Nebulized step-down budesonide vs. fluticasone in infantile asthma: A retrospective cohort study

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Abstract. The United States Food and Drug Administration has approved budesonide in infantile asthma but nebulization of infants under budesonide has the risk of relapse of asthma. The objective of the present study was to compare the effectiveness and safety of fluticasone step-down treatment with budesonide step-down treatment in infantile asthma. The data of 778 infants with confirmed asthma were included in the analysis. Infants who had received nebulized 500 μg budesonide twice daily for 6 weeks followed by 250 μg budesonide twice daily for 6 weeks were included in the BS group (n=389), while infants who had received nebulized 250 μg fluticasone twice daily for 6 weeks followed by 125 μg fluticasone twice daily for 6 weeks were included in the FC group (n=389). The data of lung function tests and a safety study were collected and analyzed. Budesonide treatment achieved a reduced specific airway resistance (sRaw; 1.28±0.11 vs. 1.21±0.10 kPa/sec; P<0.0001, q=13.45) and improved forced expiratory volume in 1 sec (FEV1; 0.977±0.068 vs. 0.997±0.085 l/sec; P<0.0001, q=5.54). In addition, fluticasone treatment achieved a reduced sRaw (1.27±0.1 vs. 1.23±0.11 kPa/sec, P<0.0001, q=7.39) and improved FEV1 (0.971±0.069 vs. 0.992±0.085 l/sec; P=0.0003, q=5.46). Of note, the efficacy of budesonide to reduce sRaw (P=0.008, q=3.69) and improve FEV1 (P<0.0001, q=6.93) was greater than that of fluticasone. The budesonide treatment group had more post-treatment symptom-free days than the fluticasone treatment group (165.56±23.15 vs. 112.21±9.45 days; P<0.0001). The step-down approach of budesonide nebulization may better support the functional and clinical outcomes with an increased number of post-treatment symptom-free days compared with fluticasone in infantile asthma (level of evidence, 3).

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Abbreviations: DICOM, Digital Imaging and Communications in Medicine; sRaw, specific airway resistance; BL, at the time of enrollment; EL, at 3 months after treatment; FEV1, forced expiratory volume in 1 sec; ACTH, adrenocorticotropic hormone

Key words: budesonide, fluticasone, forced expiratory volume, infantile asthma, inhaled corticosteroids, specific airway resistance

Introduction

Lung function is commonly declined in airway diseases and chronic airway inflammation is a characteristic of asthma (1). Airway inflammation leads to shortness of breath, hyper-responsiveness, coughing and wheezing (2). Most cases of asthma begin at the infant stage (3). Evidence suggests that infants who develop asthma have normal lung function at birth (4). Inhaled corticosteroids are generally used to control infantile asthma (5), but the use of corticosteroids is not completely safe (6). Due to the various characteristics of infantile asthma, it is difficult to assess the benefits of inhaled corticosteroids in infantile asthma (7).

Budesonide depresses the biological activities of activator protein-1 and NF-κβ (8). In addition, it is the only inhaled corticosteroid that has been approved by the United States Food and Drug Administration for infantile asthma, with approval granted in 2000 (5), but nebulization with budesonide of infants with asthma is associated with a risk of relapse (9). Furthermore, fluticasone inhibits histamine release (immunoglobulin E-dependent), was reported to achieve increased clinical outcomes and pulmonary functions in infantile asthma (10) and has low systemic effects (9). The effects reported for budesonide are similar to those of all inhaled corticosteroids, while the inhibition of histamine release from mast cells by fluticasone is not proven. In general, inhaled corticosteroids are not able to prevent immediate airway responses to allergens (only after long-term treatment), the major cause of which is mast cell degranulation (11).

The primary aim of the present non-inferiority study was to compare the capacity of fluticasone step-down treatment with that of budesonide step-down treatment to achieve specific airway resistance reduction at a level of evidence of 3. The secondary endpoint of the analysis was to test the hypothesis that step-down treatment with budesonide is associated with a longer post-treatment symptom-free time compared with that

of fluticasone step-down treatment in Chinese infants with confirmed asthma.

Materials and methods

Drugs. Fluticasone and budesonide inhalation suspension were purchased from AstraZeneca Pharma. Albuterol (Ventolin) was purchased from GlaxoSmithKline Pharmaceuticals Ltd. Cosyntropin (synthetic corticotropin) was purchased from Sandoz. Normal saline was purchased from Baxter.

Inclusion criteria. Infants who were treatment naive and required emergency treatment were included in the analysis. Patients aged from 1 day to 2 years, who presented at the outpatient setting or were admitted to the Department of Pediatrics of the Shanghai University of Medicine and Health Science (Shanghai, China) and the referring hospitals from January 2013 to the end of December 2013 of either sex with at least two episodes of asthma within two days (the criteria were according to the institutional pediatric and asthmatic guidelines) confirmed by pediatricians (minimum 3 years of experience) of the institute(s) were included in the study.

Exclusion criteria. Infants with chronic asthma, chronic lung disease, had inhaled corticosteroid(s) within 4 months previously or were unable to be nebulized by the nursing staff (minimum 3 years of experience) of the institute(s) were excluded from the study. Infants who had not completed the interventions and/or were not available for follow-up at the parent and/or the referring hospitals were excluded from the study.

Cohort. Treatments were administered as part of routine clinical care. Infants who had been nebulized with 500 μg budesonide for 6 weeks followed by 250 μg budesonide for 6 weeks (9) were included in the BS group (n=389) and infants who had been nebulized with 250 μg fluticasone propionate for 6 weeks followed by 125 μg fluticasone propionate for 6 weeks (3) were included in the FC group (n=389). Nebulization was performed with a Jet nebulizer (Famidoc Technology Co., Ltd.) for intervention purposes twice daily in the morning and in the evening. During the follow-up period, 125 μg albuterol was given to infants with a metered inhaler as and when required (dose and dosage of budesonide, fluticasone and albuterol were decided by the institutional review board itself) (10).

Data collection. Information regarding demographic characteristics, clinical conditions, physical examinations, airway reactivity, symptoms, safety study, the treatment-emergent adverse effects (events were considered as adverse effects as per the criteria set by the institutional review board) were collected from patients' Digital Imaging and Communications in Medicine (DICOM) files of the parent hospital and the referring hospitals by the nursing staff (minimum 3 years of experience) of the institute(s).

Physical examination. During and after treatment, the patients were followed up for two years or up to the age of 4±0.5 years using a questionnaire every 3 months (12) by the nursing staff (minimum 3 years of experience) of the institute(s). Physical examinations were defined as per the clinicians' opinions (as per Chinese guidelines, minimum 3 years of experience) of the institute(s).

Lung function tests. The specific airway resistance (sRaw) was evaluated by whole-body plethysmography according to Eq. 1 by pulmonologists (minimum 3 years of experience) of the institute(s) at the time of enrollment (BL) and after 3 months of treatment (EL) (13). Forced expiratory volume in 1 sec (FEV1) (14) and eucapnic voluntary hyperventilation (15) were also recorded at BL and EL. The raised-volume rapid thoracoabdominal compression technique as per the American Thoracic Society/European Respiratory Society clinical practice guidelines was used to evaluate the parameters as follows:

$$\text{sRaw} = \text{plethysmograph cabin volume} \times \frac{\text{Change in air pressure in plethysmography cabin}}{\text{Mouth air flow}}$$

An inflatable jacket, which extends from the infant's axillae to the iliac crest, was loosely wrapped around the infant's torso and the FEV1 was measured from a raised lung volume (16).

Safety study. A bolus injection of 10 μg cosyntropin was given intravenously and 1 ml blood was collected by pathologists (minimum 3 years of experience) of the institute(s) at 0, 30 and 60 min and stored in sodium citrate cuvettes for serum cortisol concentration measurements. Furthermore, fasting blood samples (1 ml) had been collected from infants in the early morning and stored in sodium citrate cuvettes for serum adrenocorticotropic hormone (ACTH) level measurements. Patients with a plasma cortisol concentration of at least 100 nM and an ACTH-stimulated plasma cortisol concentration of at least 500 nM/l at the time of enrollment or plasma cortisol that increased by at least 200 nM/l above that concentration after stimulation were considered as having normal adrenal function (17). The bioassay was performed as per the chemiluminescent immunometric assay kit (Calbiotech). Pathology was performed at BL, EL, 6 and 9 months after treatment. Physical examinations were performed and adverse events were evaluated during treatment and the follow-up period, while lung function tests were performed at 3 months after treatment only.

Follow-up evaluations. During the follow-up period, since the day of completion of treatment, the absence of at least two episodes of asthma within two days were considered as a post-treatment effect. Frequencies of 125 μg albuterol from a metered inhaler required during the follow-up period were recorded. All patients were observed for worsening of the airway condition, changes in voice, sneezing, runny nose, stuffy nose and watering of eyes during the follow-up period. No specific guidelines, scales or tests were followed for these evaluations and evaluation was performed on the basis of the opinions of the clinicians (minimum 3 years of experience) of the institute(s) and criteria set by the institutional review board.

Statistical analysis. InStat (for Windows 3.0; GraphPad Software, Inc.) was used for statistical analysis. For continuous

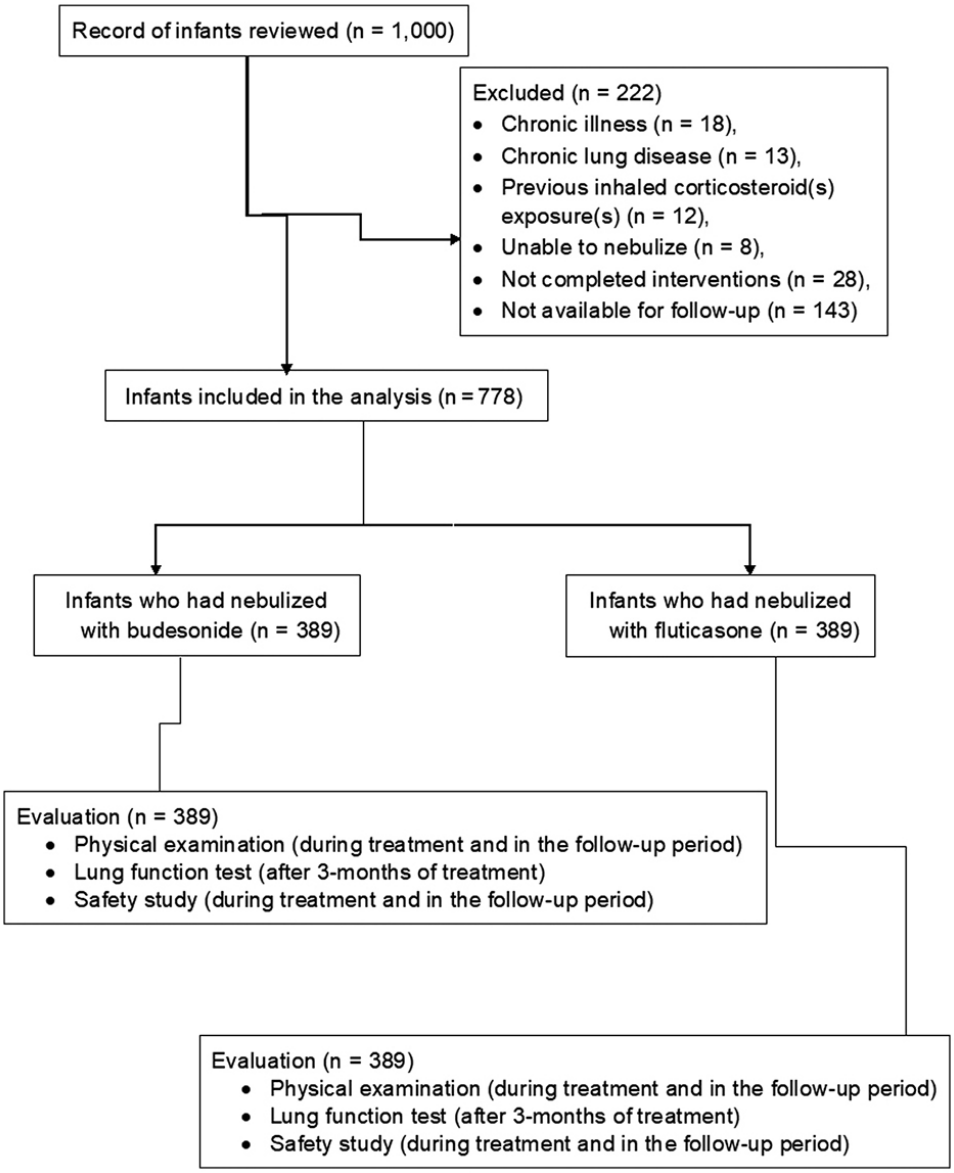

Figure 1. Flow chart of the study. Patients with at least two episodes of asthma within two days confirmed by pediatricians with minimum 3 years of experience were included in the study.

parameters, the Wilcoxon rank-sum test was applied for comparisons between two groups. For lung function tests, continuous parameters were analyzed by one-way analysis of variance for multiple comparisons. For constant parameters, the Chi-square independence test was used for comparisons between groups (18). The Tukey-Kramer multiple-comparisons test [considering critical value (q)>3.314] was used for post-hoc analysis. The results were considered significant at a 95% confidence level and $P<0.05$.

Results

Participants. Referring to the records of the institutes, a total of 1,000 infants were admitted with complaints of asthma. Among them, 28 infants had not completed the interventions and were shifted to the other hospitals with critical facilities available for emergency purposes, and were then excluded from the study. A total of 18 infants had critical illness [pediatricians' opinion; minimum 3 years of experience of the institute(s)], 13 infants had chronic lung disease from birth, 12 infants had previous exposure to inhaled corticosteroid(s), 8 infants were not able to be nebulized by the nursing staff and 143 infants had missing data from the follow-up evaluation tests from their DICOM files. Therefore, the data of those infants were excluded from the study. Finally, a total of 778 infants were included in the present retrospective cohort study. The flow diagram of the study is provided in Fig. 1.

Characteristics of infant subjects. All patients enrolled were of <2 years of age at the time of admission and directly residing in Shanghai city or in the countryside. The proportion of male infants (64%) was higher than that of female infants, 26% of infants had a history of maternal asthma and the majority of infants (60%) had presented with nighttime asthma. The other demographic data, characteristics and clinical conditions of the infants enrolled are presented in Table I.

Table I. Demographics, characteristics and clinical conditions of the infants included.

Parameters	Group		P-value
	BS (n=389)	FC (n=389)	
Age			0.227
Minimum (days)	1	1	
Maximum (months)	24	24	
Mean ± SD (months)	12.15±2.45	12.26±2.47	
Sex			0.709
Male	245 (63)	251 (65)	
Female	144 (37)	138 (35)	
Body weight (kg)	7.51±2.51	7.36±2.48	0.627
Body height (cm)	60.12±5.56	59.45±4.89	0.131
History of maternal asthma (first-level)			0.935
Yes	101 (26)	99 (25)	
No	288 (74)	290 (75)	
No. of episodes of asthma within two days[a]			0.477
2-5	281 (72)	271 (70)	
>5	108 (28)	118 (30)	
Allergic rhinitis[a]	45 (12)	51 (13)	0.586
Allergic conjunctivitis[b]	31 (8)	35 (9)	0.700
Treatment history			0.895
Bronchodilators	45 (12)	41 (11)	
Antibiotics	12 (3)	15 (4)	
Antihistamine	54 (14)	57 (15)	
None	278 (71)	276 (70)	
Time of episodes of asthma			0.770
Day	156 (40)	161 (41)	
Night	233 (60)	228 (59)	
Total Immunoglobulin E (IU/ml)	19.18±3.18	19.76±5.01	0.056
HbA1C (%)	5.99±0.71	6.01±0.75	0.906
Ethnicity			0.856
Han Chinese	349 (90)	355 (91)	
Mongolian	28 (7)	22 (6)	
Tibetan	8 (2)	8 (2)	
Hui	4 (1)	4 (1)	
sRaw (kPa/sec)	1.28±0.11	1.27±0.1	0.321
FEV1 (l/sec)	0.977±0.085	0.971±0.069	0.289
Serum cortisol level (nM)	257.51±85.51	261.62±87.61	0.699
Serum ACTH level (nM)	20.11±8.41	19.89±7.89	0.912

[a]Confirmed by pediatricians (minimum 3 years of experience) of the institute(s). [b]Confirmed by ophthalmologists (minimum 3 years of experience) of the institute(s). Constant variables are expressed as n (%) and continuous variables as the mean ± SD. Continuous parameters were subjected to one-way analysis of variance and constant parameters were subjected to the Chi-square independence test. sRaw, specific airway resistance. BS, budesonide; FC, fluticasone; FEV1, forced expiratory volume in 1 sec; ACTH, adrenocorticotropic hormone; SD, standard deviation.

Lung function tests. At EL, the budesonide treatment group had a reduced sRaw as compared with that at BL (1.28±0.11 vs. 1.21±0.1 kPa/sec; P<0.0001, q=13.45). The fluticasone treatment group also had a reduced sRaw as compared with that at BL (1.27±0.1 vs. 1.23±0.11 kPa/sec; P<0.0001, q=7.39). Of note, budesonide treatment had a greater effect to reduce sRaw than fluticasone treatment at EL (P=0.008, q=3.69; Fig. 2).

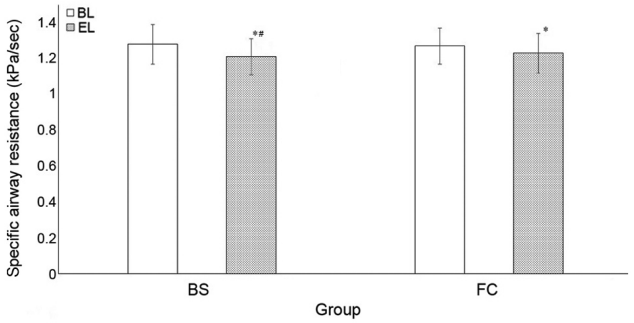

Figure 2. Specific airway resistance analysis. Values are expressed as the mean ± standard deviation (n=389 per group). P<0.05 and q>3.314 were considered to indicate statistical significance. *P<0.05 vs. BL. #P<0.05 vs. FC treatment at EL. BL, time-point of enrollment; EL, at 3 months after treatment; BS, budesonide; FC, fluticasone.

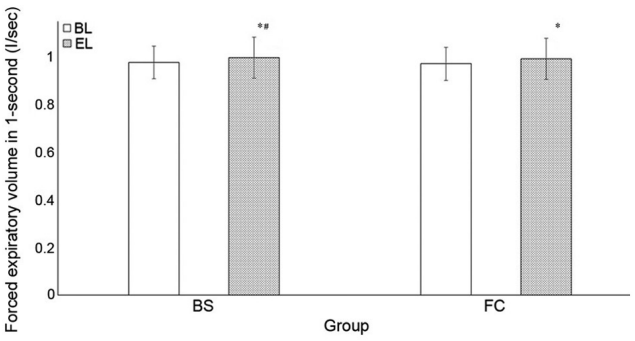

Figure 3. Forced expiratory volume in the 1-second analysis. Values are expressed as the mean ± standard deviation (n=389 per group). P<0.05 and q>3.314 were considered to indicate statistical significance. *P<0.05 vs. BL. #P<0.05 vs. FC treatment at EL. BL, time-point of enrollment; EL, at 3 months after treatment; BS, budesonide; FC, fluticasone.

At EL, the budesonide treatment group had an improved FEV1 as compared with that at BL (0.977±0.068 vs. 0.997±0.085 l/sec; P<0.0001, q=5.54). Fluticasone treatment also improved FEV1 as compared with that at BL (0.971±0.069 vs. 0.992±0.085 l/sec; P=0.0003, q=5.46). Of note, budesonide treatment had a greater capacity to improve FEV1 as compared to fluticasone treatment at EL (P<0.0001, q=6.93; Fig. 3).

Safety study. The infants enrolled had not been prescribed any type of antibiotic by the pediatrician(s) and physician(s) at the time of enrollment and during the study. Therefore, it was assumed that none of the infants had any respiratory infections during the study period. Budesonide and fluticasone nebulization had no adverse effects on adrenal functions of the treated infants at EL (Table II). In addition, at 6 and 9 months after treatment, adrenal functions were normal (data not presented).

Follow-up evaluations. Budesonide treatment had a larger number of post-treatment symptom-free days than fluticasone treatment (165.56±23.15 vs. 112.21±9.45 days; P<0.0001; Fig. 4).

During the follow-up period, albuterol had been given fewer times in the BS group than in the FC group (14.15±3.12 vs. 21.16±5.45 times; P<0.0001; Fig. 5).

In the fluticasone nebulization group, the major adverse effects were hoarseness (135 vs. 3 cases in the budesonide group; P<0.0001), exacerbations (105 vs. 35 cases; P<0.0001) and oral candidiasis (11 vs. 1 case; P=0.009), while in the budesonide group, sneezing (33 vs. 12 cases in the fluticasone group; P=0.002), runny nose (45 vs. 13 cases; P<0.0001) and watering of eyes (11 vs. 1 case; P=0.009) were the most frequent adverse effects in infants during the follow-up period (Table III).

Discussion

After 3 months of treatment, budesonide and fluticasone nebulization were proven effective in improvement of sRaw and FEV1 values and no adverse effects on adrenal function were observed. The study results regarding budesonide were similar to those of previous studies (5,10,11,17) but results regarding fluticasone were not in accordance with a previous study (3). Budesonide (19) and fluticasone (10) have potent airway anti-inflammatory action. Unlike oral therapies, nebulized therapies have a rapid onset of action (5), are successful in the stabilization of clinical symptoms (19), have the least adverse effects (5) and do not require active inspiration (20). With respect to the benefits offered by budesonide and fluticasone, the present study supported the suitability of nebulized budesonide or fluticasone in infantile asthma.

In the present study, a longer post-treatment effect was reported under budesonide intervention as compared to fluticasone treatment (P<0.0001). This result was not in line with that of a previous study (11). A possible explanation for this discrepancy is that in the present study, a step-down approach was adopted in the intervention, which improved the effectiveness of budesonide (21). The study recommended a step-down budesonide approach in infantile asthma for long-term post-treatment benefits (21).

In the BS group, fewer instances of exacerbation of asthma and hoarseness were observed compared with the FC group and previous studies on FC (3,10). Budesonide reduces the risk of exacerbations of asthma and hoarseness (22,23), as the half-life of budesonide in infants is lower than that of fluticasone (24) and the serum elimination rate of budesonide is higher than that of fluticasone (25). Asthma exacerbations lead to morbidity, increase the cost of treatment and decrease lung function (26). With regard to the adverse events encountered during the follow-up period (requirements of emergency bronchodilators), BS is more potent and suitable than FC in the infantile asthma conditions.

Several limitations of the present study should be pointed out. For instance, the study provided a retrospective analysis of observational cohorts only and lacked a control group. History of maternal asthma (18), sex, age, infections (26), and other demographic characteristics have effects on the adverse events or relapse occurring in the follow-up period, but no multivariate analysis of such parameters was performed in the present study (no adjustment for confounding factors). In a future study, a control cohort of infants (e.g. healthy and/or not treated with BS or FC) should be used to compare the frequencies of adverse effects. The addition of long-acting β-agonist with nebulized corticosteroids provides better control of asthma (27), but the present study was performed

Table II. Adrenal function evaluation at 3 months after treatment.

	Group		
Hormone	BS (n=389)	FC (n=389)	P-value
Serum cortisol (nM/l)			
0 min	335.85±95.98	349.18±101.21	0.090
1/2 h	751.52±112.12	743.49±102.21	0.494
1 h	801.12±135.42	799.21±129.51	0.974
Serum ACTH (nM/l)	26.12±9.13	27.15±9.88	0.210

Plasma cortisol that increased by at least 200 nM and above the initial concentration after stimulation was considered as indicative of a normal adrenal function. Values are expressed as the mean ± standard deviation. One-way analysis of variance was used for statistical analysis. ACTH, adrenocorticotropic hormone; BS, budesonide; FC, fluticasone.

Table III. Treatment-emergent adverse effects reported during follow-up.

	Group		
Adverse effect	BS (n=389)	FC (n=389)	P-value
Exacerbations	35 (9)	105 (27)[a]	<0.0001
Hoarseness	3 (1)	135 (35)	<0.0001
Oral candidiasis	1 (1)	11 (3)[a]	0.009
Sneezing	33 (8)[b]	12 (3)	0.002
Runny or stuffy nose	45 (12)[b]	13 (3)	<0.0001
Watering of eyes[c]	11 (3)[b]	1 (1)	0.009
Vomiting	9 (2)	2 (1)	0.069
Total	137 (35)	279 (72)	<0.0001

[a]Significant fluticasone-emergent adverse effects. [b]Significant budesonide-emergent adverse effects. [c]At the time of enrollment, allergic conjunctivitis was absent. Variables are expressed as n (%). The Chi-square independence test was used for statistical analysis. Events were considered as adverse effects as per the criteria set by the institutional review board and clinicians' opinions. BS, budesonide; FC, fluticasone.

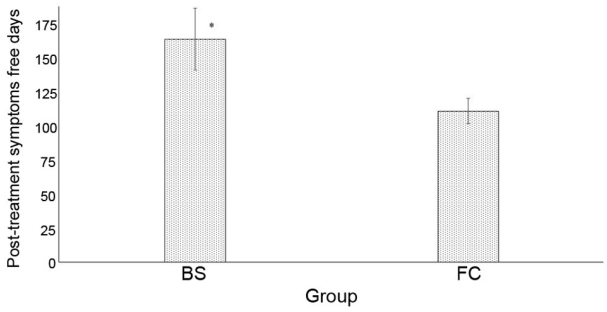

Figure 4. Analysis of post-treatment symptom-free duration. During the follow-up period, since the day of completion of treatment, the absence of at least two episodes of asthma observed within two days were considered as a post-treatment effect. One-way analysis of variance was used for statistical analysis. Values are expressed as the mean ± standard deviation (n=389 per group). *P<0.05 vs. fluticasone treatment. BS, budesonide; FC, fluticasone.

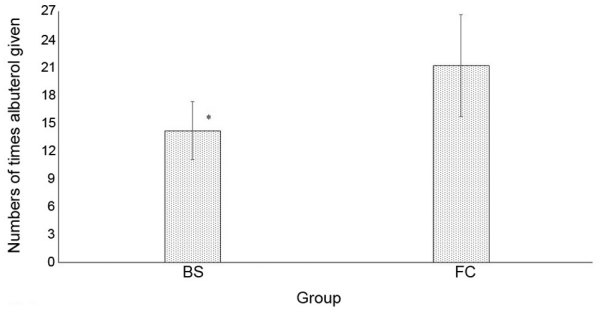

Figure 5. Number of times of 125 μg albuterol puff treatment application during the follow-up period. One-way analysis of variance was used for statistical analysis. Values are expressed as the mean ± standard deviation (n=389 per group). *P<0.05 vs. fluticasone treatment. BS, budesonide; FC, fluticasone.

using a step-down approach with nebulized corticosteroid alone. High-dose budesonide (1,000 μg) twice daily may overcome recurrence of infantile asthma (19), but interventions were performed with 500 μg budesonide twice daily followed by 250 μg budesonide twice daily. There was a potential high inter-subject variability, leading to difficulty in the interpretation of significant data. However, most of the infants were only several days and months old and only a small number of patients had an age of nearly 2 years.

In conclusion, the present retrospective observational cohort study indicated that a step-down approach of budesonide and fluticasone nebulization is effective in infantile asthma. Nebulization of infants with asthma under budesonide provided a longer post-treatment symptom-free duration and a lower risk of exacerbations than fluticasone. The study recommended that if the step-down approach for nebulization with 500 μg budesonide for 4 weeks followed by 300 μg for 4 weeks followed by 100 μg for 4 weeks with administration twice a day is successful, it should be pursued in clinical practice.

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Availability of data and materials

The datasets used and analyzed during the present study are available from the corresponding author on reasonable request.

Authors' contributions

All authors have reviewed and approved the manuscript submitted for publication. ZW was the project administrator and contributed to the design, data curation and literature review of the study. XB contributed to the conceptualization, literature review and data curation of the study. LH contributed to the conceptualization, software management/processing and literature review for the study. JZ contributed to the data curation, formal analysis and literature review for the study, and drafted, reviewed and edited the manuscript for intellectual content. The author agrees to be accountable for all aspects of work ensuring integrity and accuracy.

Ethics approval and consent to participate

The original study protocol (SSP/CL/15/13 dated 1 January 2013) was approved by the Shanghai University of Medicine and Health Science review board (Shanghai, China). The study reporting adhered to the law of China, the 2008 Helsinki Declaration and the Strengthening. The Reporting of Observational studies in Epidemiology statement. Parents/legal guardians provided informed consent for the participation of the subjects in the study at the time of hospitalization.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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