin		Cardiac		GI		Nerve		liver		Oral candiasis		phlebitis	
	moxi	levo	moxi	levo	moxi	levo	moxi	levo	moxi	levo	moxi	levo	moxi	levo
Lin et al. (2007)	2	3			2	2	1	1	1	1				
Sun and Liu (2008)	2	3			2	2	1	1	1	1				
Antonio et al. (2006)			2	11	15	20					7	7		
Zhao et al. (2008)	1	1					1		2	3			1	
Yang et al. (2009)	1	1			2	1	2	2	3	4				
Joel et al. (2005)			16	10										
Total	6	8	18	21	21	25	5	4	7	9	7	7	1	0

GI, Gastrointestine; moxi, moxifloxacin; levo, levofloxacin.

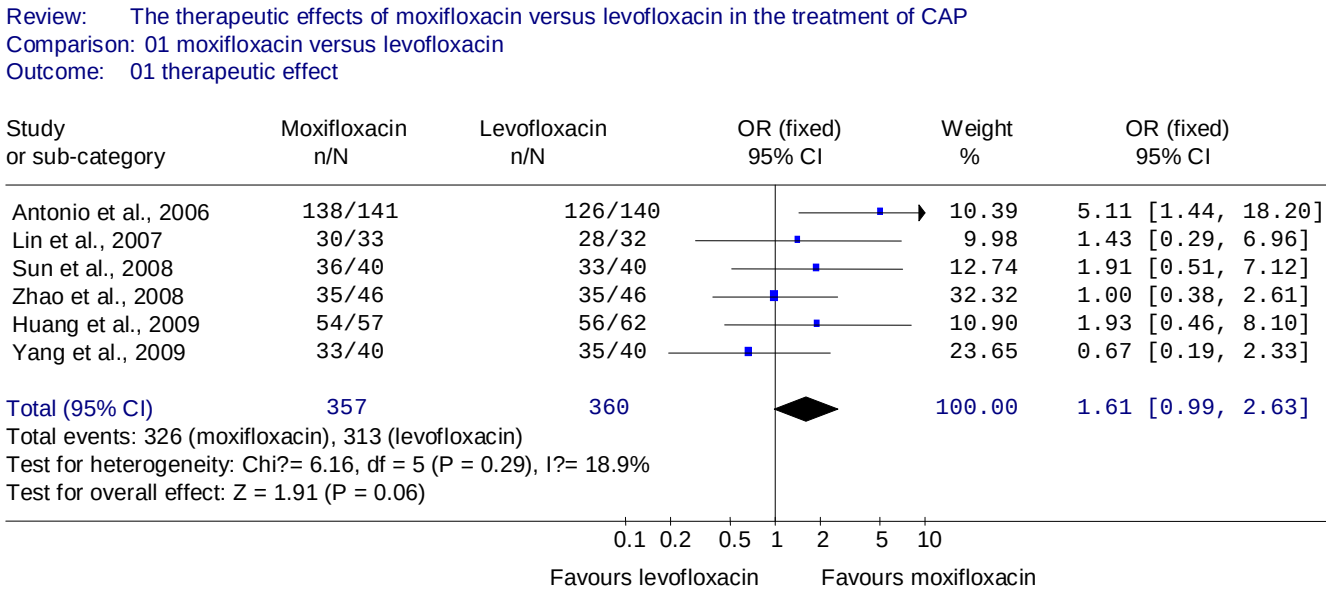

Figure 2. Meta-analysis of therapeutic effect of moxifloxacin versus levofloxacin in the treatment of CAP after removing the article by Jang L with poor Jadad score of one.

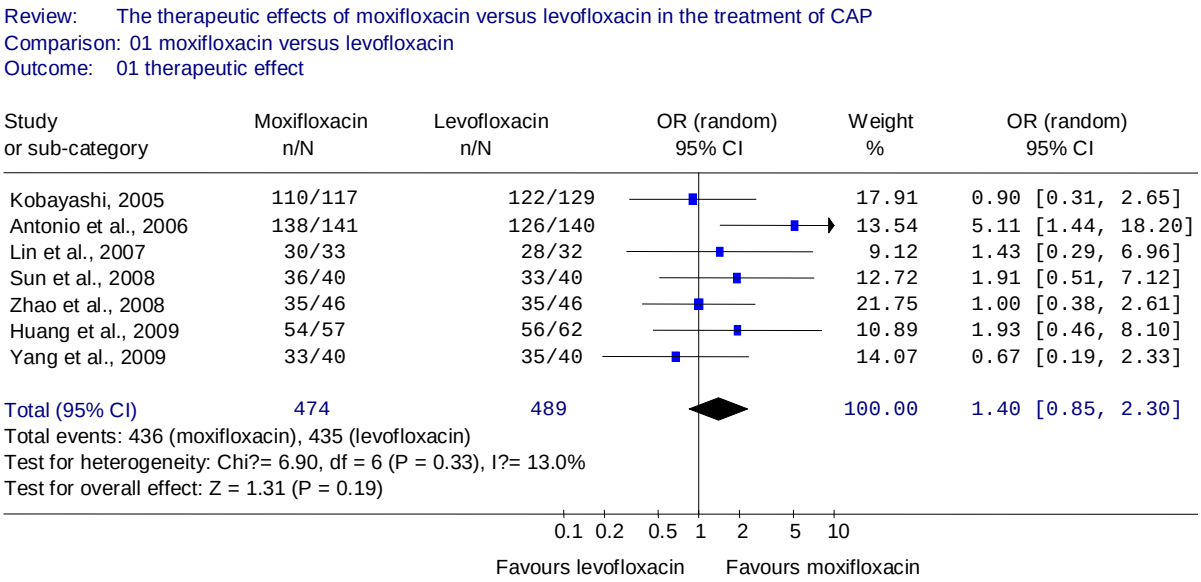

Figure 3. Meta-analysis of therapeutic effect of moxifloxacin versus levofloxacin in the treatment of CAP when the fixed effect model was changed to the random effect model.

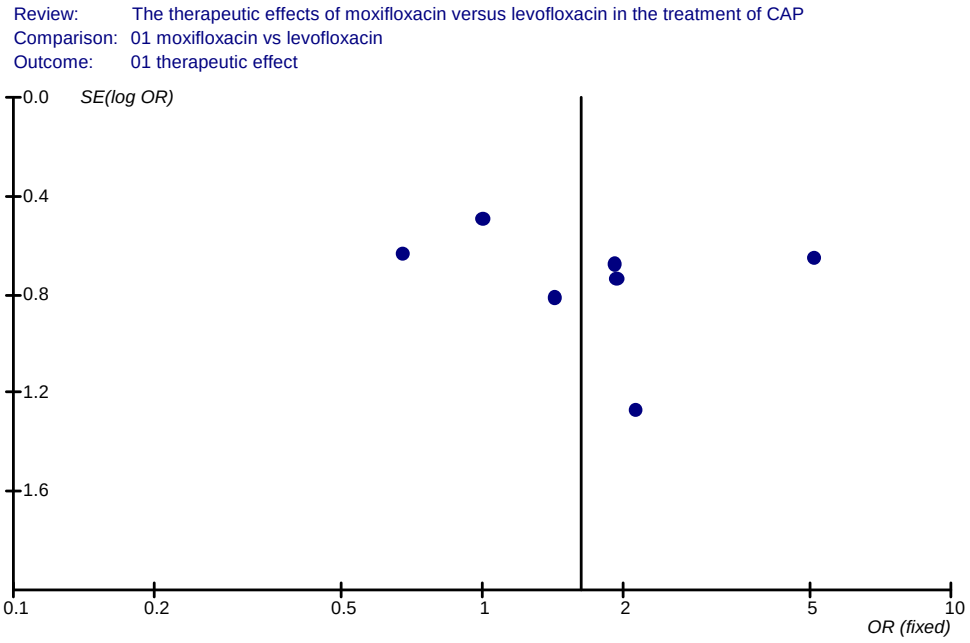

Figure 4. Funnel plot for publication bias in the therapeutic effect of moxifloxacin versus levofloxacin in the treatment of CAP.

levofloxacin (Bhavnani and Andes, 2005). Another study has shown that the concentrations of moxifloxacin and levofloxacin in ELF after single or multiple dosing schedules were 20.7 and 10.9 mg/l, respectively and in macrophages were 56.7 and 27.7 mg/l, respectively (Capitano et al., 2004), thus showing moxifloxacin is superior in achieving adequate drug concentration at the site of infection.

This meta-analysis has some limitations. First, our findings may be affected by the trials' quality included in the analysis as very few trials are double blinded. Nevertheless, a sensitivity analysis was done to find the

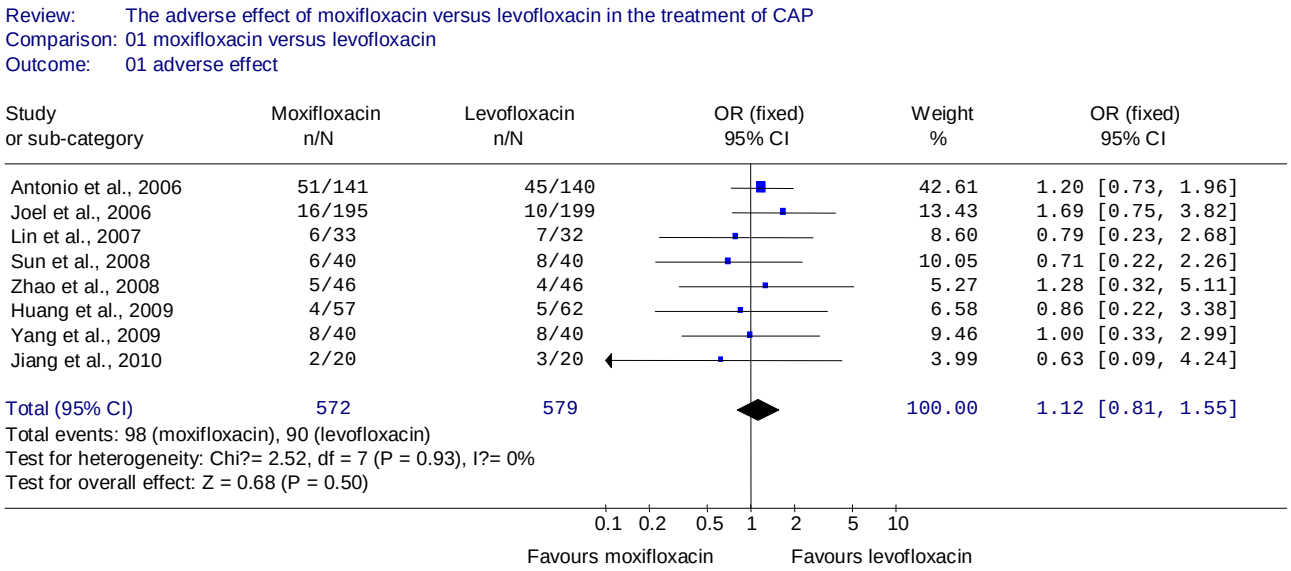

Figure 5. Meta- analysis of the adverse effect of moxifloxacin versus levofloxacin in the treatment of CAP.

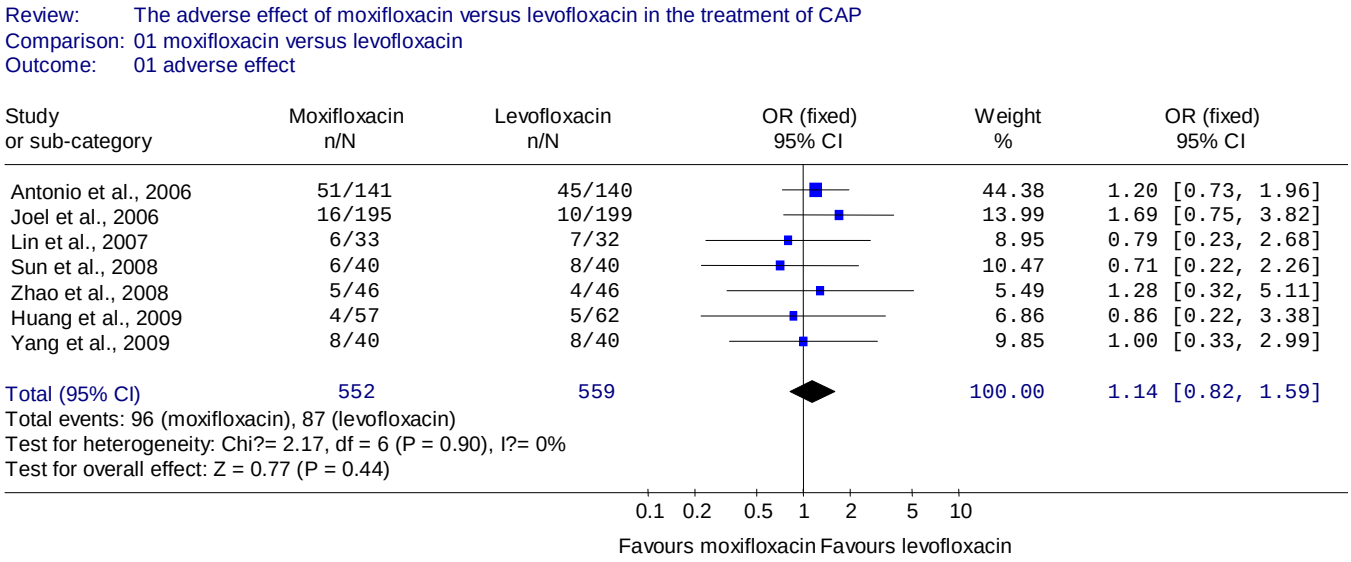

Figure 6. Meta- analysis of the adverse effect of moxifloxacin versus levofloxacin in the treatment of CAP after removing the article by Jiang L with less Jadad score of 1.0.

consistency with those of the primary analysis. Secondly, the meta-analysis is performed with a relatively small number of RCTs and we acknowledge that when a limited number of studies are used, it raises the possibility of a second order sampling error (Higgins et al., 2002). A lower threshold for the number of studies to be included in a meta –analysis has not been established yet (Higgins et al., 2002; Sterne et al., 2001). Thirdly, heterogeneity is present in some of the relevant aspects (included patients and drug administration route). However, differences among trials are unavoidable since each individual trial contains different population and uses different treatment protocols and there is always some heterogeneity even within individual trials. However, heterogeneity does not prohibit pooling of the result of such studies as individual patients are directly compared only with other patients within the same trial and not across trials (Lau et al., 1998; Thompson, 1994). One good thing in our study is that most of the included trials were not funded by industry and this might decrease bias in some access.

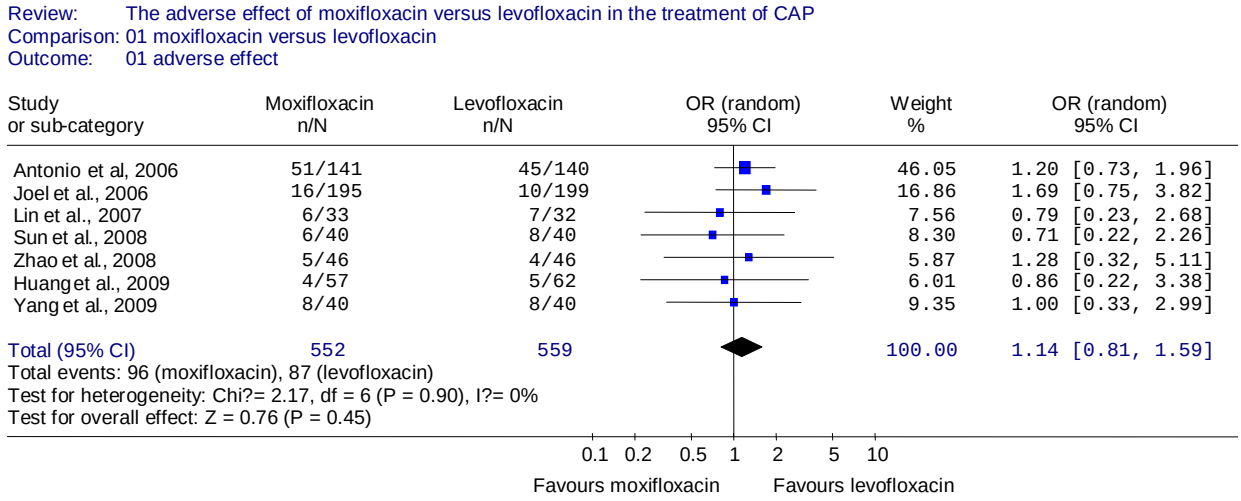

Figure 7. Meta- analysis of the adverse effect of moxifloxacin versus levofloxacin in the treatment of CAP when the fixed effect model was changed to the random effect model.

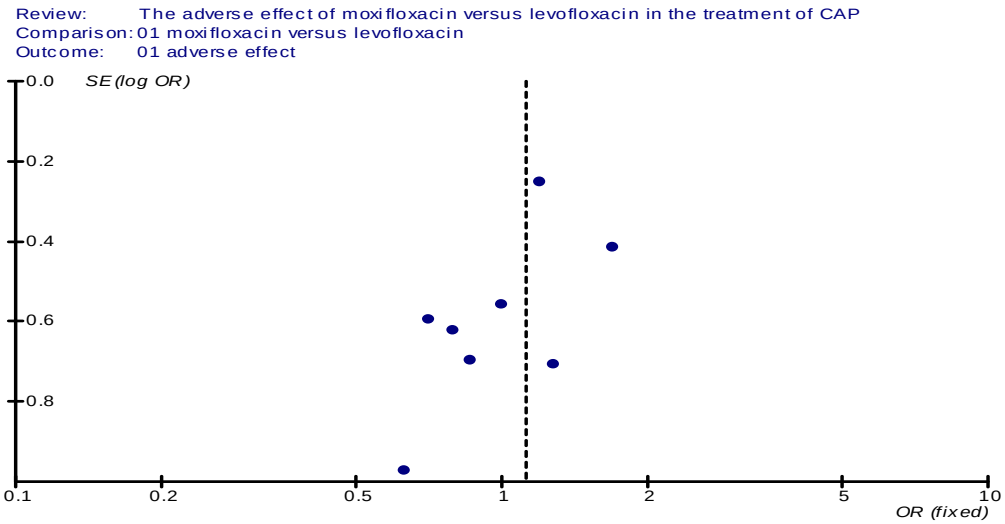

Figure 8. Funnel plot for publication bias in the adverse effect of moxifloxacin versus levofloxacin in the treatment of CAP.

Conclusion

Despite the limitations of our meta analysis, we conclude that moxifloxacin has better therapeutic effects with comparable adverse events compared with levofloxacin.

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