Efficacy and safety of tiotropium bromide in chronic obstructive pulmonary disease: a systematic review of randomized clinical trials

Eficácia e segurança do brometo de tiotrópio na doença pulmonar obstrutiva crônica. Revisão sistemática de ensaios clínicos randomizados

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ABSTRACT

Chronic obstructive pulmonary disease (COPD) is among the most prevalent pulmonary diseases. This study aimed at assessing the efficacy and safety of anticholinergic tiotropium bromide (TB) in Chronic obstructive pulmonary disease patients. This is a systematic review of randomized clinical trials performed in the Brazilian Cochrane Center. Electronic database searched: Cochrane library, Medline, LILACS, Pubmed. There were no language, date or other restrictions. Participants: Patients with Chronic obstructive pulmonary disease. Intervention: tiotropium bromide. Comparison: Other bronchodilators or placebo. Outcomes: Mortality, Chronic obstructive pulmonary disease exacerbation, hospitalizations, adverse effects. Results: 14 studies were included in this systematic review. Mortality was lower in the tiotropium bromide group when compared with the salmeterol group [statistical significance: relative risk (RR) 0.16, confidence interval 95% (CI) 0.03 to 0.89, number needed to treat (NNT) of 100]. There was not a statistical difference in the mortality outcome in the comparison between tiotropium bromide and placebo groups (RR 0.88, CI 0.74 to 1.06). Chronic obstructive pulmonary disease exacerbation decreases significantly in the tiotropium bromide group when compared to placebo (statistical significance: RR 0.85, CI 0.77 to 0.93, NNT 25), but in comparison to the salmeterol group there was no statistical difference (RR 0.93, CI 0.80 to 1.08). The number of hospitalizations was lower in the tiotropium bromide group than in the placebo group (statistical significance: RR 0.77, CI 0.59 to 0.99, NNT 50). The results indicate that tiotropium bromide is an effective once-daily bronchodilator. Tiotropium bromide was associated with consistent health benefits, including reduced chronic obstructive pulmonary disease exacerbations, hospitalizations and even mortality when compared with salmeterol.

Keywords: Pulmonary disease, chronic obstructive/drug therapy; Bronchodilator agents; Tiotropium bromide/therapeutic use; Cholinergic antagonists; Randomized controlled trial

RESUMO

A doença pulmonar obstrutiva crônica está entre as doenças pulmonares mais prevalentes. O objetivo deste estudo foi verificar a eficácia e segurança do brometo de tiotrópio em pacientes com doença pulmonar obstrutiva crônica. Trata-se de revisão sistemática de ensaios clínicos randomizados realizada no Centro Cochrane do Brasil. A estratégia de busca eletrônica foi realizada nos nas bases LILACS, MEDLINE, Biblioteca Cochrane, PubMed. Não houve restrições à linguagem e nem à data. Participaram pacientes com doença pulmonar obstrutiva crônica. A intervenção foi o uso de brometo de tiotrópio comparado a outros broncodilatadores ou placebo. Os desfechos analisados foram mortalidade, exacerbações da doença pulmonar obstrutiva crônica, hospitalização e efeitos adversos. A mortalidade foi menor no grupo brometo de tiotrópio quando comparado com o grupo salmeterol (significância estatística: risco relativo de 0,16; intervalo de confiança de 95% de 0,03-0,89, número necessário para tratar de 100). Não houve diferença estatística no desfecho mortalidade na comparação entre os grupos brometo de tiotrópio e placebo (risco relativo de 0,88; intervalo de confiança de 95% de 0,74-1,06). As exacerbações da doença pulmonar obstrutiva crônica diminuíram significantemente no grupo brometo de tiotrópio quando comparado ao placebo (significância estatística: risco relativo de 0,85; intervalo de confiança de 95% de 0,77-0,93; número necessário para tratar de 25), porém, quando comparado ao salmeterol não obteve significância estatística (risco relativo de 0,93; intervalo de confiança de 95% 0,80-1,08). O número de hospitalizações foi menor no grupo brometo de tiotrópio do que no grupo placebo (significância estatística: risco relativo de 0,77; intervalo de confiança de 95% 0,59-0,99; número necessário para tratar de 50). Os resultados indicam que o brometo de tiotrópio é um bronco-

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dilatador eficaz em dose única diária. O brometo de tiotrópio traz benefícios à saúde com resultados consistentes, incluindo redução de exacerbações da doença pulmonar obstrutiva crônica, internações e até mesmo a mortalidade quando comparados com salmeterol.

Descritores: Doença pulmonar obstrutiva crônica/quimioterapia; Broncodilatadores; Brometo de tiotrópio/uso terapêutico; Antagonistas colinérgicos; Ensaio clínico controlado aleatório

INTRODUCTION

Chronic obstructive pulmonary disease

This is a condition characterized by airflow limitation that is not fully reversible. The patient initially notices dyspnea during physical activity, but with the progression of the disease it can occur at rest. In its late stages, excessive reduction of blood oxygen can lead patients to cyanosis, as well as damage of the airways internal wall, and blood vessels that may cause hemoptysis and pulmonary hypertension. In patients with chronic bronchitis and bronchiectasis, chronic cough and sputum production are the main symptoms. The main risk factors are: tobacco smoke, occupational exposure to powders and substances through chemical vapor, indoor air pollution with little ventilation, and fuels used for cooking and heating. Low birth weight and the genetic deficiency of alpha-1 antitrypsin increase the risk of developing chronic obstructive pulmonary disease (COPD). A prevalence study using spirometry in the metropolitan region of São Paulo, in adults aged 40 years or older, showed a prevalence of COPD (forced expiratory volume 1 - FEV1 / forced vital capacity - FVC) <0.7 postbronchodilator) of 15.8% (confidence interval 95% - 95%CI 13.5-18.1).[1]

Tiotropium bromide

Tiotropium bromide (TB) is an anticholinergic drug which blocks acetylcholine receptors in the muscles preventing their contraction. TB binds selectively to the subtypes of the muscarinic receptors, M^1, M^2 and M^3. It dissociates slowly from M^1 and M^3 receptors, and quickly from M^2 receptor, promoting prolonged and fast-acting bronchodilation,[2] allowing its use once a day.[3,4] This anticholinergic has minimal side effects when compared with beta2-adrenergic agonists.[5,6] Its use is optimal for elderly patients because they are more susceptible to tachycardia and tremors caused by beta2-adrenergic agonists.[7,8] When there is a weak response to anticholinergic or beta2-adrenergic agonists used alone, the combination of these two drugs can provide a better bronchodilator response.[9,10]

The objective of this study was to assess the efficacy and safety of anticholinergic TB in COPD through a systematic review.

METHODS

The Research Ethics Committee of the Federal University of São Paulo approved the research under number 0019/10.

Setting and Design: Systematic review of randomized clinical trials performed in the Brazilian Cochrane Center. Criteria for included studies: Participants: patients with COPD. Intervention: TB versus placebo or any other drug used for treating COPD. The outcomes considered were: mortality, COPD exacerbation, hospitalizations, and adverse effects. Search for studies: The electronic search was done with no language or date restriction in the following databases: Lilacs, Medline (via PubMed), Medline (via BIREME), and Cochrane Library. Manual search carried out in medical journals in general, and in specific areas of pneumology, cardiology and internal medicine did not add new studies to the electronic search.

Selection of studies and data collection: Two reviewers independently inspected the references found by the search strategy, and applied the inclusion criteria in selected studies. After observations of the process description of allocation concealment, the classification was divided into four categories: A: means that the allocation concealment was adequately reported, B: means that the allocation concealment is not described but it is mentioned that the study is in random lists, C: means that allocation concealment was inadequate, D: means that the study is not randomized. We selected studies in categories A and B.[11] Statistical analysis: For dichotomous variables, the relative risk was calculated with confidence interval of 95% (random effects model). When there were statistical differences, the number needed to treat (NNT) or number needed to harm (NNH) was calculated. For continuous variables, we calculated the weighted mean difference (random effects model) with the range of 95% correspondingly. After finding all eligible studies, data were summarized in a metanalysis in the computer software RevMan of the Cochrane Collaboration.[12] Fourteen studies were included in this systematic review and their allocation concealment was A in 8 studies,[13-20] and B in 6 studies.[21-26]

RESULTS

According to the inclusion criteria, fourteen studies participated in this systematic review.[13-26] The total number of participants was 17688, with this number varying in each outcome and each comparison. The duration of the studies varied greatly, with the shortest time being of 29 days, and the longest of four years. Four outcomes were proposed to be evaluated in the systematic review: mortality, COPD exacerbations, hospitalizations, and adverse effects. A comparison of TB with placebo or other active drugs (salmeterol, salmeterol plus fluticasone and ipratropium) was conducted.

Outcome: mortality (Figure 1)

TB vs Placebo: Metanalysis of six studies did not show a reduction in mortality [Relative risk (RR) 0.88; 95% confidence interval (CI) 0.74 to 1.06]. TB vs Salmeterol: Metanalysis of two studies demonstrated a reduction of mortality favorable to TB group [RR 0.16; 95% CI 0.03 to 0.89, and NNT of 100]. TB vs Salmeterol + Futicasone: Analysis of one study demonstrated decreased mortality in the Salmeterol + Fluticasone group (RR

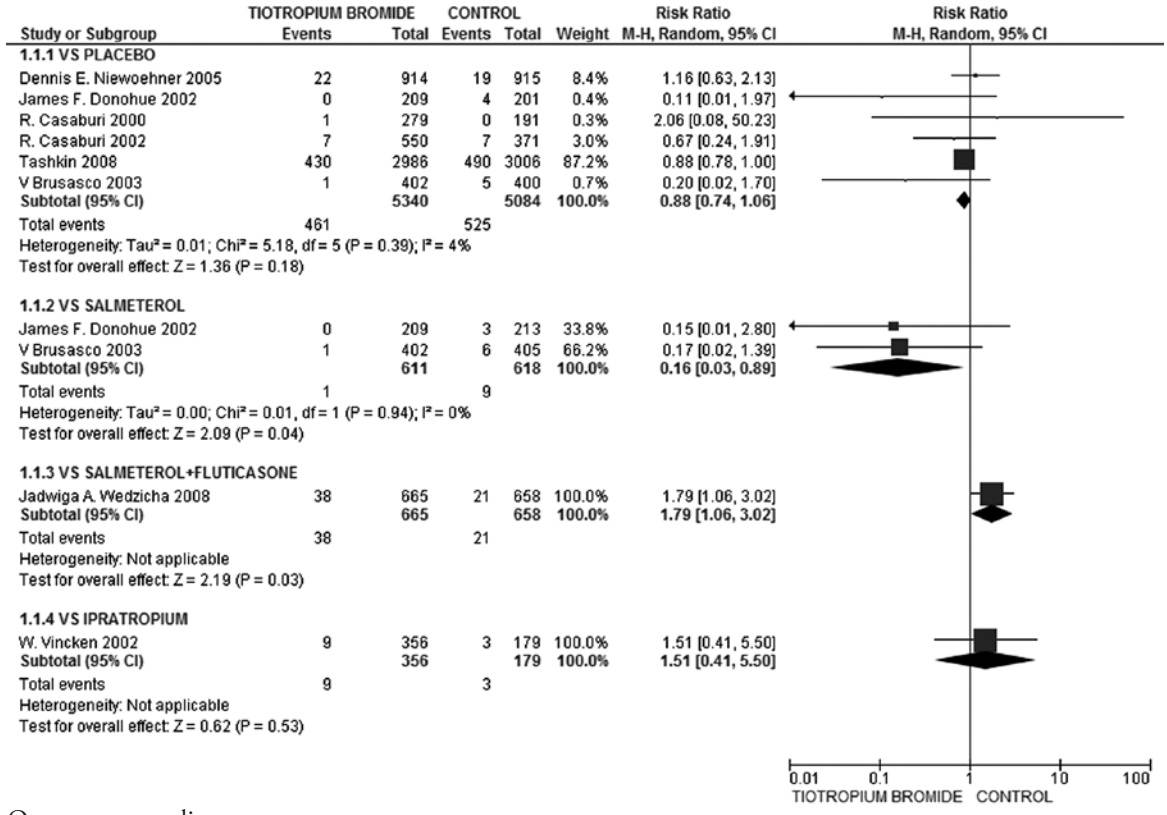

Figure 1. Outcome: mortality.

1.79; 95% CI 1.06 to 3.02 and NNT=33). TB vs Ipratropium: There was no change in mortality in the comparison between groups (RR 1.51; 95% CI 0.41 to 5.50).

Outcome: chronic obstructive pulmonary disease exacerbations (Figure 2)

TB vs Placebo: There was a statistically significant reduction in COPD exacerbations in the TB group in the metanalysis of 10 studies (RR 0.85; 95% CI 0.78 to 0.94; NNT=20). TB vs Salmeterol: In this metanalysis (two studies), there was no difference in the number of COPD exacerbations between the groups (RR 0.93; 95% CI 0.80 to 1.08). TB vs Salmeterol + Fluticasone: Only one study made the analysis and there was no statistical difference between groups (RR 0.95; 95% CI of 0.87 to 1.04). TB vs Ipratropium: The TB group reduced COPD exacerbations significantly in this metanalysis with two studies (RR 0.78; 95% CI 0.63 to 0.95; NNT=16).

Outcome: hospitalizations (Figure 3)

TB vs Placebo: Metanalysis of five studies favorable to the TB group with significantly reduced hospitalizations (RR 0.73; 95% CI 0.56 to 0.95; NNT=33). TB vs salmeterol, TB vs salmeterol + fluticasone and TB vs ipratropium: there was not a statistical difference in the analysis of the groups (RR 0.74; 95% CI 0.53 to 1.05; RR 0.81, 95% CI 0.62 to 1.06; RR 0.62, 95% CI 0.36 to 1.07, respectively).

Outcome: adverse effects (Figure 4)

TB vs placebo: Eight studies constituted a metanalysis which did not show significant difference between groups (RR 0.98; 95% CI 0.90 to 1.07). TB vs salmeterol: analysis of a study that showed a statistically significant reduction of adverse effects on the salmeterol group (RR 4.75; 95% CI 2.13 to 10.61). TB vs salmeterol + fluticasone: In this comparison, one study made the analysis and found no significant difference between groups (RR 0.94; 95% CI 0.87 to 1.02). TB vs ipratropium: Metanalysis of two studies showed statistical significant differences favorable to the ipratropium group (RR 1.71; 95% CI 1.07 to 2.72; NNT=20) (Table 1).

DISCUSSION

This systematic review showed that TB did not reduce mortality compared to placebo and ipratropium but, compared to salmeterol, TB reduced one death in each 100 patients studied. Although it seems to be little, the data for this metanalysis with two studies showed statistical significance favoring the TB group that has never been demonstrated in isolated studies or other metanalysis. Tiotropium reduced COPD exacerbations compared with placebo or ipratropium, but it was not statistically different when compared to salmeterol. The number of hospitalizations was significantly decreased in the TB group only when compared to placebo. The benefits observed with tiotropium for exacerbations and related hospitalizations

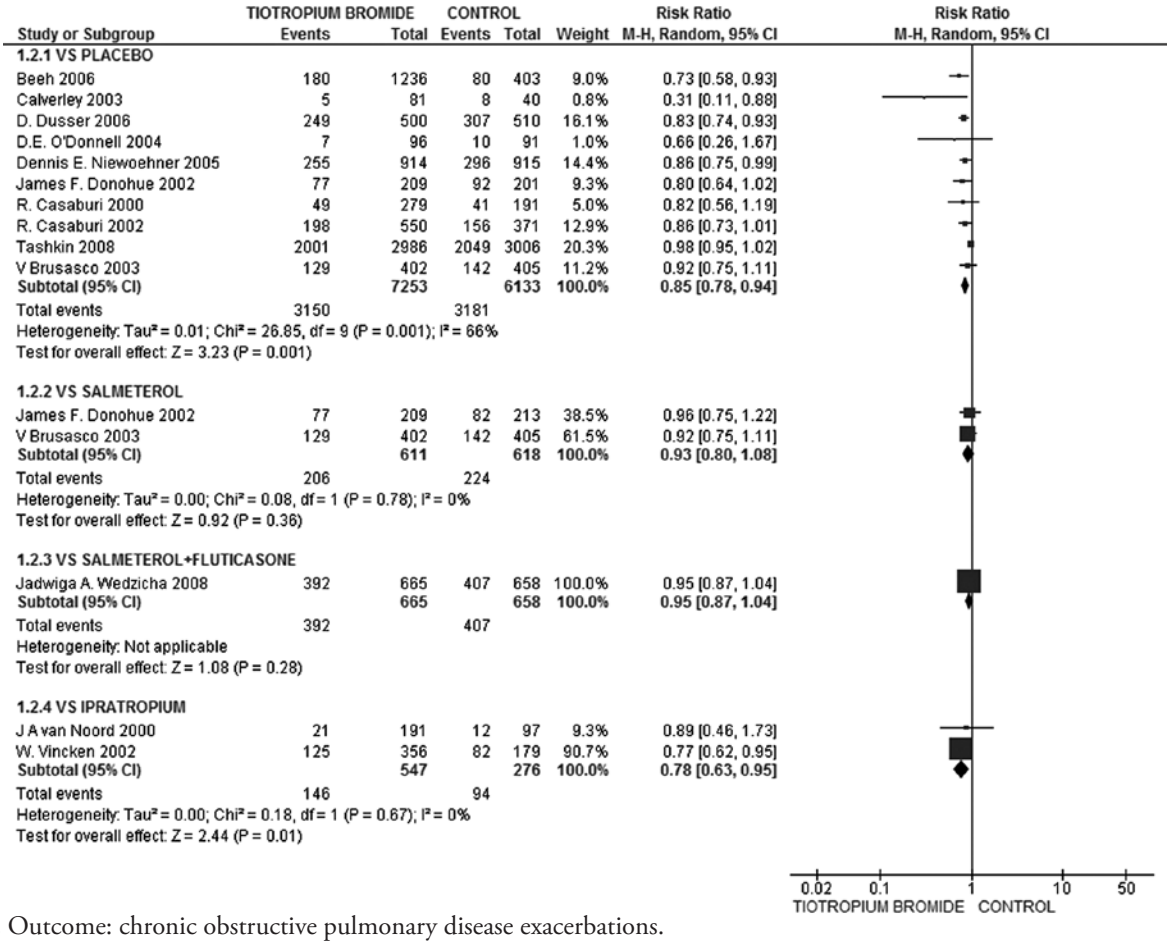

Figure 2. Outcome: chronic obstructive pulmonary disease exacerbations.

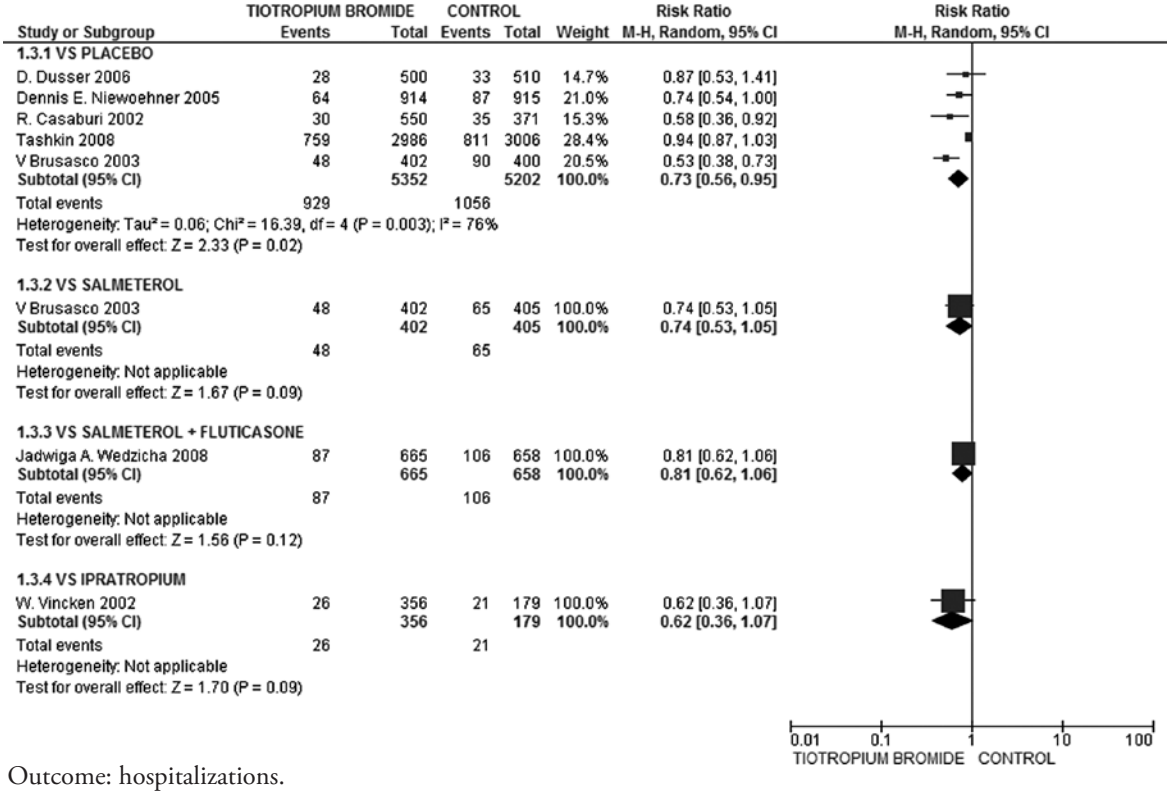

Figure 3. Outcome: hospitalizations.

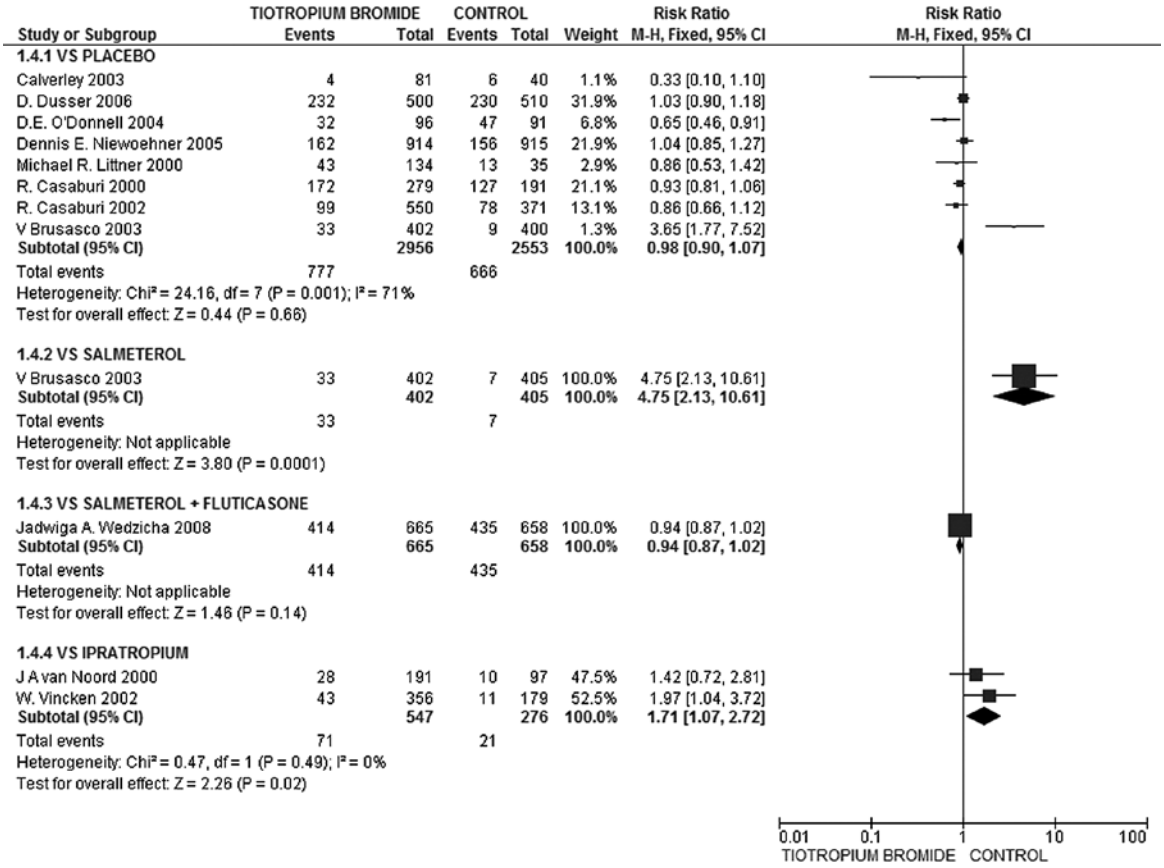

Figure 4. Outcome: adverse effects.

Table 1. Summary results

Outcomes	Comparison: TB VS	Results
Mortality	Placebo	Metanalysis (6 studies): not statistically different
	Salmeterol	Metanalysis (2 studies): statistical significance favours TB
	Salmeterol + Fluticasone	Analysis (1 study): statistical significance favours salmeterol + fluticasone
	Ipratropium	Analysis (1 study): no statistical significance
COPD exacerbations	Placebo	Metanalysis (10 studies): statistical significance favours TB
	Salmeterol	Metanalysis (2 studies): not statistically different
	Salmeterol + fluticasone	Analysis (1 study): not statistically different
	Ipratropium	Metanalysis (2 studies): statistical significance favours TB
Hospitalizations	Placebo	Metanalysis (5 studies): statistical significance favours TB
	Salmeterol	Analysis (1 study): not statistically different
	Salmeterol + fluticasone	Analysis (1 study): not statistically different
	Ipratropium	Analisys (1 study): not statistically different
Adverse effects	Placebo	Metanalysis (8 studies): not statistically different
	Salmeterol	Analysis (1 study): statistical significance favours Salmeterol
	Salmetrol + fluticasone	Analysis (1 study): not statistically different
	Ipratropium	Metanalysis (2 studies): statistical significance favours Ipratropium

TB: tiotropium bromide.

were large and clinically important, although it does not differ significantly from the other active drugs. TB had significantly more adverse effects than ipratropium and salmeterol.

The results regarding COPD exacerbations, hospitalizations and adverse effects were highly heterogeneous (I^2=66%, 76% and 71% respectively) when TB was compared to placebo

(metanalysis with more studies). These heterogeneities were probably caused by different definitions of these outcomes.

Consistent with some of these findings, another systematic review published in 2006 (with a lower number of participants and studies) found similar results in reducing COPD exacerbations compared to placebo and ipratropium. The hospitalizations were also significantly reduced when TB was compared with placebo, but there was no change in comparison to ipratropium. There were no statistically significant differences in all-cause mortality between TB and placebo, ipratropium, or salmeterol.[27]

A Brasilian study published in 2011 made a review of the pharmacological treatment of COPD. This review showed that the majority of the studies demonstrated that the medications evaluated provided symptom relief, and prevented exacerbations.[28]

CONCLUSIONS

The present systematic review results indicate that TB is an effective once-daily bronchodilator. TB was associated with consistent health outcome benefits, including reduced COPD exacerbations, hospitalizations, and even mortality when compared to salmeterol.

Implications for practice

The bronchodilator action of TB, once daily dose, makes it one of the best drugs in COPD treatment.

Implications for research

There are enough studies with a significant number of participants; therefore, there is no need for further studies with this drug.

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