

The efficacy and safety of fluticasone propionate/formoterol compared with fluticasone propionate/salmeterol in treating pediatric asthma: a systematic review and meta-analysis

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Abstract

Objective: To evaluate the efficacy and safety of fluticasone propionate/formoterol (FP/FORM) versus fluticasone propionate/salmeterol (FP/SAL) in treating pediatric asthma during a 12-week treatment cycle.

Methods: Randomized controlled trials of FP/FORM compared with FP/SAL in treating pediatric asthma were searched systematically using Medline, Embase, and the Cochrane Controlled Trials Register.

Results: Two articles including 546 patients were evaluated. The FP/SAL group showed obvious improvements in pre-dose forced expiratory volume in 1 s (FEV₁) from day 0 to 84, asthma symptom scores, and sleep disturbance scores compared with the FP/FORM group; however, the FP/FORM group had improved peak expiratory flow rate (PEFR). In terms of 2-hour post-dose FEV₁ from day 0 to 84, 2-hour forced expiratory flow at 25%, 50%, and 75%, and 2-hour forced vital capacity, we observed no significant differences between the two groups. For safety, including patients with at least one adverse event, bronchitis, cough, or pharyngitis, both groups had similar incidences, differing only in incidence of nasopharyngitis.

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Conclusion: Compared with FP/FORM, FP/SAL showed a clear improvement in pre-dose FEV₁, asthma symptom scores, and sleep disturbance scores. However, FP/FORM resulted in improved PEFR with a lower incidence of nasopharyngitis.

Keywords

Pediatric asthma, meta-analysis, randomized controlled trial, fluticasone, formoterol, salmeterol

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Introduction

Pediatric asthma is a significant public health disease worldwide. About 300 million people suffer from asthma worldwide according to the World Health Organization; at the current rate of growth, asthma is estimated to affect 400 million people by 2025.¹ Nearly a quarter of a million people die prematurely of asthma each year, and most of these deaths are preventable.² Asthma is the most common chronic disease among children and is ranked in the top 20 in children's disability-adjusted life years.³

In the Global Initiative for Asthma (GINA) guidelines, the combination of low-dose inhaled corticosteroid (ICS) and long-acting β_2 -agonist (LABA) is proposed as a third-step optional scheme for children in whom asthma is hard to control by ICS alone, although the preferred intensive treatment for this age group is an intermediate dose of ICS.⁴ The single inhaler combination therapy of ICS and LABA has been proven to boost treatment compliance and enhance the effectiveness of treatment compared with random combinations of two drugs because it guarantees simultaneous management of ICS.^{5,6}

Multiple ICS/LABA proposals are available for treating asthma in teenagers and adults, but few are approved for children aged 4 to 12 years. In Europe, fluticasone propionate/salmeterol (FP/SAL) 100/50 μ g

b.i.d. is used as a dry powder inhaler or as a pressurized metered-dose inhaler in patients aged 4 years.⁷ Currently, formoterol fumarate, as a rapid-acting LABA, shows similar speed to the short-acting β_2 -agonist (SABA). Fluticasone propionate/formoterol (FP/FORM) combination therapy was tested in some studies among adults with mild-severe asthma and demonstrated good therapeutic effects for asthma; this combination might provide an alternative choice for pediatric asthma.⁸⁻¹¹

We performed a meta-analysis to evaluate the efficacy and safety of FP/FORM compared with FP/SAL in treating pediatric asthma during a 12-week treatment cycle.

Materials and methods

Study protocol

The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) checklist was used for this systematic review of randomized controlled trials (RCTs).¹²

Search strategy

We searched Medline, Embase, and Cochrane Controlled Trials Register databases (before 3 March 2019) to investigate the efficacy of FP/FORM in treating pediatric asthma compared with FP/SAL.

The search term was “fluticasone, formoterol, salmeterol, pediatric asthma and RCT”. The study was restricted to research published in English. If necessary, authors were contacted to provide further information from their study. The references of related articles were also searched.

Inclusion criteria and trial selection

Inclusion criteria were as follows: (1) FP/FORM versus FP/SAL in treating pediatric asthma was studied; (2) full-text content could be obtained; (3) accurate data were provided and could be analyzed (including values of parameters and total number of subjects); (4) the trial was a randomized controlled study; and (5) the duration of treatment was 12 weeks. If two articles

described the same experiment, we included the later study. When the same group of researchers investigated a certain subject group in multiple experiments, each study was included. A PRISMA diagram of selection is shown in Figure 1.

Quality assessment

The Jadad scale was used to assess the quality of each RCT,¹³ and RCTs were graded in line with principles derived from the *Cochrane Handbook for Systematic Reviews of Interventions* (v5.10).¹⁴ Every article was evaluated and classified based on quality assessment criteria: “A” if the study satisfied all quality criteria; “B” if the study had one or more ambiguous quality criteria and the study had a moderate

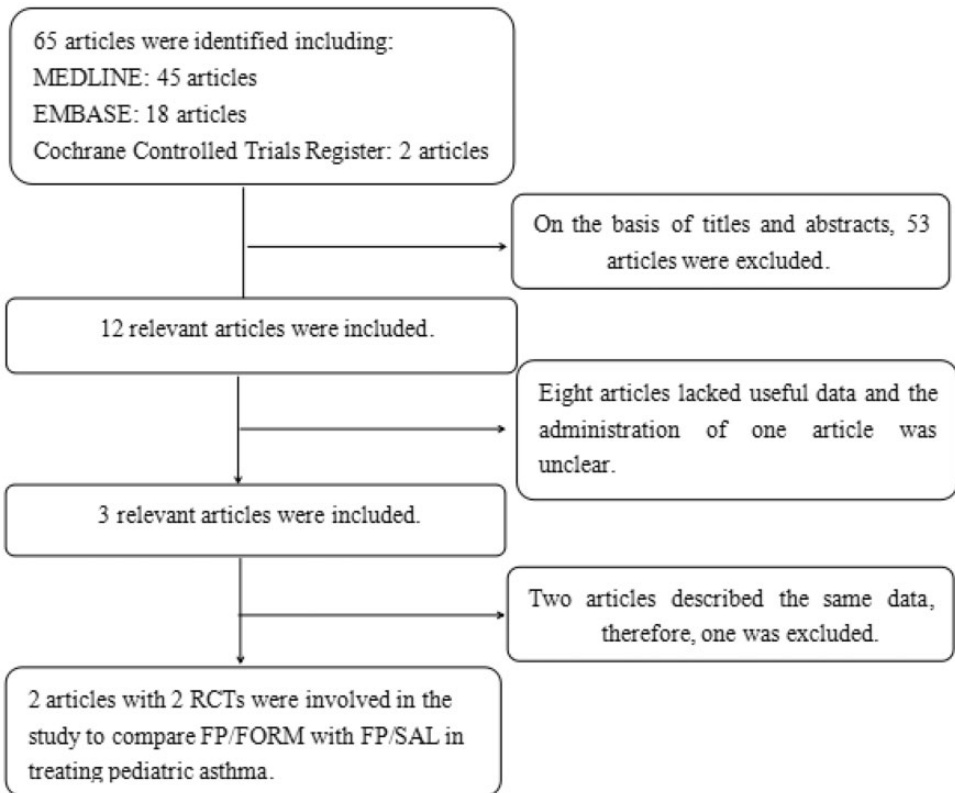


Figure 1. Flowchart of the study selection process. RCT, randomized controlled trial.

risk of bias; and “C” if the study had a high risk of bias and met few of the quality criteria. All authors assessed the quality of the RCTs and agreed with the final assessments. Differences regarding the quality assessment were resolved through discussion among authors.

Data extraction

Two authors independently collected data from articles based on predetermined criteria. The following information was collected: (1) year of publication; (2) abbreviations of authors' first names; (3) intervention method; (4) sample size; (5) data on the change in pre-dose forced expiratory volume in 1 s (FEV_1) from day 0 to 84; 2-hour post-dose FEV_1 from day 0 to 84, peak expiratory flow rate (PEFR), 2-hour forced expiratory flow at 25%, 50%, and 75% (2-hour FEF_{25} , FEF_{50} , FEF_{75}), 2-hour forced vital capacity (FVC), asthma symptom scores, sleep disturbance scores, patients with at least one adverse event (AE), bronchitis, cough, nasopharyngitis, and pharyngitis. No ethical approval was required for this systematic review.

Statistical analyses and meta-analysis

RevMan version 5.3.0 (Cochrane Collaboration, Oxford, UK) was used to analyze the difference between the two groups.¹⁵ We analyzed the data of the change in pre-dose FEV_1 from day 0 to 84, 2-hour post-dose FEV_1 from day 0 to 84, PEFR, 2-hour FEF_{25} , 2-hour FEF_{50} , 2-hour FEF_{75} , 2-hour FVC, asthma symptom scores, and sleep disturbance scores. We also studied the difference of patients with at least one AE, bronchitis, cough, nasopharyngitis, and pharyngitis. We used mean difference (MD) as an evaluation factor for continuous data, and the effects of the odds ratio (OR) to evaluate dichotomous data. We analyzed comparable data

by using 95% confidence intervals (CI).¹⁵ A fixed model was suitable for studies if $P > 0.05$; otherwise, a random-effects model was chosen. Inconsistent results were analyzed using the I^2 statistic, which represents the proportion of heterogeneity across trials. We considered $P < 0.05$ to indicate statistical significance.

Results

Characteristics of individual studies

Our study found 65 articles in the databases; 53 of these were excluded after scrutiny of their abstracts and titles. Of the remaining 12 articles, 8 were excluded due to lack of effective data and 1 because drug management was not clear. Two articles described the same data set, one of which was excluded. Thus, two articles containing two RCTs^{16,17} were used to analyze FP/FORM versus FP/SAL in treating pediatric asthma during a 12-week treatment cycle. The data of each RCT are given in Table 1, and baseline data are shown in Table 2.

Quality of the individual studies

Both studies were RCTs, and each specified the randomization process. Each RCT had an appropriate calculation of sample size and an intention-to-treat analysis (Table 3). The funnel plot was highly symmetrical and the two circles were contained in the large triangle; thus, no evidence of bias was found (Figure 2).

Efficacy

Change in pre-dose FEV_1 and 2-hour post-dose FEV_1 from day 0 to 84. Both studies (273 patients in the FP/FORM group and 273 in the FP/SAL group) had data on pre-dose FEV_1 and 2-hour post-dose FEV_1 from day 0 to 84 (Figure 3). For the change in pre-dose FEV_1 from day 0 to 84,

Table 1. Details of the individual studies in the meta-analysis.

Study	Therapy in experimental group	Therapy in control group	Sample size		Method	Follow-up time (weeks)	Dosage		Main inclusion criteria	Main exclusion criteria
			Experimental	Control			Experimental	Control		
Emeryk et al. (2016)	Fluticasone /formoterol	Fluticasone /salmeterol	106	105	Inhalation	12	100 µg + 10 µg	100 µg + 50 µg	Patients aged 4 to 12 years who have had asthma for at least 6 months. Eligible patients had an FEV ₁ between 60% and 100% of predicted normal levels following appropriate with holding of asthma medication and documented FEV ₁ reversibility of at least 15%.	Patients with any clinically significant disease or abnormality, a clinically relevant upper or lower respiratory infection within 4 weeks prior to screening or significant non-reversible pulmonary disease.
Ploszczuk et al. (2018)	Fluticasone /formoterol	Fluticasone /salmeterol	167	168	Inhalation	12	100 µg + 10 µg	100 µg + 50 µg	Male and female patients, aged 5 to <12 years, with persistent asthma for ≥6 months, with FEV ₁ ≥60% to ≤90% predicted, ≥15% FEV ₁ reversibility.	Patients with potentially brittle asthma evidenced by life-threatening asthma within the past year, hospitalization or an emergency room visit for asthma within the past 6 months, with a clinically significant upper or lower respiratory infection within 4 weeks.

FEV₁, forced expiratory volume in 1 second.

Table 2. Baseline characteristics of individual study.

Study	Group	Age (years)	Sex (Male/female)	Race (Caucasian /Asian)	Duration of asthma (years)	Asthma characteristics		
						FEV ₁ (presalbutamol; L)	FEV ₁ (% predicted)	FEV ₁ reversibility (%)
Emeryk et al. (2016)	Fluticasone /formoterol	8.8 ± 2.10	72/34	106/0	>6 months	1.53 ± 0.34	82.0 ± 9.50	23.7 ± 9.40
	Fluticasone /salmeterol	8.5 ± 2.20	73/32	105/0		1.54 ± 0.44	82.5 ± 9.50	25.5 ± 9.90
Ploszczuk et al. (2018)	Fluticasone /formoterol	8.4 ± 1.81	109/58	164/3	3.5 ± 2.36	1.48 ± 0.36	73.8 ± 6.76	24.1 ± 10.49
	Fluticasone /salmeterol	8.6 ± 1.80	113/55	165/3	3.5 ± 2.43	1.50 ± 0.36	73.5 ± 7.63	24.9 ± 9.75

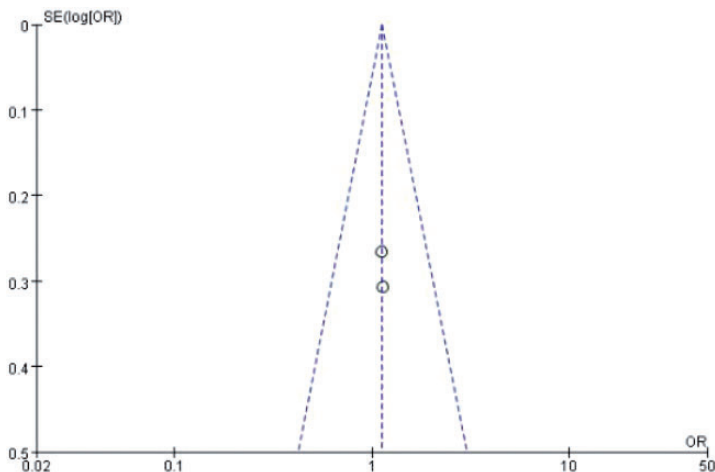
Data presented as mean ± SD; FEV₁, forced expiratory volume in 1 second.

Table 3. Quality assessment of individual studies.

Study	Allocation sequence generation	Allocation concealment	Blinding	Loss to follow-up	Calculation of sample size	Statistical analysis	Level of quality	ITT analysis
Emeryk et al. (2016)	A	C	C	I	Yes	ANCOVA	C	Yes
Ploszczuk et al. (2018)	A	A	A	0	Yes	ANCOVA	A	Yes

A, almost all quality criteria met; low risk of bias; B, one or more quality criteria met; moderate risk of bias; C, one or more criteria not met; high risk of bias.

ANCOVA, analysis of covariance; ITT, intention-to-treat.

**Figure 2.** Funnel plot of the studies included in our meta-analysis. OR, odds ratio; SE, standard error.

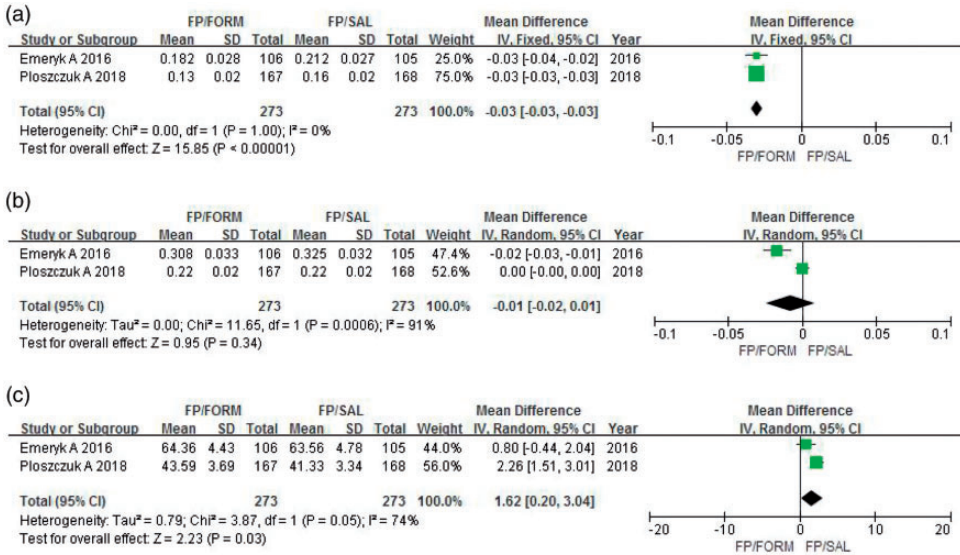


Figure 3. Forest plots showing changes in (a) pre-dose forced expiratory volume in 1 second; (b) 2-hour post-dose forced expiratory volume in 1 s; and (c) peak expiratory flow rate. FP/FORM, fluticasone propionate/formoterol; FP/SAL, fluticasone propionate/salmeterol; SD, standard deviation; IV, inverse variance; CI, confidence interval; df, degrees of freedom.

a fixed-effects model was used. The estimated MD was -0.03 and 95% CI was -0.03 to -0.03 ($P < 0.00001$). This result showed that FP/SAL was better than FP/FORM in change of pre-dose FEV₁ from day 0 to 84. For the change in 2-hour post-dose FEV₁ from day 0 to 84, a random-effects model showed that MD was -0.01 and 95% CI was -0.02 to -0.01 ($P = 0.34$), indicating that the FP/SAL and FP/FORM groups did not differ significantly in change of 2-hour post-dose FEV₁ from day 0 to 84.

PEFR. Both studies (273 patients in the FP/FORM group and 273 in the FP/SAL group) had data on PEFR (Figure 3). A random-effects model showed that MD was 1.62 and 95% CI was 0.20 to 3.04 ($P = 0.03$). The FP/FORM group was significantly different from the FP/SAL group in improving PEFR.

Two-hour FEF₂₅, FEF₅₀, and FEF₇₅. Both studies (273 patients in the FP/FORM group and 273 in the FP/SAL group) were used to analyze the change in 2-hour FEF₂₅, 2-hour FEF₅₀, and 2-hour FEF₇₅. The fixed-effects model showed that the two groups did not differ in terms of 2-hour FEF₂₅ (MD 0.05, 95% CI -0.09 to 0.19; $P = 0.47$), 2-hour FEF₅₀ (MD 0.04, 95% CI -0.06 to 0.15; $P = 0.41$), or 2-hour FEF₇₅ (MD -0.03 , 95% CI -0.10 to 0.04; $P = 0.40$) (Figure 4).

Two-hour FVC. Both studies included data on 2-hour FVC. A fixed-effects model showed that MD was -0.00 and 95% CI was -0.01 to 0.01 ($P = 0.43$) (Figure 5). We found no difference between the FP/FORM and FP/SAL groups for the change in 2-hour FVC.

Asthma symptom scores and sleep disturbance scores. Both studies (273 patients in the FP/FORM group and 273 in the FP/SAL

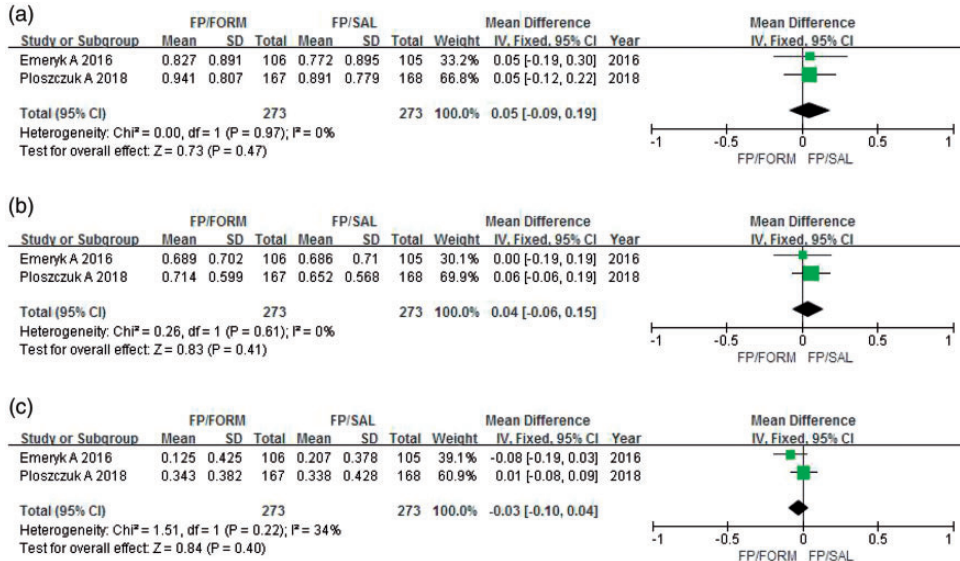


Figure 4. Forest plots showing changes in (a) 2-hour forced expiratory flow at 25%; (b) 2-hour forced expiratory flow at 50%; and (c) 2-hour forced expiratory flow at 75%. FP/FORM, fluticasone propionate/formoterol; FP/SAL, fluticasone propionate/salmeterol; SD, standard deviation; IV, inverse variance; CI, confidence interval; df, degrees of freedom.

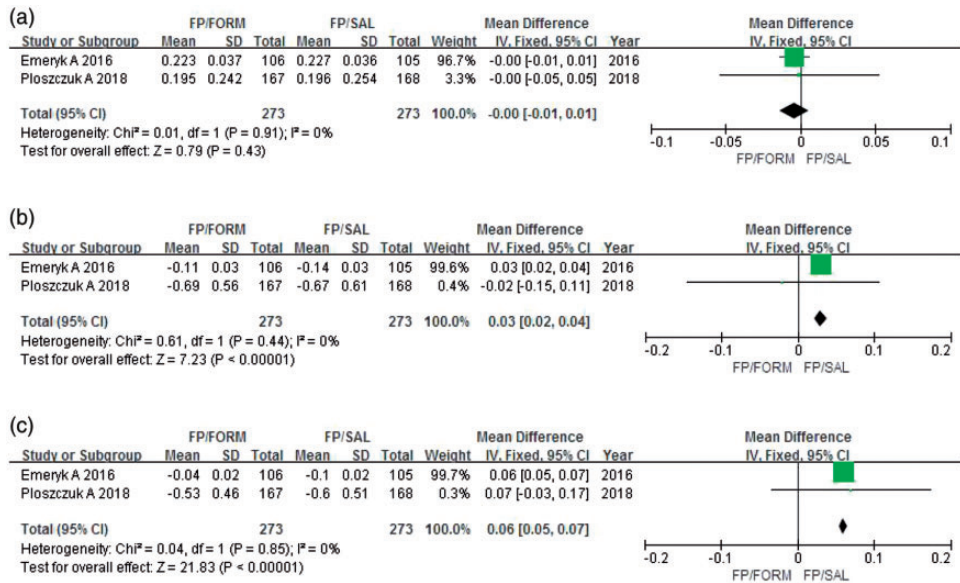


Figure 5. Forest plots showing changes in (a) 2-hour forced vital capacity; (b) asthma symptom score; and (c) sleep disturbance score. FP/FORM, fluticasone propionate/formoterol; FP/SAL, fluticasone propionate/salmeterol; SD, standard deviation; IV, inverse variance; CI, confidence interval; df, degrees of freedom.

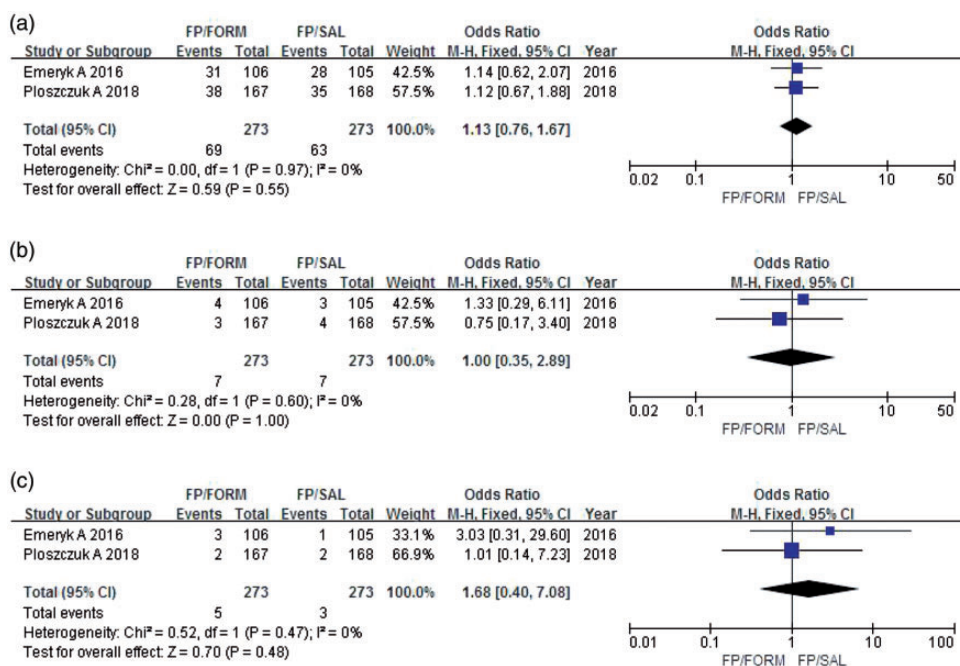


Figure 6. Forest plots showing numbers of patients with (a) at least one adverse event; (b) bronchitis; and (c) cough. FP/FORM, fluticasone propionate/formoterol; FP/SAL, fluticasone propionate/salmeterol; M-H, Mantel-Haenszel; CI, confidence interval; df, degrees of freedom.

group) included data on asthma symptom scores and sleep disturbance scores (Figure 5). The FP/SAL group had a significant reduction in asthma symptom score (MD 0.03, 95% CI 0.02 to 0.04; $P < 0.00001$) and sleep disturbance score (MD 0.06, 95% CI 0.05 to 0.07; $P < 0.00001$) compared with the FP/FORM group (Figure 5).

Safety

Patients with at least one AE, bronchitis, or cough. Both studies (546 patients) were involved in the analysis (Figure 6). The FP/FORM group did not differ from the FP/SAL group in the prevalence of patients with at least one AE (OR 1.13, 95% CI 0.76 to 1.67; $P = 0.55$), bronchitis (OR 1.00, 95% CI 0.35 to 2.89; $P = 1.00$), or cough (OR 1.68, 95% CI 0.40 to 7.08; $P = 0.48$).

Nasopharyngitis and pharyngitis. Both studies (546 patients) were involved in the analysis (Figure 7). For nasopharyngitis, a fixed-effects model had an OR of 0.37 and 95% CI of 0.15 to 0.91 ($P = 0.03$), showing a higher incidence in the FP/SAL group. For pharyngitis, the two groups did not differ (OR 1.00, 95% CI 0.37 to 2.70, $P = 1.00$).

Discussion

ICS is the cornerstone of asthma management in pediatric patients; however, asthma is often not adequately controlled by ICS alone.¹⁸ The LABA represent an available treatment option but their application has rarely been studied in children.¹⁹ Formoterol and salmeterol, as two types of LABA, have been evaluated in several

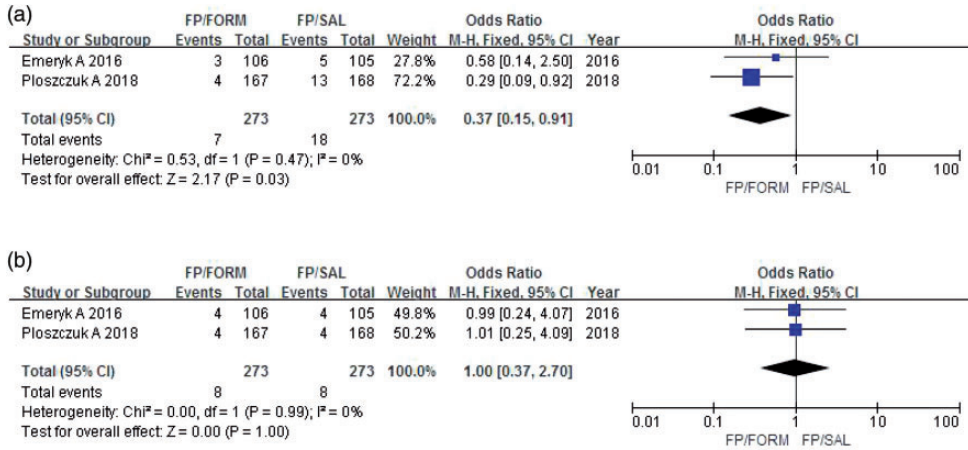


Figure 7. Forest plots showing numbers of patients with (a) nasopharyngitis; and (b) pharyngitis. FP/FORM, fluticasone propionate/formoterol; FP/SAL, fluticasone propionate/salmeterol; M-H, Mantel-Haenszel; CI, confidence interval; df, degrees of freedom.

studies and are approved for use in adults and adolescents with mild to severe asthma in Europe, Asia, and more than 30 other countries.^{20,21}

We compared the efficacy and safety of FP/FORM and FP/SAL in treating pediatric asthma during a 12-week treatment cycle. We found that the FP/SAL group showed clear improvements in change in pre-dose FEV₁ from day 0 to 84, asthma symptom scores, and sleep disturbance scores compared with the FP/FORM group; however, the FP/FORM group showed a greater improvement in PEFR. For 2-hour post-dose FEV₁ from day 0 to 84, 2-hour FEF₂₅, 2-hour FEF₅₀, 2-hour FEF₇₅, and 2-hour FVC, we observed no significant differences between the two groups. One RCT¹⁶ found that preliminary efficacy analysis of changes in 2-hour post-dose FEV₁ from day 0 to 84 showed that FP/FORM was not inferior to FP/SAL. Płoszczuk et al.¹⁷ demonstrated that during the 12-week treatment period, scores of asthma symptoms, percentage of asymptomatic days, percentage of sleep disorders, percentage of days without arousal, and percentage of days with asthma control

were significantly improved in all treatment groups, and there was no difference between the groups.

All LABA have pharmacological and clinical characteristics with some basic differences.^{22,23} The occurrence and duration of bronchodilation are affected by the time required for inhaled LABA to reach and maintain an effective concentration at the receptor site, both of which are related to the physical and chemical characteristics of the LABA.²⁴ The difference in physical and chemical properties between formoterol and salmeterol may explain the acceleration of formoterol.²⁵ Relatively high water solubility and mild oleophilicity ensure rapid access of the inhaled formoterol β -2-adrenoceptor to bronchial smooth muscle cells and fast bronchodilation. In contrast, salmeterol has low water solubility and high lipophilic activity and thus its action is slower.²⁵ In addition, the absorption of formoterol by airway smooth muscle cells is dependent on the organic cation transporter 3 (OCT3), whereas the absorption of the non-charged lipophilic salmeterol depends on the OCT transporter. Importantly, glucocorticoids inhibit OCT3 and may increase

the presence of formoterol β -2-adrenoceptor in the membrane, thereby increasing the effect of formoterol.^{26,27} The lipophilic properties of salmeterol and formoterol also explain why these drugs prolong bronchodilation.²⁵ In vitro, formoterol has a slightly shorter duration of action than salmeterol in small airways;²⁵ however, there was no difference in duration of effect in clinical studies of patients with asthma.²⁸ The lipophilicity of formoterol and salmeterol is sufficient to allow them to easily enter and be stored in the cell membrane, making a “warehouse” from which drugs are available for use in the β -2-adrenoceptor bronchial smooth muscle cells for a long time.²⁴ This is in contrast to SABA, such as salbutamol, which is removed from tissues more quickly after inhalation because of its high water solubility.

In terms of safety, including patients with at least one AE, bronchitis, cough, or pharyngitis, the FP/FORM group had similar incidences to the FP/SAL group with the exception of nasopharyngitis ($P=0.03$). Emeryk et al.¹⁶ showed that 29.2% of patients in the FP/FORM group and 26.7% in the FP/SAL group experienced at least one AE and that the most commonly recorded AEs were nasopharyngitis (in 2.8% and 4.8% of patients, respectively), pharyngitis (3.8% in both groups), and bronchitis (3.8% and 2.9% of patients respectively). During the 24-week extension phase in the study of Emeryk et al.¹⁶, the incidence of AEs was similar to that of the 12-week trial: nasopharyngitis, pharyngitis, and bronchitis were the most frequent, but no patients were discontinued due to AEs and no deaths occurred during the study, suggesting that long-term treatment with FP/FORM was well tolerated. However, some studies have found no significant difference between the drugs in terms of outcomes or cost, and physicians were advised to use the drug with a lower price in their country.^{29,30}

Compared with FP/FORM, FP/SAL showed an obvious improvement in pre-dose FEV₁, asthma symptom scores, and sleep disturbance scores; however, FP/FORM had a greater effect in improving PEFR and had a lower incidence of nasopharyngitis.

Currently, the sustained improvement in pre-dose FEV₁ with FP/SAL versus FP/FORM is consistent with the known pharmacology of the 2 LABAs and with the greater improvement in asthma control for the former, particularly with respect to the decrease in nocturnal awakenings. These results for FP/SAL would seem to outweigh the better PEFR with FP/FORM and the unexplained difference in occurrence of nasopharyngitis. More high-quality RCTs are needed to confirm these findings.

The quality of the included RCTs in our meta-analysis was high. We could not assess the long-term efficacy, safety, or tolerance of FP/FORM and FP/SAL, and our analysis may have been affected by selection bias due to differences in characteristics between selected and unselected subjects. However, meta-analysis can guide head-to-head comparisons in some ways. To determine the safety and tolerability of FP/FORM and FP/SAL treatments for childhood asthma, more high-quality RCTs and appropriate subjects are needed.

Conclusion

Compared with FP/FORM, treatment with FP/SAL resulted in an obvious improvement in pre-dose FEV₁, asthma symptom scores, and sleep disturbance scores. However, FP/FORM had a better effect on improving PEFR, with a lower incidence of nasopharyngitis.

Author contributions

All authors participated in the design of this study. Renzheng Guan, Yanli Liu, and Haiyan Hu performed the statistical analysis;

Dunqiang Ren, Jinfeng Li, and Tao Xu collected important background information; Renzheng Guan drafted the manuscript; Haiyan Hu conceived of this study, participated in the design, and helped to draft the manuscript. All authors read and approved the final manuscript.

Declaration of conflicting interest

The authors declare that there is no conflict of interest.

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References

- Masoli M, Fabian D, Holt S, et al. The global burden of asthma: executive summary of the GINA Dissemination Committee report. *Allergy* 2004; 59: 469–478.
- Nakayasu H, Araga S, Takahashi K, et al. Two cases of adult Down's syndrome presenting parietal low uptake in 123I-IMP-SPECT. *Clin Neurol* 1991; 31: 557–560.
- Vos T, Flaxman AD, Naghavi M, et al. Years lived with disability (YLDs) for 1160 sequelae of 289 diseases and injuries 1990–2010: a systematic analysis for the Global Burden of Disease Study 2010. *Lancet* 2012; 380: 2163–2196.
- Global Initiative for Asthma. GINA Global Strategy for Asthma Management and Prevention, 2016; <http://ginasthma.org/>
- Ni Chroinin M, Lasserson TJ, Greenstone I, et al. Addition of long-acting beta-agonists to inhaled corticosteroids for chronic asthma in children. *Cochrane Database Syst Rev* 2009; 8: CD007949.
- Murphy K and Bender B. Treatment of moderate to severe asthma: patient perspectives on combination inhaler therapy and implications for adherence. *J Asthma Allergy* 2009; 2: 63–72.
- Halpin D, Gray J, Edwards S, et al. Budesonide/formoterol versus salmeterol/fluticasone in COPD: a systematic review and adjusted indirect comparison of pneumonia in randomised controlled trials. *Int J Clin Pract* 2011; 65: 764–774.
- Bodzenta-Lukaszyk A, Pulka G, Dymek A, et al. Efficacy and safety of fluticasone and formoterol in a single pressurized metered dose inhaler. *Respir Med* 2011; 105: 674–682.
- Bodzenta-Lukaszyk A, Buhl R, Balint B, et al. Fluticasone/formoterol combination therapy versus budesonide/formoterol for the treatment of asthma: a randomized, controlled, non-inferiority trial of efficacy and safety. *J Asthma* 2012; 49: 1060–1070.
- Kaiser K and Pertseva T. Long-term safety and efficacy of fluticasone propionate/formoterol fumarate combination therapy in patients with asthma. *Prim Care Respir J* 2013; 22: A1–A18.
- Papi A, Mansur AH, Pertseva T, et al. Long-term fluticasone propionate/formoterol fumarate combination therapy is associated with a low incidence of severe asthma exacerbations. *J Aerosol Med Pulm Drug Deliv* 2016; 29: 346–361.
- Moher D, Liberati A, Tetzlaff J et al. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *Ann Intern Med* 2009; 151: 264–269.
- Jadad AR. *Randomised controlled trials*. London: BMJ Publishing Group, 1998.
- Higgins JP and Green S (eds). *Cochrane handbook for systematic reviews of interventions*. version 5.1.0 [Internet]. The Cochrane Collaboration, 2011 [updated 2011 Mar; cited 2017 May 10]. Available from: www.cochrane-handbook.org.
- DerSimonian R and Laird N. Meta-analysis in clinical trials. *Control Clin Trials* 1986; 7: 177–188.
- Emeryk A, Klink R, McIver T, et al. A 12-week open-label, randomized, controlled trial and 24-week extension to assess the efficacy and safety of fluticasone propionate/formoterol in children with asthma. *Ther Adv Respir Dis* 2016; 10: 324–337.
- Płoszczuk A, Bosheva M, Spooner K, et al. Efficacy and safety of fluticasone propionate/formoterol fumarate in pediatric asthma patients: a randomized controlled trial. *Ther Adv Respir Dis* 2018; 12: 1753466618777924. DOI: 10.1177/1753466618777924.

18. Kaiser SV, Huynh T, Bacharier LB, et al. Preventing exacerbations in preschoolers with recurrent wheeze: a meta-analysis. *Pediatrics* 2016; 137: e20154496.
19. Ducharme FM, Gagnon R, Benard B, et al. Cessation of long-acting beta2-agonist in children with persistent asthma on inhaled corticosteroids. *Eur Respir J* 2016; 48: 558–560.
20. Mansur AH and Kaiser K. Long-term safety and efficacy of fluticasone/formoterol combination therapy in asthma. *J Aerosol Med Pulm Drug Deliv* 2013; 26: 190–199.
21. Malone R, La Force C, Nimmagadda S, et al. The safety of twice-daily treatment with fluticasone propionate and salmeterol in pediatric patients with persistent asthma. *Ann Allergy Asthma Immunol* 2005; 95: 66–71.
22. Roux FJ, Grandordy B and Douglas JS. Functional and binding characteristics of long-acting/ β_2 -agonists in lung and heart. *Am J Respir Crit Care Med* 1996; 153: 1489–1495.
23. Santus P, Radovanovic D, Paggiaro P, et al. Why use long acting bronchodilators in chronic obstructive lung diseases? An extensive review on formoterol and salmeterol. *Eur J Intern Med* 2015; 26: 379–384.
24. Lötvall J. Pharmacological similarities and differences between β_2 -agonists. *Respir Med* 2001; 95: S7–S11.
25. Anderson GP, Lindén A and Rabe KF. Why are long-acting beta-adrenoceptor agonists long-acting? *Eur Respir J* 1994; 7: 569–578.
26. Horvath G, Mendes ES, Schmid N, et al. Rapid nongenomic actions of inhaled corticosteroids on long-acting β_2 -agonist transport in the airway. *Pulm Pharmacol Ther* 2011; 24: 654–659.
27. Tronde A, Gillen M, Borgström L, et al. Pharmacokinetics of budesonide and formoterol administered via 1 pressurized metered-dose inhaler in patients with asthma and COPD. *J Clin Pharmacol* 2008; 48: 1300–1308.
28. Cazzola M, Page CP, Rogliani P, et al. β_2 -Agonist therapy in lung disease. *Am J Respir Crit Care Med* 2013; 187: 690–696.
29. Velayati A, Hosseini SA, Sari AA, et al. 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: 483–490.
30. Singhanian N, Dhamija R, Lodha R, et al. Salmeterol vs. formoterol: a comparison of rapid bronchodilator effect in a randomized controlled trial. *Indian Pediatr* 2008; 45: 225–228.