Efficacy and safety of conventional long acting β2-agonists: systematic review and meta-analysis

Abstract

Background: Chronic obstructive pulmonary disease (COPD) is usually considered one of the leading causes of death worldwide, so finding proper therapeutic strategies for this disease is of high importance. In this meta-analysis, we reviewed the existing literature on the efficacy and safety of conventional long acting beta agonists (LABAs) in COPD patients.

Methods: We searched MEDLINE and Google scholar to identify relevant articles. We limited data to double-blinded randomized controlled trials (RCTs). Data of 14,832 COPD subjects including 7540 patients under a β2 agonist (cases) and 7292 taking placebo (controls) retrieved from 20 randomized controlled trials and were enrolled into this meta-analysis. Evaluated outcomes included overall mortality, exacerbations and tolerance to the drug.

Results: The analysis of survival showed no significant difference between those taking LABAs or placebo (relative risk (RR): 0.945, 95% confidence interval (CI): 0.821-1.088, P=0.432). Exacerbation rate, however, was significantly lower among the cases than among the controls (RR: 0.859, 95%CI: 0.800-0.922, p<0.001). Similar observation was detected in analyzing the rate of drug withdrawal in patients of the two groups with patients under placebo having significantly higher rate of drug discontinuation due to adverse events or disease symptoms (RR:0.821, 95% CI: 0.774-0.871; p<0.007).

Conclusion: In conclusion, we found that the use of conventional LABA therapy in COPD patients is associated with a lower exacerbation rate of the disease as well as higher tolerance to the drug, but no survival advantage is expectable. Substitution of LABAs with new agents is recommended.

Keywords: COPD, β2-Agonists, drug, chronic obstructive pulmonary disease, meta analysis

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Pharmacotherapy is a major therapeutic approach to COPD patients which consists of prescription of several agents including bronchodilators, such as β2-agonists and inhaled corticosteroids. Due to our purpose in the treatment of COPD which is a better management of patients’ symptoms, reduce exacerbations and prevent death rate, we need to know how much our treatment strategies are safe and efficient.

The long-acting β2-agonists formoterol and salmeterol have long been used to improve lung function and reduce symptoms and improve outcome in COPD patients. There are studies both in favor of using these agents in the mentioned patients and against them, but to have the most comprehensive view on the topic of efficacy and safety of these conventional β2-agonists, there is a need to conduct systematic review of the randomized controlled trials published on this issue. For the same reason, we performed this study to review the existing literature and to conduct a meta-analysis to find the efficacy and safety of conventional β2 agonists in COPD patients.

**Methods**

To conduct our systematic review, the primary search was done using the keywords “salmeterol” and “COPD” within the time-span of 1990-2013. A repeat of the search using “formoterol” instead of “randomized controlled trial” was performed to expand the included studies. Again, the literature search was repeated using the terms “long-acting beta agonist” and “efficacy” or “safety” or “exacerbation” or “withdrawal” or “randomized controlled trial”. A literature search was performed using Pubmed database, which we believe provided relatively the largest published data of the most relevant studies in the field of pulmonary diseases. We also tried to boost our search on citations of the found articles to find potential reports which were not indexed in Pubmed or retrieved through Pubmed search.

In our search, overall, 892 studies were found in the literature search in Pubmed database using the mentioned keywords. Then found titles of the studies were screened to find appropriate studies associated with our systematic review, and randomized controlled trials. Finally, 20 randomized controlled trials investigating the efficacy and safety of salmeterol or formoterol on the disease course, drug tolerance and survival of COPD patients were enrolled into the Meta-analyses (table 1) (5-24). The analysis was performed in three major study variables: exacerbations, drug withdrawal and patient’s survival.

**Statistical analysis:** The meta-analysis has been performed using software Stata v.9.0 (Stata corp, TX, USA).

**Table 1. The included randomized controlled trials**

| Trial | Trial author (year) | Reference no. | Year | Case group (n) | Control (n) | Beta agonist |
|-------|---------------------|---------------|------|----------------|-------------|--------------|
| 1     | W. Szafranski et al. (2003) | 5             | 2003 | 201            | 205         | Formoterol   |
| 2     | Peter Calverley et al. (2003) | 6             | 2003 | 372            | 361         | Salmeterol   |
| 3     | Peter M.A. Calverley et al. (2007) | 7             | 2007 | 1521           | 1524        | Salmeterol   |
| 4     | Nicola A. Hanania et al. (2003) | 8             | 2003 | 177            | 185         | Salmeterol   |
| 5     | P.M. Calverley et al. (2003) | 9             | 2003 | 255            | 256         | Formoterol   |
| 6     | Christine R Jenkins et al. (2009) | 10            | 2009 | 1521           | 1524        | Salmeterol   |
| 7     | Andrea Rossi et al. (2002) | 11            | 2002 | 214            | 220         | Formoterol   |
| 8     | M. Wadbo et al. (2002) | 12            | 2002 | 61             | 60          | Formoterol   |
| 9     | Donald A. Mahler et al. (1999) | 13            | 1999 | 135            | 143         | Salmeterol   |
| 10    | Donald A. Mahler et al. (2002) | 14            | 2002 | 160            | 181         | Salmeterol   |
| 11    | Kenneth R Chapman et al. (2002) | 15            | 2002 | 201            | 207         | Salmeterol   |
| 12    | Ronald Dahl et al. (2001) | 16            | 2001 | 194            | 200         | Formoterol   |
| 13    | Ronald Dahl et al. (2010) | 17            | 2010 | 434            | 432         | Formoterol   |
| 14    | V Brusasco et al. (2003) | 18            | 2003 | 405            | 400         | Salmeterol   |
| 15    | James F. Donohue et al. (2002) | 19            | 2002 | 213            | 201         | Salmeterol   |
| 16    | G. Boyd et al. (1997) | 20            | 1997 | 229            | 227         | Salmeterol   |
| 17    | Rudolf A. Baumgartner et al. (2007) | 21            | 2007 | 144            | 143         | Salmeterol   |
| 18    | B. CELLI et al. (2003) | 22            | 2003 | 554            | 271         | Salmeterol   |
| 19    | Malcolm Campbell et al. (2005) | 23            | 2005 | 215            | 217         | Formoterol   |
| 20    | O. Kornmann et al. (2011) | 24            | 2011 | 334            | 335         | Salmeterol   |
Results

Data of 14,832 COPD subjects including 7540 patients under a β2 agonist and 7292 patients taking placebo were retrieved from 20 randomized controlled trials and were enrolled into this meta-analysis. From the 7540 COPD patients under a β2 agonist, 1574 were taking formoterol and the remaining 5966 patients were under salmeterol therapy.

Analysis of survival: Figure 1 summarizes the data of the analysis. Analysis of survival of patients in the two groups showed no significant difference between those taking beta agonists or placebo (relative risk (RR): 0.945, 95% confidence interval (CI): 0.821-1.088, p=0.432, z=0.79; figure 1).

Reanalysis of data including only the patients receiving one of the beta-agonists did not change the results. No significant heterogeneity has been observed among the survival data of the included studies, indicating a high reliability value for the analysis (P=0.486; heterogeneity χ²=7.48 (d.f.=8) I-squared= 0%).

Exacerbations: Figure 2 summarizes the data of the analysis. Analysis of the rates of the patients experiencing exacerbation episodes within the trial period, however, showed that COPD patients taking β2 agonist were significantly less likely to develop an exacerbation episode (RR: 0.859, 95%CI: 0.800-0.922, p<0.001, z=4.19; figure 2). The heterogeneity of the included studies in the exacerbation rate was significantly high (p=0.007, Heterogeneity χ²=31.62 (d.f.=15) I-squared= 52.6%). However, reanalysis of data censoring data of any individual study did not change the significant effect of beta agonists on exacerbation rates, suggesting that none of the studies had such a high magnitude on the analysis individually that was able to skew the results of analysis of the overall studies.

Tolerance to therapy: Figure 3 summarizes the data of the analysis. Similar observation was detected in analyzing the rate of drug withdrawal in patients of the two groups with patients under placebo having significantly higher rate of drug discontinuation due to adverse events or disease symptoms (RR:0.821, 95% CI: 0.774-0.871; p<0.007, z= 6.52; figure 3). Like what we observed in the analysis of survival, the heterogeneity rate was not significantly high for tolerance to the therapy (P=0.5, heterogeneity χ² =18.34 (d.f.=19) I-squared=0%).
Figure 2. Forest plot of meta-analysis of 16 randomized controlled trials investigating disease exacerbations of COPD patients using conventional β₂ agonists compared to placebo

Figure 3. Forest plot of meta-analysis of 20 randomized controlled trials investigating symptom-related treatment withdrawal of COPD patients using conventional β₂ agonists compared to placebo
Discussion

Despite the fervent debate over the use of long-acting β2 agonists (LABAs) in the treatment of COPD (25), these agents still play a central role in the management of the disease, and are usually considered an inevitable part of treatment regimen in COPD in the majority of clinics (26). In vitro studies have demonstrated that LABAs can boost the Th2 inflammatory pathway by inhibiting interleukin (IL)-12 and interferon (IFN)-γ (27). In vivo, most studies have suggested that β2-agonists increase airway hyper-responsiveness (28). On the other hand, in clinical trials, there are controversial data on the safety and effectiveness of conventional LABAs on the symptoms and outcome of patients with COPD. This urged us to make some comprehensive search study of the current literature so we can reach to a reliable conclusion on the matter based on all the valuable data coming from randomized controlled trials from the literature.

In this meta-analysis, we showed that conventional LABAs have no survival advantage for COPD patients. Similar findings were reported by a previous meta-analysis, except that they had compared survival effects of inhaled LABAs with corticosteroids (29); while in the current study, we compared it to the placebo which we believe will reveal more fundamental evidence from potential survival effects of LABAs on COPD patients. Our data suggest that LABAs do not only have significantly lesser survival effects than inhaled steroids, but also, it seemed that no outcome effect is expected to be achieved through them. On the other hand, as it has been shown later in the current study, LABAs can improve some of the very important aspects of the disease therapy like alterations in exacerbation rates and good tolerance to the treatment.

These findings may promote one to presume some survival benefits for LABAs as well. But this discrepancy might be explainable in part with a reported increased risk for adverse events associated with therapy with LABAs in COPD patients (30). LABAs may have adverse cardiovascular effects, deteriorating cardiovascular health in COPD patients with high predisposition to concomitant cardiac disorders (31); and this necessitates caution in administering this family of agents to COPD patients with simultaneous cardiovascular disease (32). Another explanation was provided by TORCH trial that clearly demonstrated long-term use of LABAs for a period of three years was associated with a lower risk of mortality, as compared to placebo (7). Putting together, in short term use of LABAs in COPD patients, no survival advantage is expectable, while it is possible that if patients are controlled for concomitant cardiovascular diseases, and they use LABAs for long-term periods, drug administration shows some life advantages in them. In fact, some new evidence has come to the literature suggesting survival benefits of using cardioselective β1 blockers in COPD patients (33). Thus, we recommend future studies to be conducted prescribing cardioselective β1 blockers simultaneous to LABAs to evaluate whether this combination can promise some survival advantage in this patient population. No need to remind that these studies should strongly adhere to the ethical measures to provide their participants with the highest possible safety and support.

An interesting finding of the current study which we believe is more novel than the remaining is the higher tolerability of therapy with LABAs than the placebo. This finding is of some value and suggests that using LABAs is not quite worthless, and any have some relieving effects on COPD symptoms. However, the lack of strong evidence for survival benefit for LABAs puts them on competition with anticholinergic agents including ipratropium bromide inhaler.

The lesser rate of COPD exacerbations in patients under therapy with LABAs is another significant finding of this study. It has been well demonstrated that exacerbation episodes are associated with significant higher rates of either short- or long-term survival (34). Only in-hospital mortality of COPD patients admitted with disease exacerbation has been reportedly over 8% (35, 36). Longer term outcome of acute exacerbation of COPD was also high with up to about 50% mortality rate during the first two years post hospitalization (37). The number of exacerbations experienced by each patient was also a determinant of survival (38). Thus, potential survival advantages which may be expected from LABAs in COPD patients are probably compromised by its cardiovascular burden, leaving no significant survival benefit for these drugs. This finding promotes us to try to substitute these highly commonly used agents with other agents, which provide similar symptomatic advantages while having more cost-effectiveness and less side effects, and they can be more available to a larger patient population.

This study has some limitations. Most importantly, due to a shortage in the number of studies evaluating long-term
survival effects of therapy with conventional LABAs in COPD patients, we were not able to analyze this issue. Moreover, censoring the cardiovascular side effects of LABAs from the analysis was not possible. To sum it up, evidence does not suggest any significant survival effect for LABAs in COPD patients, and we recommend to substitute agents of this group with new groups of drugs with more cost-effective values, and/or less side effects. Newly introduced agents which may suggest survival benefit should also be considered for future randomized trials. In conclusion, we found that using conventional LABA therapy in COPD patients is associated with a lower exacerbation rate of the disease as well as higher tolerance to the drug; but no survival advantage can be expected from them. Future studies with more controlled conditions and longer follow-up periods are recommended.

References
1. World Health Report. Geneva: World Health Organization, 2012. Available at: http://www.who.int/mediacentre/factsheets/fs315/en/. Accessed Aug 19, 2013.
2. World Health Report. Geneva: World Health Organization, 2012. Available at: http://www.who.int/respiratory/copd/World_Health_Statistics_2008/en/. Accessed Aug 19, 2013.
3. Monteagudo M, Rodríguez-Blanco T, Llagostera M, et al. Factors associated with changes in quality of life of COPD patients: A prospective study in primary care. Respir Med 2013; 107: 1589-97.
4. Aburto M, Esteban C, Moraza FJ, et al. COPD exacerbation: mortality prognosis factors in a respiratory care unit. Arch Bronconeumol 2011; 47: 79-84.
5. Szafranski W, Cukier A, Ramirez A, et al. Efficacy and safety of budesonide/formoterol in the management of chronic obstructive pulmonary disease. Eur Respir J 2003; 21: 74-81.
6. Calverley P, Pauwels R, Vestbo J, et al. Combined salmeterol and fluticasone in the treatment of chronic obstructive pulmonary disease: a randomised controlled trial. Lancet 2003; 361: 449-56.
7. Calverley PM, Anderson JA, Celli B, et al. Salmeterol and fluticasone propionate and survival in chronic obstructive pulmonary disease. N Engl J Med 2007; 356: 775-89.
8. Hanania NA, Darken P, Horstman D, et al. The efficacy and safety of fluticasone propionate (250 microg)/salmeterol (50 microg) combined in the Diskus inhaler for the treatment of COPD. Chest 2003; 124: 834-43.
9. Calverley PM, Boonsawat W, Cseke Z, et al. Maintenance therapy with budesonide and formoterol in chronic obstructive pulmonary disease. Eur Respir J 2003; 22: 912-9.
10. Jenkins CR, Jones PW, Calverley PM, et al. Efficacy of salmeterol/fluticasone propionate by GOLD stage of chronic obstructive pulmonary disease: analysis from the randomised, placebo-controlled TORCH study. Respir Res 2009; 10: 59.
11. Rossi A, Kristufek P, Levine BE, et al. Comparison of the efficacy, tolerability, and safety of formoterol dry powder and oral, slow-release theophylline in the treatment of COPD. Chest 2002; 121: 1058-69.
12. Wadbo M, Löfdahl CG, Larsson K, et al. Effects of formoterol and ipratropium bromide in COPD: a 3-month placebo-controlled study. Eur Respir J 2002; 20: 1138-46.
13. Mahler DA, Donohue JF, Barbee RA, et al. Efficacy of salmeterol xinafoate in the treatment of COPD. Chest 1999; 115: 957-65.
14. Mahler DA, Wire P, Horstman D, et al. Effectiveness of fluticasone propionate and salmeterol combination delivered via the Diskus device in the treatment of chronic obstructive pulmonary disease. Am J Respir Crit Care Med 2002; 166: 1084-91.
15. Chapman KR, Arvidsson P, Chuchalin AG, et al. The addition of salmeterol 50 microg bid to anticholinergic treatment in patients with COPD: a randomized, placebo controlled trial. Chronic obstructive pulmonary disease. Can Respir J 2002; 9: 178-85.
16. Dahl R, Greffhorst LA, Nowak D, et al. Inhaled Formoterol dry powder versus ipratropium bromide in chronic obstructive pulmonary disease. Am J Respir Crit Care Med 2001; 164: 778-84.
17. Dahl R, Chung NF, Buhl R, et al. Efficacy of a new once-daily long-acting inhaled beta2-agonist indacaterol versus twice-daily formoterol in COPD. Thorax 2010; 65: 473-9.
18. Brusasco V, Hodder R, Miravitlles M, et al. Health outcomes following treatment for six months with once
daily tiotropium compared with twice daily salmeterol in patients with COPD. Thorax 2003; 58: 399-404.
19. Donohue JF, van Noord JA, Bateman ED, et al. A 6-month, placebo-controlled study comparing lung function and health status changes in COPD patients treated with tiotropium or salmeterol. Chest 2002; 122: 47-55.
20. Boyd G, Morice AH, Pounsford JC, et al. An evaluation of salmeterol in the treatment of chronic obstructive pulmonary disease (COPD). Eur Respir J 1997; 10: 815-21.
21. Baumgartner RA, Hanania NA, Calhoun WJ, et al. Nebulized arformoterol in patients with COPD: a 12-week, multicenter, randomized, double-blind, double-dummy, placebo- and active-controlled trial. Clin Ther 2007; 29: 261-78.
22. Celli B, Halpin D, Hepburn R, et al. Symptoms are an important outcome in chronic obstructive pulmonary disease clinical trials: results of a 3-month comparative study using the Breathlessness, Cough and Sputum Scale (BCSS). Respir Med 2003; 97: S35-43.
23. Campbell M, Eliraz A, Johansson G, et al. Formoterol for maintenance and as-needed treatment of chronic obstructive pulmonary disease. Respir Med 2005; 99: 1511-20.
24. Kornmann O, Dahl R, Centanni S, et al. Once-daily indacaterol versus twice-daily salmeterol for COPD: a placebo-controlled comparison. Eur Respir J 2011; 37: 273-9.
25. Wijesinghe M, Perrin K, Harwood M, Weatherall M, Beasley R. The risk of asthma mortality with inhaled long acting beta-agonists. Postgrad Med J 2008; 84: 467-72.
26. Celli BR, MacNee W; ATS/ERS Task Force. Standards for the diagnosis and treatment of patients with COPD: a summary of the ATS/ERS position paper. Eur Respir J 2004; 23: 932-46.
27. Panina-Bordignon P, Mazzeo D, Lucia PD, et al. Beta2-agonists prevent Th1 development by selective inhibition of interleukin 12. J Clin Invest 1997; 100: 1513-9.
28. Taylor DR. The beta-agonist saga and its clinical relevance: on and on it goes. Am J Respir Crit Care Med 2009; 179: 976-8.
29. Kliber A, Lynd LD, Sin DD. The effects of long-acting bronchodilators on total mortality in patients with stable chronic obstructive pulmonary disease. Respir Res 2010; 11: 56.
30. Salpeter SR,Ormiston TM, Salpeter EE. Cardiovascular effects of beta-agonists in patients with asthma and COPD: a meta-analysis. Chest 2004; 125: 2309-21.
31. Cazzola M, Imperatore F, Salzillo A, et al. Cardiac effects of formoterol and salmeterol in patients suffering from COPD with pre-existing cardiac arrhythmias and hypoxemia. Chest 1998; 114: 411-5.
32. Cazzola M, Matera MG, Donner CF. Inhaled beta2-adrenoceptor agonists: cardiovascular safety in patients with obstructive lung disease. Drugs 2005; 65: 1595-610.
33. Gestel YR, Hoeks SE, Sin DD, et al. Impact of cardioselective β-Blockers on mortality in patients with chronic obstructive pulmonary disease and atherosclerosis. Am J Respir Crit Care Med 2008; 178: 695-700.
34. Seneff MG, Wagner DP, Wagner RP, Zimmerman JE, Knaus WA. Hospital and 1-year survival of patients admitted to intensive care units with acute exacerbation of chronic obstructive pulmonary disease. JAMA 1995; 274: 1852-7.
35. Groenewegen KH, Schols AM, Wouters EF. Mortality and mortality-related factors after hospitalization for acute exacerbation of COPD. Chest 2003; 124: 459-67.
36. Gunen H, Hacievliyagil SS, Kosar F, et al. Factors affecting survival of hospitalised patients with COPD. Eur Respir J 2005; 26: 234-41.
37. Connors AF Jr, Dawson NV, Thomas C, et al. Outcomes following acute exacerbation of severe chronic obstructive lung disease. The SUPPORT investigators (Study to Understand Prognoses and Preferences for Outcomes and Risks of Treatments). Am J Respir Crit Care Med 1996; 154: 959-67.
38. Soler-Cataluña JJ, Martínez-García MA, Román Sanchez P, et al. Severe acute exacerbations and mortality in patients with chronic obstructive pulmonary disease. Thorax 2005; 60: 925-31.