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 tiofropio 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 bancos LILACS, MEDLINE, Biblioteca Cochrane, PubMed. Não houve restrições à língua e nem à data. Participaram pacientes com doença pulmonar obstrutiva crônica. A intervenção foi o uso de brometo de tiofropio comparado a outros broncodilatadores ou placebo. Os desfechos analisados foram mortalidade, exacerbações da doença pulmonar obstrutiva crônica, hospitalizações e efeitos adversos. A mortalidade foi menor no grupo brometo de tiofropio 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 tiofropio 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 significativamente no grupo brometo de tiofropio 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% de 0,80-1,08). O número de hospitalizações foi menor no grupo brometo de tiofropio do que no grupo placebo (significância estatística: risco relativo de 0,77; intervalo de confiança de 95% de 0,59-0,99; número necessário para tratar de 50). Os resultados indicam que o brometo de tiofropio é um bronco-
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, M₁, M₂ and M₃. It dissociates slowly from M₁ and M₃ receptors, and quickly from M₂ receptor, promoting prolonged and fast-acting bronchodilation, allowing its use once a day. This anticholinergic has minimal side effects when compared with beta2-adrenergic agonists. 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. 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. Fourteen studies were included in this systematic review and their allocation concealment was A in 8 studies, and B in 6 studies. METHODS

The Research Ethics Committee of the Federal University of São Paulo approved the research under number 0019/10.
Tiotropium bromide in chronic obstructive pulmonary disease

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 metaanalysis of 10 studies (RR 0.85; 95% CI 0.78 to 0.94; NNT=20). TB vs Salmeterol: In this metaanalysis (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 metaanalysis 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 metaanalysis 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 metaanalysis with two studies showed statistical significance favoring the TB group that has never been demonstrated in isolated studies or other metaanalysis. 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.
Table 1. Summary results

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<td>Ipratropium</td>
<td>Metanalysis (2 studies): statistical significance favours Ipratropium</td>
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TB: tiotropium bromide.

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.

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.
(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 Brazilian 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.\(^30\)

**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.

**REFERENCES**


