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Review Article

Comparison of tiotropium and salmeterol for treating COPD: a systematic review and meta-analysis

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Abstract: Introduction: Tiotropium and salmeterol showed some potential in alleviating chronic obstructive pulmonary disease (COPD). But the results remained controversial. We conducted a systematic review and meta-analysis to compare the efficacy and safety of tiotropium and salmeterol in patients with COPD. Methods: PubMed, EMbase, Web of science, EBSCO, and Cochrane library databases were systematically searched. Randomized controlled trials (RCTs) assessing the effect of tiotropium versus salmeterol on COPD were included. Two investigators independently searched articles, extracted data, and assessed the quality of included studies. The primary outcome was exacerbation of the disease. Meta-analysis was performed using the fixed or random-effect model when appropriate. Results: Four RCTs involving 9257 patients were included in the meta-analysis. Overall, compared with salmeterol in patients with COPD, tiotropium could significantly reduce exacerbation (RR = 0.89; 95% CI = 0.86 to 0.92; P<0.001), and improved average FEV1 response over 12 h (mean difference = 56.95; 95% CI = 17.75 to 96.15; P = 0.004), peak FEV1 (mean difference = 64.44; 95% CI = 28.18 to 100.70; P = 0.0005) as well as SGRQ scores improvement at least 4 units (RR = 1.18; 95% CI = 1.05 to 1.34; P = 0.007). In addition, less serious adverse events was found following tiotropium treatment than those of salmeterol (RR = 0.77; 95% CI = 0.66 to 0.89; P = 0.0005). Conclusion: Compared to salmeterol treatment, tiotropium treatment was associated with significantly reduced exacerbation, and improved lung function in patients with COPD.

Keywords: Tiotropium, salmeterol, chronic obstructive pulmonary disease (COPD), efficacy, meta-analysis

Introduction

It was widely accepted that chronic obstructive pulmonary disease (COPD) has become a leading cause of disability and death worldwide [1-4]. Exacerbations of COPD could result in instability, worsening of clinical status, various complications, reduced health status and physicalactivity, deterioration of lung function, and even death [5-9].

It was recommended that a long-acting anticholinergic drug or a long-acting β2-agonist served as the first-line maintenance therapy for moderate-to-very-severe COPD [1, 10], and they had the ability to reduce symptoms, improve life quality and lung function, and reduce the risk of exacerbations and hospitalizations [11-13]. Tiotropium was known as an inhaled anticholinergic to provide sustained bronchodilation through prolonged M3 receptor blockade [14-16]. Tiotropium was reported to alleviate exacerbation, and improve lung function, dyspnea and life quality in patients with COPD [12, 17-19], and significantly improved post-dose FEV1 and FVC response than a long-acting β2-agonist salmeterol [20]. In contrast to this promising finding, however, previous study revealed that there was no significant difference of exacerbations and exacerbation-related hospitalizations between tiotropium and salmeterol [21]. Considering these inconsistent effects, we therefore conducted a systematic review and meta-analysis of RCTs to compare the efficacy and safety of tiotropium and salmeterol for the treatment of COPD.

Materials and methods

This systematic review and meta-analysis were conducted according to the guidance of the Preferred Reporting Items for Systematic

Reviews and Meta-analysis statement [22] and the *Cochrane Handbook for Systematic Reviews of Interventions* [23]. All analyses were based on previous published studies, and thus no ethical approval and patient consent were required.

Literature search and selection criteria

PubMed, EMbase, Web of science, EBSCO, and the Cochrane library were systematically searched from inception to October 2016, with the following keywords: tiotropium, and salmeterol, and chronic obstructive pulmonary disease or COPD. To include additional eligible studies, the reference lists of retrieved studies and relevant reviews were also hand-searched and the process above was performed repeatedly until no further article was identified. Conference abstracts meeting the inclusion criteria were also included.

The inclusion criteria were as follows: study population, patients with COPD; intervention, tiotropium; control, salmeterol; outcome measure, exacerbation; and study design, RCT.

The exclusion criteria included a history of asthma, allergic rhinitis, atopy, use of supplemental oxygen and upper respiratory tract infection.

Data extraction and outcome measures

The following information was extracted from the included RCTs: first author, publication year, sample size, baseline characteristics of patients, intervention of tiotropium, intervention of salmeterol, study design, exacerbation, average FEV1 response over 12 h, peak FEV1 and SGRQ score improvement at least 4 units. The author would be contacted to acquire the data when necessary.

The primary outcome was exacerbation of COPD. Secondary outcomes included average FEV1 response over 12 h, peak FEV1 and SGRQ score improvement at least 4 units.

Quality assessment in individual studies

The Jadad Scale was used to evaluate the methodological quality of each RCT included in this meta-analysis [24]. This scale consisted of three evaluation elements: randomization (0-2 points), blinding (0-2 points), dropouts and withdrawals (0-1 points). One point would be allocated to each element if they have been mentioned in article, and another one point would be given if the methods of randomization and/or blinding had been detailed and appropriately described. If methods of randomization and/or blinding were inappropriate, or dropouts and withdrawals had not been recorded, then one point was deducted. The score of Jadad Scale varied from 0 to 5 points. An article with Jadad score ≤ 2 was considered to be of low quality. If the Jadad score ≥ 3, the study was thought to be of high quality [25].

Statistical analysis

Mean differences (MDs) with 95% confidence intervals (CIs) for continuous outcomes (average FEV1 response over 12 h, peak FEV1) and risk ratios (RRs) with 95% CIs for dichotomous outcomes (exacerbation, SGRQ score improvement at least 4 units, serious adverse events) were used to estimate the pooled effects. Heterogeneity was tested using the Cochran Q statistic ($p<0.1$) and quantified with the I^2 statistic, which described the variation of effect size that was attributable to heterogeneity across studies. An I^2 value greater than 50% indicated significant heterogeneity. The value of the I^2 statistic was used to select the appropriate pooling method: fixed-effects models were used for $I^2<50\%$ and random-effects models were applied for $I^2>50\%$. Sensitivity analysis was performed to detect the influence of a single study on the overall estimate via omitting one study in turn when necessary. Owing to the limited number (<10) of included studies, publication bias was not assessed. $P<0.05$ in two-tailed tests was considered statistically significant. All statistical analyses were performed with Review Manager Version 5.3 (The Cochrane Collaboration, Software Update, Oxford, UK).

Results

Literature search, study characteristics, and quality assessment

Figure 1 showed the diagram of meta-analysis search strategy and selection process. In all, 935 studies in the first search seemed to be potentially relevant. 307 duplicates were removed. A total of 621 studies were excluded (irrelevant subjects) on the basis of initial

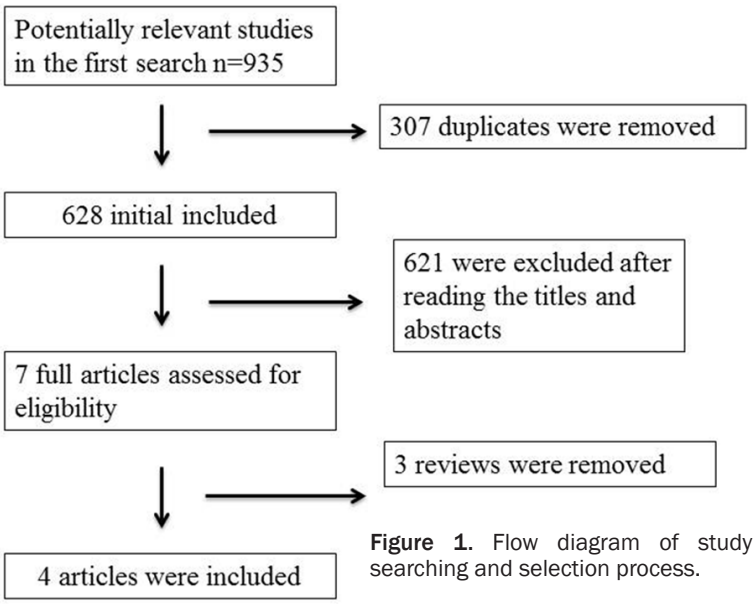

Figure 1. Flow diagram of study searching and selection process.

screening of the titles and abstracts. And 3 reviews were removed. The remaining 4 articles were included in the meta-analysis [10, 20, 21, 26].

The baseline characteristics of the four eligible RCTs in the meta-analysis were summarized in **Table 1**. The four studies were published between 2002 and 2011, and sample sizes ranged from 422 to 7375 with a total of 9257. All four included studies reported patients taking 18 μg of tiotropium once daily or 50 μg of salmeterol twice daily, but the follow-up time varied from 12 weeks to 1 year.

Among the four RCTs, three studies reported the exacerbation [10, 20, 21], two studies reported the average FEV1 response over 12 h [21, 26], two studies reported the peak FEV1 [21, 26] and two studies reported the SGRQ score improvement at least 4 units [20, 26]. Jadad scores of the four included studies varied from 3 to 5, all four studies were considered to be high-quality ones according to quality assessment.

Primary outcome: exacerbation of COPD patients

An exacerbation of COPD patients was defined as the increased symptom of COPD (cough, sputum, wheezing, dyspnea, or chest tightness), with at least one symptom lasting 3 days [10]. This outcome data was analyzed with a fixed-effects model, the pooled estimate of the three included RCTs suggested that tiotropium was associated with a significantly reduced exacerbation compared to salmeterol (RR = 0.89; 95% CI = 0.86 to 0.92; P<0.001), with no heterogeneity among the studies (I^2 = 0%, heterogeneity P = 0.91) (**Figure 2**).

Secondary outcomes

Average FEV1 response over 12 h and peak FEV1 response were performed to evaluate the severity of COPD. Compared with salmeterol, tiotropium resulted in significantly increased average FEV1 response over 12 h (mean difference = 56.95; 95% CI = 17.75 to 96.15; P = 0.004; **Figure 3**) and peak FEV1 (mean difference = 64.44; 95% CI = 28.18 to 100.70; P = 0.0005; **Figure 4**) in patients with COPD.

The SGRQ was a disease specific instrument to assess dyspnoea and it contained 50 items in three subscales (symptoms, activity, and impact). Each response had an empirically derived weight. More patients in tiotropium group showed SGRQ scores improvement at least 4 units than those in salmeterol group (RR = 1.18; 95% CI = 1.05 to 1.34; P = 0.007; **Figure 5**).

Adverse events

Serious adverse events were defined as any potentially life-threatening deterioration in health status. Tiotropium was found to result in less serious adverse events than salmeterol (RR = 0.77; 95% CI = 0.66 to 0.89; P = 0.0005; **Figure 6**).

Discussion

Our meta-analysis suggested that compared to salmeterol, tiotropium significantly decreased exacerbation, improved average FEV1 response over 12 h and peak FEV1 response, as well as increased patients with SGRQ score improvement at least 4 units. These results indicated that tiotropium treatment was better to maintain lung function compared to salme-

Table 1. Characteristics of included studies

NO.	Author	Study design	Tiotropium group						Salmeterol group						Jada scores
			Number	Age (mean ± SD)	Methods	Current smoker (%)	Duration of COPD	Average FEV1 (L)	Number	Age (mean ± SD)	Methods	Current smoker (%)	Duration of COPD	Average FEV1 (L)	
1	Vogelmeier 2011	RCT	3707	62.9±9.0	18 μg of tiotropium once daily, plus placebo twice daily for 1 year	48.0	8.0±6.7 years	1.41±0.47	3669	62.8±9.0	50 μg of salmeterol twice daily, plus placebo once daily for 1 year	48.3	7.9±6.5 years	1.41±0.45	5
2	Briggs 2005	RCT	328	64.2±8.6	18 ug once daily for 12 weeks	34.5	9.4±6.5 years	1.04±0.37	325	64.6±7.8	50 ug twice daily for 12 weeks	36.6	9.4±6.8 years	1.05±0.39	4
3	Brusasco 2003	RCT	402	63.8±8.0	18 ug once daily plus placebo for 6 months	-	9.0±7.3 years	1.12±0.39	405	64.1±8.5	50 ug twice daily plus placebo for 6 months	-	9.9±8.0 years	1.07±0.38	4
4	Donohue 2002	RCT	209	64.5±7.9	18 ug once daily plus placebo for 6 months	-	9.2±7.8 years	1.11±0.39	213	64.6±8.1	50 ug twice daily plus placebo for 6 months	-	10.4±8.2 years	1.07±0.37	3

Figure 2. Forest plot for the meta-analysis of exacerbation of COPD patients: Exacerbations of COPD indicated instability or worsening of the patient's clinical status and progression of the disease.

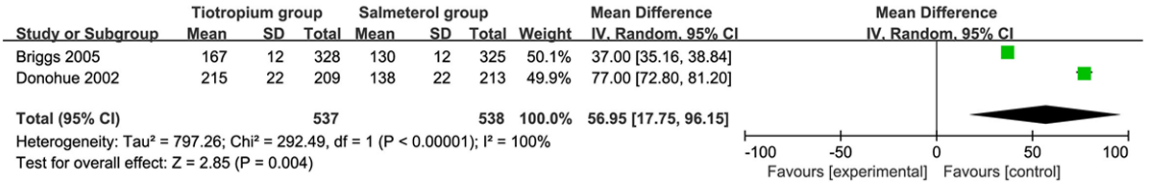

Figure 3. Forest plot for the meta-analysis of FEV1 response: average value over 12 h.

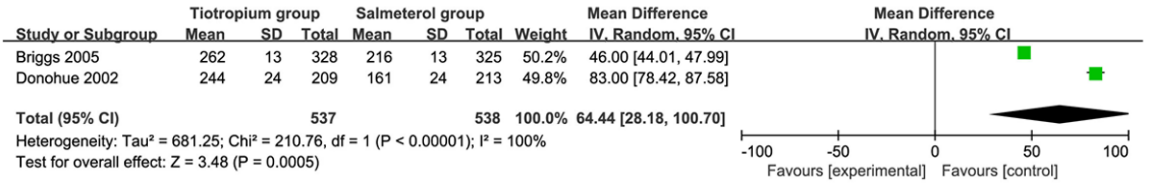

Figure 4. Forest plot for the meta-analysis of FEV1: peak value for assessing lung function.

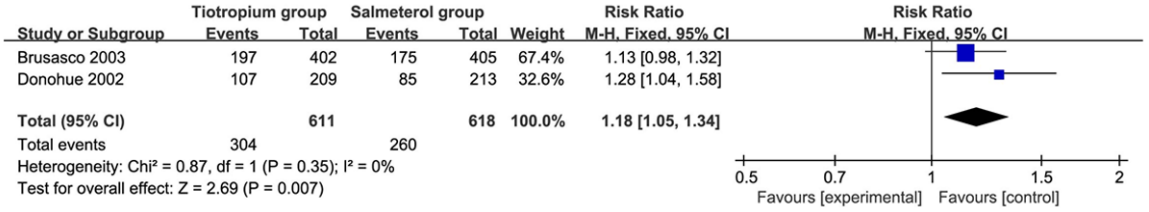

Figure 5. Forest plot for the meta-analysis of SGRQ score improvement at least 4 units: SGRQ score was used to asssess health related quality of life.

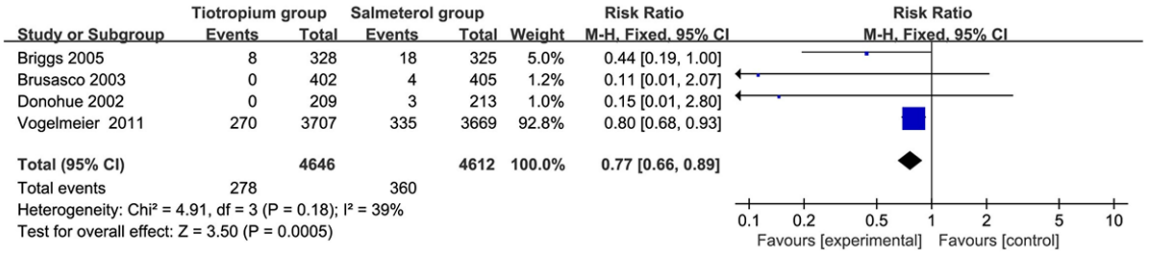

Figure 6. Forest plot for the meta-analysis of serious adverse events.

terol treatment. To the best of our knowledge, this was the first meta-analysis to compare the treatment efficacy of tiotropium and salmeterol in patients with COPD.

COPD was defined as a disease of airflow limitation. Airflow and progressive physiological impairment were applied to assess the severity of COPD [27, 28]. Exacerbation of disease could lead to breathlessness, limitations in activity, and adverse consequences on health status [29, 30]. Exacerbations resulted in a deleterious effect on the morbidity and mortality of patients with COPD by increasing hospitalization, worsening lung function and health-related quality of life, and decreasing survival [31-33]. It was crucial to prevent exacerbations for COPD [34]. Both tiotropium and salmeterol were reported to not only reduce airflow limitation and hyperinflation, but also directly or indirectly inhibited various aspects of lung inflammation [35, 36]. Treatment using tiotropium or salmeterol promoted patients shifting from the high-risk (frequent) to the low-risk (infrequent) exacerbation phenotype, and this treatment could prevent patients with low risk of exacerbations to aggravate into the high-risk group [37]. But the detailed mechanisms medicating their inhibition of exacerbations remained elusive, and their action might be influenced by the differences of the aerosolizing systems, the particle size of the aerosols, and the distribution of drug in the lung [10].

The frequency of exacerbations increased in parallel with the severity of COPD [38, 39]. One observational study demonstrated that 22% of patients with GOLD Stage II disease suffered from two or more exacerbations during 1 year of follow-up. In constrast, 47% of patients with GOLD Stage IV disease resulted in more frequent exacerbations [40]. Patients with fewer than two exacerbations per year were classified as “infrequent exacerbators”, whereas those experiencing two or more exacerbations per year were classified as “frequent exacerbators” [40, 41]. Few studies have investigated the influence of pharmacotherapy on COPD exacerbations in patients with different subsets of exacerbation phenotype. Higher efficacy of tiotropium was confirmed to prolong the time to first COPD exacerbation and to reduce the frequency of COPD exacerbations regardless of exacerbation phenotype [37]. In addition, tiotropium significantly reduced the risk of exacerbation which was similar in patients with or without inhaled glucocorticoids, indicating that the efficacy of tiotropium was independent of inhaled glucocorticoids [27]. Both tiotropium and salmeterol were reported to have safety profiles [42, 43]. And our meta-analysis suggested that patients in the tiotropium-treated group were revealed to have significantly reduced serious adverse events compared to those in the salmeterol group.

Several limitations should be taken into account. Firstly, the total included trials were limited and only four studies met the inclusion criteria. Different severity of COPD and treatment time, might have an influence on the pooled results. Next, tiotropium or salmeterol could serve as an adjunctive therapy to standard pharmacological treatment and could not replace pharmacological treatment. Finally, some unpublished and missing data might lead bias to the pooled effect.

Conclusions

Tiotropium treatment had important ability to prevent exacerbation, maintain lung function and reduce serious adverse events compared to salmeterol treatment. Tiotropium shall be recommended in patients with COPD.

Disclosure of conflict of interest

None.

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