Review Article

Comparison of the effectiveness and safety of formoterol versus salmeterol in the treatment of patients with asthma: A systematic review and meta-analysis

Ashraf Velayati[1], Seyed Alireza Hosseini[2], Ali Akbari Sari[3], Farideh Mohtasham[4], Mostafa Ghanei[5], Mohsen Yaghoubi[6], Reza Majdzadeh[7]

[1]Department of Educational Management, Economics and Policy, School of Medical Education, Shahid Beheshti University of Medical Sciences, [2]Food and Drug Research Center, Food and Drug Organization, [3]Department of Health Management and Economics, School of Public Health, Tehran University of Medical Sciences, [4]Knowledge Utilization Research Center, Tehran University of Medical Sciences, [5]Chemical Injuries Research Center, Baqiyatallah University of Medical Sciences, [6]Department of Community Medicine, School of Medicine, Clinical Knowledge Management Unit, Iran University of Medical Sciences, [7]Department of Epidemiology and Biostatistics, School of Public Health, Tehran University of Medical Sciences, Tehran, Iran

Background: Formoterol and salmeterol are two long-acting β2-agonists given by inhalation, with bronchodilating effects lasting for at least 12 h after a single administration. Formoterol has a faster onset of action compared with salmeterol. The aim of this study was to perform a systematic review and meta-analysis on the data published from previous review in order to calculate pooled estimates of effectiveness and safety assessment of formoterol and salmeterol in treatment of patients with asthma. **Materials and Methods:** In this study, we conducted an electronic search for medical citation databases including Cochrane, PubMed, Scopus, PsycInfo, and IranMedex. Besides manual search of the databases that record randomized clinical trials, conference proceedings, and journals related to asthma were included. Studies were evaluated by two independent people based on inclusion and exclusion criteria, and the common outcomes of studies were entered into the RevMan 5.0.1 software, after evaluation of studies and extraction of data from them; and in cases where there were homogeneous studies, meta-analysis was performed, and for heterogeneous studies, the results were reported qualitatively. **Results:** Of the 1539 studies initially found, 13 were included in the study. According to the meta-analysis conducted, no significant difference was found between the inhalation of formoterol 12 μg and salmeterol 50 μg in the two outcomes of mean forced expiratory volume 1 s (FEV1), 12 h after inhalation of medication and Borg score (A frequently used scale for quantifying breathlessness) after inhalation of medication. In addition, salmeterol was more effective than formoterol in the two outcomes of percent decrease in FEV1 after inhalation of methacholine and the number of days without an attack. Since the two outcomes of FEV1 30-60 min after inhalation of medication and morning peak expiratory flow after inhalation of medication were heterogeneous, they had no meta-analysis capabilities, and its results were reported qualitatively. **Conclusion:** The data from included studies shows that, more efficacy has been achieved with Salmeterol, especially in some outcomes such as the percent decrease in FEV1 after inhalation of Methacholine, and the number of days without an attack; and therefore, the administration of Salmeterol seems to be beneficial for patients, compared with Formoterol.

Key words: Asthma, formoterol, salmeterol

How to cite this article: Velayati A, Hosseini SA, Akbari Sari A, Mohtasham F, Ghanei M, Yaghoubi M, Majdzadeh R. Comparison of the effectiveness and safety of formoterol versus salmeterol in the treatment of patients with asthma: A systematic review and meta-analysis. J Res Med Sci 2015;20:483-90.

INTRODUCTION

Now-a-day, chronic lung diseases are among the most prevalent diseases causing disability and mortality, among which asthma, as one of the most common diseases, has significant prevalence and incidence. Asthma is a chronic inflammatory disease of the airways that leads to airway narrowing through the processes of inflammation and smooth muscle contraction in airway walls (bronchoconstriction). Symptoms include periodic attacks of wheezing, shortness of breath, tightness in the chest, and coughing, particularly at night or in the early morning.[1,2] According to the studies, 5% of the world's population that is about 300 millions of people worldwide, are currently infected with the disease whose prevalence increases by 50% for every 10 years.[3] Worldwide, approximately 180,000 deaths annually are related to asthma although the mortality rate has generally declined since the year 1980.[3,4]

Address for correspondence: Assoc. Prof. Ali Akbari Sari, Department of Health Management and Economics, School of Public Health, Tehran University of Medical Sciences, Tehran, Iran. E-mail: akbarisari@tums.ac.ir
Received: 09-06-2014; **Revised:** 07-10-2014; **Accepted:** 06-07-2015

Study of the prevalence of asthma symptoms, according to a meta-analysis on the country-level which was performed by Heidarnia *et al*. between 1378 and 1383, showed that the prevalence of the symptoms is different in children in different regions of the country and varies between 2.7% in Kerman and 35.4% in Tehran. According to this study, the mean prevalence of asthma symptoms across the country were obtained in 13.14% (95% confidence interval [CI]: 9.97-16.30%).[5] Formoterol and salmeterol are two long-acting β2-agonist given by inhalation, with bronchodilating effects lasting for at least 12 h after a single administration.[6,7] Both of these drugs have become valuable complements in the regular treatment of asthmatic patients who are not satisfactorily controlled with inhaled corticosteroids.[8] Formoterol has a faster onset of action within 5 min compared with salmeterol that has a slower onset of action within 15-20 min.[9]

In today's world where there are limited resources to meet unlimited health care needs of the people, the importance of informed decision-making with the least chance of error in the health sector and the lack of resources in our country is essential, because the use of a new drug in the treatment can be accompanied by various complications and different tolerance levels, and significant price difference can be found between the use of existing drugs and a new drug. This study is conducted to evaluate the safety and effectiveness of formoterol versus salmeterol in the treatment of patients with asthma.

MATERIALS AND METHODS

We conducted a systematic review and meta-analysis. Different phases of the study included searching, screening, and selecting of studies, extracting data and data cleaning and analyzing.

Search strategy

To retrieve related studies, we used a sensitive search strategy in medical citation databases including, Cochran Library, PubMed, Scopus, PsycInfo, and IranMedex. In addition, we performed manual search of the databases that record randomized clinical trials, conference proceedings, and journals related to asthma such as American Academy of Allergy, Asthma and Immunology, American Thoracic Society, Asia Pacific Society of Respirology, British Thoracic Society Winter Meeting, and other journal such as Allergology International, Clinical Drug Investigation, American Journal of Respiratory and Critical Care Medicine, Journal of Asthma, and Canadian Respiratory Journal. Also, we checked health.govandopen.gov in case of complication of medications. In order to find the dissertation proposal, Dissertation Abstracts Online was searched, and then an alert was generated in Google Scholar during the execution of new articles to be achieved.

In search protocol, we were used in the combination of the MeSH terms "formoterol," "salmeterol" and "asthma."

The last search in databases was performed on July 10, 2012. Search was updated on February 24, 2013 but new records were not found.

The following search strategy was conducted for library Cochrane and then adapted to the other resources.

#1Formoterol#Atock#3Oxeze#4Oxis#5Foradil#6Foradile #7Perforomist#8EFormoterol#9eFormoterol#10Aerolizer# 11BD 40A#12AstraZeneca#13Formoterol fumarate#143-formylamino-4-hydroxy-alpha#15arFormoterol#16Schering (brand of Formoterol fumarate)#17Atimos #18(#1 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #15 OR #17)#19Salmeterol#20Serevent#21GlaxoWellcome(brandof Salmeterolxinafoate)#22Salmeterol xinafoate #23(#19 OR #20 OR #21 OR #22)#24(#18 AND #23)#25Asthma#26MeSH descriptor Asthma explode all trees#27(#25 OR #26) #28(#24 AND #27).

We did not limit our search to a certain language or time period to avoid missing possibly related works. Besides, we factored in manual reference checking and citation tracking of related paper. All the studies inserted in the EndNoteX4 Thomson Reuters's software and duplicates were excluded, and then the titles and abstracts were reviewed based on inclusion and exclusion criteria.

Inclusion criteria

Clinical trials that have designed as crossover or parallel studies or have conducted as double-blind or open, or have compared adult asthmatic patients treated with formoterol and salmeterol, were entered into the study.

Exclusion criteria

The following were excluded from the study: Trials that have been performed *in vitro* and trials that have examined the patients suffering from diseases with differential diagnosis of asthma (such as chronic obstructive pulmonary disease, exercise-induced asthma, nocturnal asthma, and asthma in children), the use of formoterol in combination with other drugs such as budesonide, and the use of salmeterol in combination with other drugs such as fluticasone.

Study selection

Full-text of the relevant studies was critically appraised for eligibility criteria by two researchers independently. The third colleague assessed the papers in case of disagreement. Formoterol unrelated and duplicated

articles were excluded based on title and abstract. Flow diagram of studies included in the systematic review is shown in Figure 1.

Quality assessment

Studies that met the inclusion criteria of our review were independently evaluated by two researchers in a qualitative manner, according to Cochran indices. Also we used the Jadad quality assessment scale (JADAD scale) in order for quality assessment.

Although the quality was not used as a case for excluding studies, it was considered in the final conclusion when evaluating the results of studies.

Data synthesis

Data extraction forms were designed for the data extracted from papers, which were checked by the second person. Common outcomes of papers were entered into the RevMan 5.0.1 Cochrane Collaboration's software: The outcomes of this study were entered into the "Data Analysis" section of the software in a continuous quantitative manner; the sub-outcomes entered the data of related studies; and the mean difference and CI (95%) were calculated based on a fixed-effect model. Homogeneity and heterogeneity were evaluated using I^2 and Chi-square tests based on the P value. For the outcomes of homogeneous studies, the meta-analysis data were used in this study while the data were qualitatively reported for the outcomes of heterogeneous studies.

RESULTS

One thousand three hundred and thirty-six of 1536 articles found in this study remained after removing duplicate cases: Thirty-three studies met the study's inclusion criteria on the basis of title and abstract; and concerning eight articles whose original printed versions were not found, the decision was made based on the titles and abstracts available, according to inclusion and exclusion criteria of the study. Thirteen of 25 studies were excluded, the reason for exclusion are described in Table 1. At last, 12 studies whose data are listed in Table 2 met the inclusion criteria of the review. Flow diagram of selecting studies is shown in Figure 1.

The total number of participants in the 12 studies was 1661. The outcomes selected in these studies were forced expiratory volume 1 s (FEV1) and Borg score in two studies, FEV1 in six studies, peak expiratory flow (PEF) in one study, episode-free days (EFDs) and quality of life in one study, and PEF and EFDs in one study, as well as FEV1 and PEF

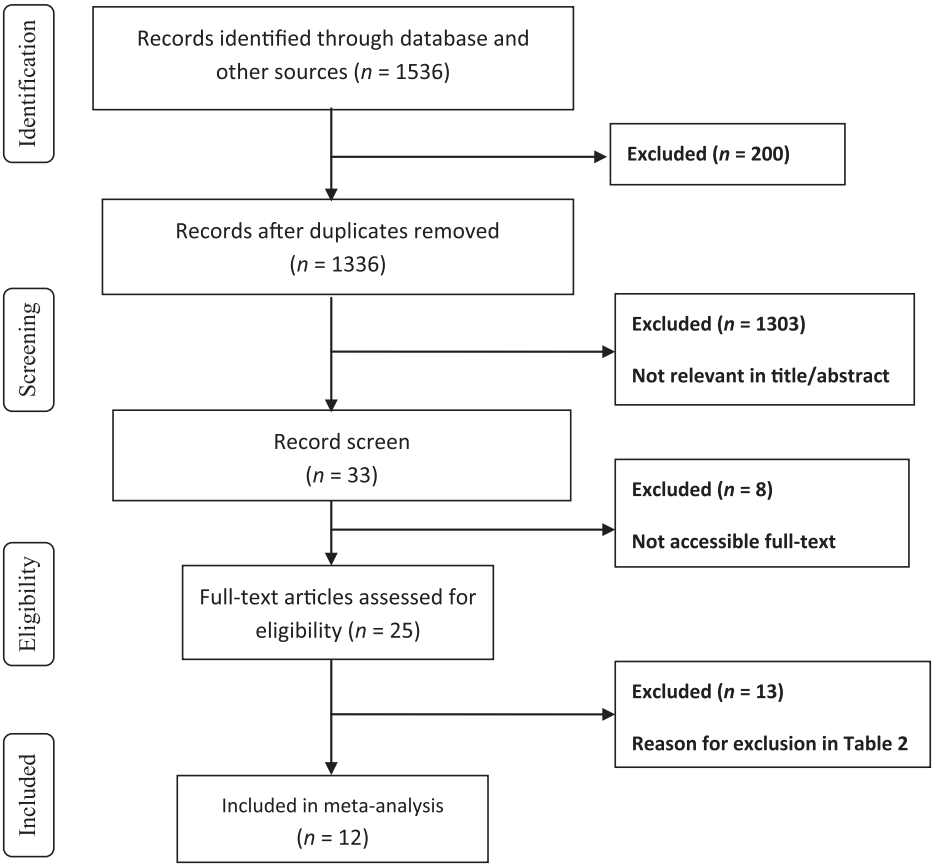

Figure 1: Flowchart of the selection process records

in one study. The doses of salmeterol were equal to 50 μg twice daily in nine studies, 100 μg twice daily in one study, both doses in one study, and uncertain dose in one study. The doses of formoterol were equal to 12 μg twice daily in eight studies, 24 μg twice daily in one study, 12 and 24 μg in one study, doses of 6, 12, and 24 μg in one study, and uncertain dose in one study.

The results of evaluating the homogeneity and heterogeneity of studies, which was done based on I^2 and Chi-square tests according to the *P* value, are as follows.

Meta-analysis of the outcomes with mean forced expiratory volume 1 s, 12 h after inhalation of the drug

Three studies of Palmqvist *et al.*,[23] Grembiale *et al.*,[24]

Table 1: Reason for exclusion of 13 studies

First author	Year	Reason for exclusion
Singhania *et al.*[10]	2008	The study was conducted in a population of children that were not consistent in our study
Lee *et al.*[11]	2004	Combination of medication was used in the intervention and comparison
Richter *et al.*[12]	2002	Asthma due to exercise has been considered
van der Woude *et al.*[13]	2001	Combination of medication was used in the intervention and comparison
Lipworth *et al.*[14]	2000	The study was performed on patients with a specific genotype
Aziz *et al.*[15]	1998	Formoterol and salmeterol were not used in this study
Tan *et al.*[16]	1997	Formoterol and salmeterol were not used in this study
Brambilla *et al.*[17]	2003	Combination of medication was used in the intervention and comparison
van Veen *et al.*[18]	2003	The effect of these drugs was compared with short-acting drugs
Schermer *et al.*[19]	2004	The study was conducted in patients with persistent asthma
Politiek *et al.*[20]	1999	Combination of medication was used in the intervention and comparison
Eryonucu *et al.*[21]	2005	Effects on heart rate changes were measured
Cates and Lasserson[22]	2010	Combination of medication was used in the intervention and comparison

Table 2: Details of included studies specification

First author	Year	Country	Study setting and time period	Sample	Dosage of salmeterol	Dosage of formoterol	Outcome	Quality score
Rutten-van	1998	UK, Switzerland Sweden, France, Spain, Italy	RCT 6 months	482	50 μg Twice a day	12 μg Twice a day	EFDs Quality of life	2
John J. Condemi	2001	USA	RCT 6 months	528	50 μg Twice a day	12 μg Twice a day	EFDs PEF	2
Julia A. Nightingale	2002	UK	RCT 4 months	528	50 μg Twice a day	12 μg Twice a day	PEF FEV1	4
Klaus F. Rabe	1993	Germany	RCT 1-day	12	50 μg 100 μg Once a day	12 μg 24 μg Once a day	FEV1	2
Campbell	1999	UK	RCT 8 weeks	469	50 μg Twice a day	12 μg Twice a day	PEF	2
Palmqvist	1997	Sweden	RCT 12 h	28	50 μg NA	6 μg 12 μg 24 μg NA	FEV1	4
H. J van der Woude	2001	Netherland	RCT 2 weeks	19	100 μg Twice a day	24 μg Twice a day	FEV1 Borg score	5
Hanneke J. van der Woude	2004	Netherland	RCT 4 days	21	50 μg Twice a day	12 μg Twice a day	FEV1 Borg score	4
Rosa D. Grembiale	2002	Italy	RCT 3 days	10	50 μg Twice a day	12 μg Twice a day	FEV1	2
Alison Grove	1996	UK	RCT 12 h	10	50 μg NA	12 μg NA	FEV1	1
Brian J. Lipworth	1998	Scotland	RCT 10 days	10	50 μg Twice a day	12 μg Twice a day	FEV1	1
Valentine Lemaigre	2006	Belgium	RCT NA	30	NA	NA	FEV1	2

NA =Not available; RCT = Randomized clinical trials; FEV1 = Forced expiratory volume in 1 s; PEF = Peak expiratory flow; EFDs = Episode-free days

and Rabe *et al.*[25] were included following outcomes. These studies were homogeneous, and meta-analysis was performed ($\chi^2 = 0.14$, $P = 0.93$, $I^2 = 0\%$). Forest plot of these studies is shown in Figure 2.

According to the meta-analysis results, mean difference was −0.02 (−0.22, 0.18); there is no difference between formoterol 12 μg and salmeterol 50 μg in mean FEV1 at 12 h after inhalation of medication. According to the JADAD score of studies with this outcome, this lack of difference appears to be valid in the mean FEV1.

Meta-analysis of the outcomes with reduced forced expiratory volume 1 s after inhalation of methacholine

Two studies from van der Woude *et al.*[26,27] were included in this analysis. These studies were homogeneous, and meta-analysis was performed ($\chi^2 = 0.44$, $P = 0.51$, $I^2 = 0\%$). Forest plot of these studies is shown in Figure 3.

According to the meta-analysis results, this is a significant difference as 5.23 (1.11-9.34). Therefore, the use of salmeterol 50 μg after inhalation of methacholine reduced more the FEV1 than that of formoterol 12 μg; in these two studies, the ratio dosage of formoterol to salmeterol is same and these studies are similar in this regard, so this point has been considered as restitution of this analysis, and these results should be taken with caution. Also, van der Woude study was sponsored by AstraZeneca Company but in another study did not mention the conflict of interest.

Meta-analysis of outcomes with the number of days without an attack

Two studies of Rutten-van Mölken *et al.*[28] and Condemi[29] were included in this analysis. These studies were homogeneous, and meta-analysis was performed ($\chi^2 = 0.00$, $P = 0.96$, $I^2 = 0\%$). Forest plot of these studies is shown in Figure 4.

According to the meta-analysis results, mean difference was 1.71 (0.19, 3.22); this difference is statistically significant, and therefore, the number of days without an attack after use of salmeterol 50 μg is more than that of formoterol 12 μg. However, the difference was not clinically comparable, and their results should be taken with caution because a review of the quality evaluation of these two articles indicates a medium quality. These studies were sponsored by Novartis Company.

Meta-analysis of the outcome with Borg score after inhalation of drugs

Two studies from van der Woude were included in this analysis.[26,27] These studies were homogeneous, and meta-analysis was performed ($\chi^2 = 0.05$, $P = 0.82$, $I^2 = 0\%$). Forest plot of these studies is shown in Figure 5.

According to the meta-analysis results, this difference is not statistically significant as 0.06 (−1.95, 2.06) and, therefore, there is no difference in the score after inhalation of 50 μg salmeterol and 12 μg formoterol, in these two studies, the ratio dosage of formoterol to salmeterol is same and two studies are similar in this regard, so this point has been considered as restitution of this analysis, and these results should be taken with caution. Also, van der Woude was sponsored by

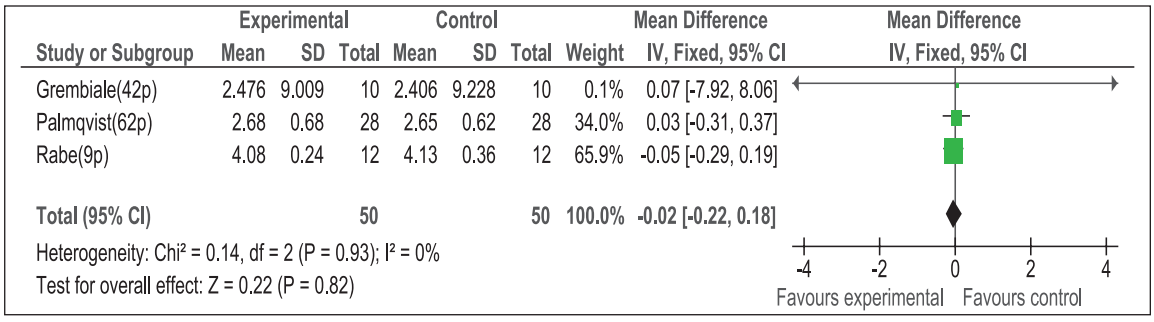

Figure 2: Forest plot of the outcome with mean forced expiratory volume 1 s, 12 h after inhalation of the drug

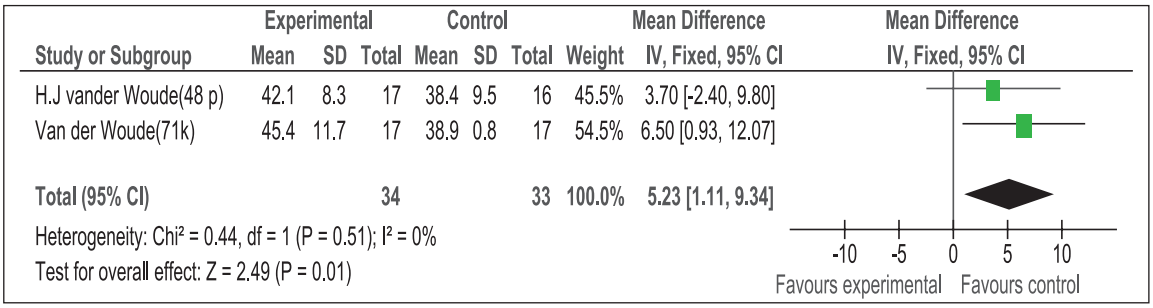

Figure 3: Forest plot of the outcomes with reduced forced expiratory volume 1 s after inhalation of methacholine

AstraZeneca company but in another study did not mention the conflict of interest.

DISCUSSION

According to the study result, there was no difference found between salmeterol (12 μg) and formoterol (50 μg) in two meta-analyses, and in two other meta-analyses, the results were also in favor of salmeterol (50 μg). Due to their heterogeneous nature, the two outcomes of FEV1 30-60 min after inhalation of medication and morning PEF after inhalation of medication had no meta-analysis capabilities, whose results were reported qualitatively. In both meta-analyses, there were two studies where, for each outcome, they were in favor of the intervention group (formoterol 12 μg) in one study and in favor of the control group (salmeterol 50 μg) in another study. There is also evidence about the safety and effectiveness of formoterol and salmeterol that are as follows.

The complaints observed in the two drug groups of salmeterol and formoterol were similar in the studies by Campbell and Rutten-van the latter of which was funded by the Novartis Corporation.[28] Condemi's study, which was funded by the Novartis Corporation, showed that the complications of upper respiratory tract infection, aggravation of asthma, headache, and rhinitis in the formoterol group were more than those in the salmeterol group, while the complications of viral infections, sinusitis, bronchitis, cough, pharyngitis, and pain in the salmeterol group were more than those in the formoterol group. In Nightingale's study, complaints observed in the formoterol group were more than those in the salmeterol group.[30]

The most common side complaints reported in the study of Condemi were upper respiratory tract infection, asthma, viral infection, sinusitis, bronchitis, headache, rhinitis, and cough; no deaths were reported in any of the groups.[29]

In Campbell's study, in total, 1171 side effects were reported during the study (during implementation and duration of treatment) by 390 cases, several of whom had reported more than one adverse complication. In this study, the complications observed in both drug groups were almost identical and statistically insignificant. In Nightingale's study, the complications observed are (17 of 35 patients, 49%) in the formoterol group, and (13 of 33 patients, 39%) in the salmeterol group, type of complications is not mentioned in this study; during the study, one patient in the formoterol group had suffered a transient ischemic attack. In the study by Rutten-van *et al*., 11 of 241 patients in the formoterol group and 12 of 241 patients in the salmeterol group have had complications. However, they were not noted in the study. Also, the side effects of these drugs were not mentioned in other studies.

Only 2 of the 4 studies where side effects of the drugs have been documented have reported details of the observed complications, and the others had just mentioned the number of complications observed. Brands of formoterol used in the four studies include Novartis in two studies, Oxis in one study, and Foradil in one study; and brands of salmeterol used are GlaxoSmithKline in two studies, Serevent and Glaxo-Wellcome in one study, and Serevent in one study. Formoterol 12 μg and salmeterol 50 μg were prescribed twice daily in all 4 studies. Whereas the duration of use was not mentioned in two studies, in two other

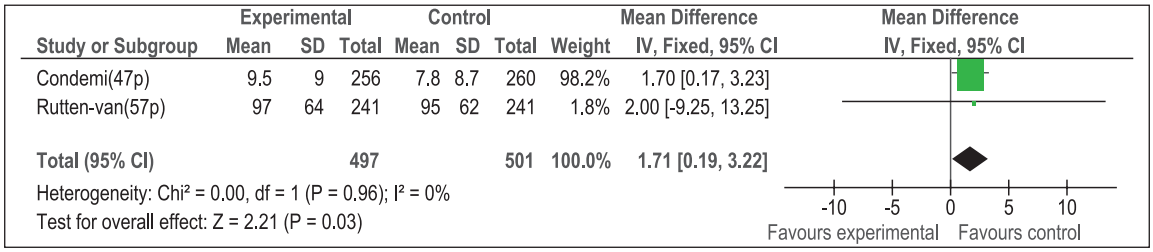

Figure 4: Forest plot of outcomes with the number of days without an attack

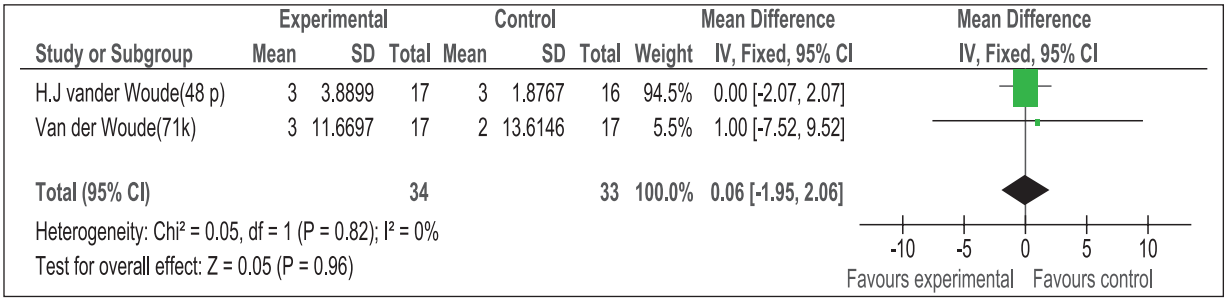

Figure 5: Forest plot of the outcome with Borg score after inhalation of drugs

studies, the drug was administrated for 24 weeks (108 days) and 166 (±36) days.

Taking salmeterol 50 μg after inhalation of methacholine can reduce more the FEV1 than formoterol 12 μg (P = 0.01, CI = [1.11, 9.34]). The number of days without an attack after taking salmeterol 50 μg is the more than that after taking formoterol 12 μg (P = 0.03, CI = [0.19, 3.22]). In mean FEV1 at 12 h after inhalation of medication, there is no difference between formoterol 12 μg and salmeterol 50 μg (P = 0.82, CI = [−0.22, 0.18]). Also, there is no difference in the score after inhalation of 50 μg salmeterol and 12 μg formoterol (P = 0.956, CI = [−1.95, 2.06]).

In the studies included in the review, there were no significant differences between the two drugs, in terms of efficiency and efficacy. Furthermore, in the study by Rutten-van *et al*., there was no significant difference between the two drugs in terms of outcomes and/or costs, and physicians in each country were advised to use the drug with a lower price, which seems to be in line with the results of this project.[10] Overall, the safety and effectiveness of formoterol seem to be not more than those of salmeterol; and compared to formoterol, the administration of salmeterol appears to be beneficial for patients, because salmeterol is being domestically produced in Iran and is readily available in pharmacies in the country.

Limitation of this study

The weaknesses of this study include lack of access to some databases such as EMBASE, due to the database being closed in Iran and not finding the full-text of eight studies that had been conducted on this subject, but there were no published articles about them.

ACKNOWLEDGMENTS

The authors thank the NIHR (Iran National Institute of Health Research) staffs for their support.

AUTHOR'S CONTRIBUTIONS

AV: Literature search, Data gathering, Analysis and interpretation of data. AH: Study conception and design, Analysis and interpretation of data. AS: Study conception and design, Critical revision. FM: Literature search, Data gathering. MGh: Study conception and design.RM: Study conception and design, Critical revision. MY: Drafting of manuscript.

REFERENCES

1. British Thoracic Society, Scottish Intercollegiate Guidelines Network. British Guideline on the Management of Asthma. Edinburgh: SIGN; 2005. http://www.ncbi.nlm.nih.gov/pubmed/12653493.
2. Global Initiative for Asthma. Pocket Guide for Asthma Management and Prevention. http://www.ginasthma.org/documents/1: GINA; 2005.
3. Global Initiative for Asthma. Global Strategy for Asthma Management and Prevention — Updated; 2007. Available from: http://www.ginasthma.com.
4. Braman SS. FCCP - The Global Burden of Asthma. http://www.ncbi.nlm.nih.gov/pubmed/16840363.
5. Heidarnia MA, Entezari A, Moein M, Mehrabi Y, Pourpak Z. Prevalence of asthma symptom in Iran: a meta-analysis. Research in Medicine 2007;31:217-25. http://pejouhesh.sbmu.ac.ir/browse.php a_code=A-10-1-363&slc_lang=en&sid=1.
6. Derom EY, Pauwels RA. Time course of bronchodilating effect of inhaled formoterol, a potent and long acting sympathomimetic. Thorax 1992;47:30-3.
7. Derom EY, Pauwels RA, Van der Straeten ME. The effect of inhaled salmeterol on methacholine responsiveness in subjects with asthma up to 12 hours. J Allergy Clin Immunol 1992;89:811-5.
8. Nelson HS. Beta-adrenergic bronchodilators. N Engl J Med 1995;333:499-506.
9. Jeppsson AB, Källström BL, Waldeck B. Studies on the interaction between formoterol and salmeterol in guinea-pig trachea *in vitro*. Pharmacol Toxicol 1992;71:272-7.
10. Singhania N, Dhamija R, Lodha R, Kabra SK. Salmeterol vs. formoterol: A comparison of rapid bronchodilator effect in a randomized controlled trial. Indian Pediatr 2008;45:225-8.
11. Lee DK, Currie GP, Hall IP, Lima JJ, Lipworth BJ. The arginine-16 beta2-adrenoceptor polymorphism predisposes to bronchoprotective subsensitivity in patients treated with formoterol and salmeterol. Br J Clin Pharmacol 2004;57:68-75.
12. Richter K, Janicki S, Jörres RA, Magnussen H. Acute protection against exercise-induced bronchoconstriction by formoterol, salmeterol and terbutaline. Eur Respir J 2002;19:865-71.
13. van der Woude HJ, Winter TH, Aalbers R. Decreased bronchodilating effect of salbutamol in relieving methacholine induced moderate to severe bronchoconstriction during high dose treatment with long acting beta2 agonists. Thorax 2001;56:529-35.
14. Lipworth BJ, Dempsey OJ, Aziz I. Functional antagonism with formoterol and salmeterol in asthmatic patients expressing the homozygous glycine-16 beta(2)-adrenoceptor polymorphism. Chest 2000;118:321-8.
15. Aziz I, Tan KS, Hall IP, Devlin MM, Lipworth BJ. Subsensitivity to bronchoprotection against adenosine monophosphate challenge following regular once-daily formoterol. Eur Respir J 1998;12:580-4.
16. Tan KS, McFarlane LC, Lipworth BJ. Effects of oral and inhaled corticosteroid on lymphocyte beta2-adrenoceptor function in asthmatic patients. Br J Clin Pharmacol 1997;44:565-8.
17. Brambilla C, Le Gros V, Bourdeix I, Efficacy of Foradil in Asthma (EFORA) French Study Group. Formoterol 12 microg BID administered via single-dose dry powder inhaler in adults with asthma suboptimally controlled with salmeterol or on-demand salbutamol: A multicenter, randomized, open-label, parallel-group study. Clin Ther 2003;25:2022-36.
18. van Veen A, Weller FR, Wierenga EA, Jansen HM, Jonkers RE. A comparison of salmeterol and formoterol in attenuating airway responses to short-acting beta2-agonists. Pulm Pharmacol Ther 2003;16:153-61.
19. Schermer TR, Hoff WJ, Greefhorst AP, Creemers JP, Sips AP, Westbroek J, *et al*. Profiles of measured and perceived bronchodilation. A placebo-controlled cross-over trial comparing formoterol and salmeterol in moderate persistent asthma. Pulm Pharmacol Ther 2004;17:205-12.
20. Politiek MJ, Boorsma M, Aalbers R. Comparison of formoterol, salbutamol and salmeterol in methacholine-induced severe bronchoconstriction. Eur Respir J 1999;13:988-92.

21. Eryonucu B, Uzun K, Güler N, Tuncer M, Sezgi C. Comparison of the short-term effects of salmeterol and formoterol on heart rate variability in adult asthmatic patients. Chest 2005;128:1136-9.
22. Cates CJ, Lasserson TJ. Regular treatment with formoterol and an inhaled corticosteroid versus regular treatment with salmeterol and an inhaled corticosteroid for chronic asthma: Serious adverse events. Cochrane Database Syst Rev 2010;20:CD007694.
23. Palmqvist M, Persson G, Lazer L, Rosenborg J, Larsson P, Lötvall J. Inhaled dry-powder formoterol and salmeterol in asthmatic patients: Onset of action, duration of effect and potency. Eur Respir J 1997;10:2484-9.
24. Grembiale RD, Pelaia G, Naty S, Vatrella A, Tranfa CM, Marsico SA. Comparison of the bronchodilating effects of inhaled formoterol, salmeterol and salbutamol in asthmatic patients. Pulm Pharmacol Ther 2002;15:463-6.
25. Rabe KF, Jörres R, Nowak D, Behr N, Magnussen H. Comparison of the effects of salmeterol and formoterol on airway tone and responsiveness over 24 hours in bronchial asthma. Am Rev Respir Dis 1993;147 (6 Pt 1):1436-41.
26. van der Woude HJ, Postma DS, Politiek MJ, Winter TH, Aalbers R. Relief of dyspnoea by beta2-agonists after methacholine-induced bronchoconstriction. Respir Med 2004;98:816-20.
27. van der Woude HJ, Aalbers R. Unaltered perception of dyspnoea during treatment with long-acting b2-agonists. Eur Respir J 2001; 18:269-71.
28. Rutten-van Mölken MP, van Doorslaer EK, Till MD. Cost-effectiveness analysis of formoterol versus salmeterol in patients with asthma. Pharmacoeconomics 1998;14:671-84.
29. Condemi JJ. Comparison of the efficacy of formoterol and salmeterol in patients with reversible obstructive airway disease: A multicenter, randomized, open-label trial. Clin Ther 2001;23:1529-41.
30. Nightingale JA, Rogers DF, Barnes PJ. Comparison of the effects of salmeterol and formoterol in patients with severe asthma. Chest 2002;121:1401-6.

Source of Support: Nil, **Conflicts of Interest:** None declared.