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Original Research Article

COMPARISON OF BRONCHODILATORY EFFECT OF INHALED FORMOTEROL+BUDESONIDE VERSUS INHALED SABUTAMOL+ BUDESONIDE IN MILD ACUTE EXACERBATION OF ASTHMA IN CHILDREN OF 6-12 YEARS -RANDOMISED CONTROLLED TRIAL

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Abstract: ***BACKGROUND:*** Short-acting beta-agonist (SABA) such as salbutamol is being conventionally used in managing pediatric asthma exacerbations. This study assessed the onset and effectiveness of inhaled formoterol (a long-acting beta-agonist with rapid onset of action) in combination with budesonide, compared with standard Salbutamol+Budesonide therapy in children of 6-12 years of age with mild asthma exacerbation. ***METHODS:*** A randomized controlled trial was conducted at a rural tertiary care center, involving 90 children aged 6–12 years presenting with mild asthmatic exacerbations. Participants were randomized into two groups: Group A received inhaled Formoterol+Budesonide; Group B received inhaled Salbutamol+Budesonide. Outcome measures included were symptomatic improvement, the Pediatric Asthma Severity Score (PASS), Peak Expiratory Flow Rate (PEFR), and incidence of adverse effects at 5, 10, 30, and 60 minutes post-treatment. ***RESULTS:*** Symptomatic improvement was seen in 77.7 % of children in Salbutamol+Budesonide group compared to 46.6% of children in Formoterol+Budesonide group at 5 minutes(p value 0.002). However, thereafter symptomatic improvement in both groups was comparable. PASS score and PEFR showed comparable improvement in both groups starting from five mins. Adverse events were minimal in both groups; tachycardia occurred slightly more frequently in the salbutamol group, though not statistically significant. ***CONCLUSION:*** Inhaled Formoterol+Budesonide has rapid onset and is effective and well-tolerated similar to Salbutamol.+Budesonide for the management of mild asthma exacerbations in children. Considering Formoterol's prolonged duration of action and lesser side effects, it may serve as a viable reliever option.

Keywords: Salbutamol, Formoterol, Budesonide, Peak Expiratory Flow Rate (PEFR), Pediatric Asthma Severity Score (PASS), Tachycardia

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INTRODUCTION

Asthma is one of the most prevalent chronic respiratory diseases in children, significantly affecting quality of life and contributing to substantial healthcare utilization worldwide.(1) In children aged 6–12 years, prevalence of asthma is 5-20% globally and 5–10% in India.(2) Acute exacerbations contribute substantially to morbidity and healthcare utilization in this age group. Early and effective management is essential to prevent functional decline and future severe episodes.

Conventional guidelines recommend use of short-acting β_2-agonists (SABA) such as salbutamol for quick relief, which is combined with inhaled corticosteroids (ICS) like budesonide to improve anti-inflammation and prevent lung remodeling. (1) Formoterol, a long-acting β_2-agonist (LABA) with a rapid onset of action (3–5 minutes), offers the potential to act both as a reliever and controller when combined with ICS. This combination may reduce the frequency of SABA use, improve adherence, and provide prolonged bronchodilation.(3)

While studies conducted in adults suggest comparable or superior outcomes with formoterol-budesonide therapy, evidence in children particularly those with mild acute exacerbations is limited.(4) However, children's airways, drug absorption, and response to treatment differ from adults, making it important to study for age-specific data.(5) Considering the limited amount of data available for children, especially within the Indian context, this study aims to directly compare the effects of inhaled Formoterol+Budesonide and inhaled Salbutamol+Budesonide in children aged 6-12 years experiencing mild asthma attacks. This study aims to address this gap and support more evidence-based decision-making in pediatric asthma care.

MATERIALS AND METHODS

Study Design and Setting: This open label randomized controlled trial was conducted at the Department of Pediatrics, M.V.J. Medical College & Research Hospital, Hoskote, Bangalore, Karnataka, a rural tertiary care hospital in India.

Study Population: Children aged 6–12 years presenting with mild acute asthma exacerbations, as defined by the Paediatric Asthma Severity Score (PASS), were screened for eligibility.

The Pediatric Asthma Severity Score (PASS) is a clinical scoring system that quantifies asthma severity based on respiratory rate, oxygen requirement, wheeze, retractions and dyspnea to objectively assess the degree of airway obstruction each graded from 1 to 3 based on severity. Asthma severity classified as mild (score 5–7), moderate (8–11), and severe (12–15) according to the Pediatric Asthma Severity Score (PASS).(7)

Inclusion Criteria: Age 6–12 years, with mild acute exacerbation of asthma defined by PASS presenting to pediatric OPD/ emergency.

Exclusion Criteria: Children with associated pneumonia or chronic illness apart from allergy and asthma (like tuberculosis, cystic fibrosis, congenital heart diseases) and those unable to perform PEFR

90 children presenting to our hospital with mild asthma exacerbations, meeting inclusion and exclusion criteria, were enrolled in the study after written informed consent. Details of history and physical examination including symptoms with their duration, past history, history of atopy, type of asthma control, family history of allergy and medications used were recorded in a structured proforma. Asthma control was classified as controlled, partially controlled, or uncontrolled based on the Global Initiative for Asthma (GINA) 2022 guidelines.(5) They were randomised into two groups with computer generated random table charts.

Group A: Formoterol (12 µg) + Budesonide (200 µg)

Group B: Salbutamol (200 µg) + Budesonide (200 µg)

Table 1: Paediatric Asthma Severity Score (PASS)

Score	1	3
Respiratory rate		
2 to 3 yr	≤ 34	≥ 40
4 to 5 yr	≤ 30	≥ 36
6 to 12 yr	≤ 26	≥ 31
Older than 12 yr	≤ 23	≥ 28
Oxygen Requirements	> 90% on room air	< 85% on room air
Auscultation	Normal breath sounds or end-expiratory wheeze only	Inspiratory and expiratory wheezing or diminished breath sounds
Retractions	≤ One site	≥ Three sites
Dyspnoea	Speaks in sentences, coos and babbles	Speaks in single words/short phrases/grunting

Intervention: 2 actuations administered via MDI with spacer. Baseline and follow-up at 5, 10, 15, 30, 45 and 60minutes.

Primary Outcome: Change in PEFR.
Secondary Outcomes: PASS score changes, symptomatic improvement, adverse effects.

Statistical Analysis: Data was entered into Microsoft excel data sheet and analysed using SPSS Software. Baseline parameters were compared. Mean and Standard deviation were used to summarize the continuous variables. Inter group comparison of PASS and PEFR was done at 5, 10, 15, 30, 45 and 60 mins. Chi square test was used for comparing proportions and 't-test' for continuous variables. P value of <0.05 was considered significant.
Ethics: Approved by Institutional Ethics Committee (Ref no: MVJMC&RH/IEC-72/2023). Informed consent obtained from parents/ guardians and from children where applicable.

RESULTS

A total of 103 children between 6 to 12 years of age, with acute exacerbation of asthma presenting to Pediatric department in MVJMC&RH were enrolled in our study conducted over a period of 2 years from January 2023 to January 2025. Thirteen of them were excluded from the study, as they were unable to do PEFR or had associated pneumonia or congenital heart disease. Ninety children were enrolled in the study and randomized to 2 groups- 45 to salbutamol+ budesonide group and 45 in formoterol+budesonide group. All children were hemodynamically stable throughout the study period.

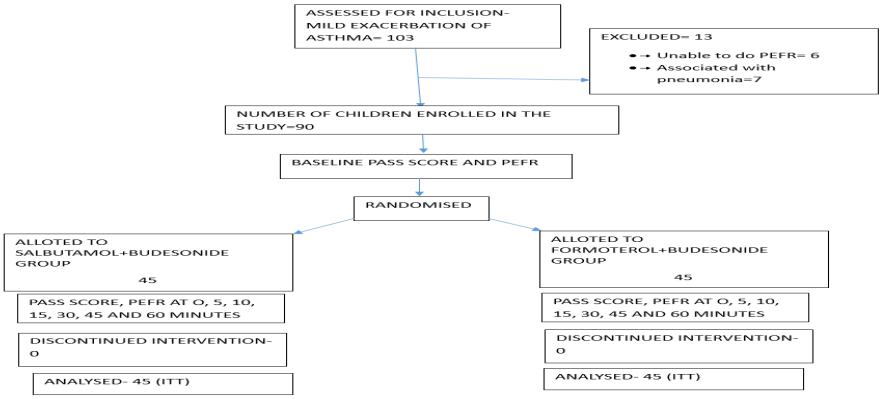

Figure-1 Trial profile Abbreviations – ITT-Intention to Treat

Baseline Characteristics: Comparable in both groups (Table 2).

PARAMETER	SALBUTAMOL + BUDESONIDE N (%) / Mean ± SD	FORMOTEROL + BUDESONIDE N (%) / Mean ± SD	P VALUE
AGE			
1. 6–8 years	18 (40.2%)	11 (24.4%)	
2. 9–10 years	9 (20%)	9 (20%)	
3. 11–12 years	18 (40%)	25 (55.5%)	
4. Mean age	9.2 ± 2.32	10.16 ± 2.17	0.243
SEX			
1. Male	32 (71.1%)	27 (60%)	0.267
2. Female	13 (28.8%)	18 (40%)	
PAST HISTORY			
1. Chronic cough	11 (24.4%)	17 (37.7%)	0.172
2. Daytime symptoms	5 (11.1%)	5 (11.1%)	1.000
3. Night-time symptoms	8 (17.7%)	14 (31.1%)	0.141
4. Exertion-induced symptoms	23 (51%)	29 (64.4%)	0.200
5. Seasonal variation	42 (93.3%)	41 (91.1%)	0.694
6. H/O nebulisation	45 (100%)	44 (97.7%)	0.315
7. Positive response to nebulisation	45 (100%)	42 (93.3%)	0.078
PERSONAL HISTORY			
1. Allergic rhinitis	17 (37.7%)	14 (31.1%)	0.506
2. Allergic conjunctivitis	3 (6.6%)	4 (8.8%)	0.694
3. Atopic dermatitis	2 (4.4%)	4 (8.8%)	0.398
FAMILY HISTORY OF ASTHMA/ATOPY	15 (33.3%)	7 (15.5%)	0.050
H/O ASTHMA			
1. Newly diagnosed	6 (14%)	11 (24.4%)	0.204
2. Known case	39 (86.6%)	34 (75.5%)	
Diagnosis based on			
1. Clinical	38 (84.4%)	31 (68.8%)	0.204
2. Clinical + spirometry	7 (15.5%)	14 (31.1%)	
TYPE OF ASTHMA CONTROL			
1. Controlled	7 (15.5%)	7 (15.5%)	0.510
2. Partially controlled	30 (66.6%)	24 (53.3%)	
3. Poorly controlled	1 (2.2%)	2 (4.4%)	
PRIOR LONG-TERM MEDICATION			
1. No treatment	9 (20%)	12 (26.6%)	0.523
2. ICS (Budesonide)	19 (42.2%)	14 (31.1%)	
3. Formoterol+ICS	17 (37.7%)	19 (42.2%)	
AGE OF ONSET OF SYMPTOMS	7.85± 3.09 (mean ± SD)	8.66 ± 3.144 (mean ± SD)	0.224
PRESENT ILLNESS – **1. SYMPTOMS**			
a) Fever	9 (20%)	8 (17.7%)	0.788
b) Cough	44 (97.7%)	44 (97.7%)	1.000
c) Running nose	24 (53.3%)	25 (55.5%)	0.832
d) Wheeze	2 (4.4%)	7 (15.5%)	0.078
e) Chest tightness	2 (4.4%)	6 (13.3%)	0.138
2. **EXAMINATION FINDINGS**			
a) Respiratory rate score 2 (26–30/min)	23 (51%)	21 (46.6%)	0.670
b) SpO_2 score 2 (<90%)	0	0	0
c) Retractions	0	0	0

d) Rhonchi	40 (88.8%)	37 (82.2%)	0.368
e) Bilateral decreased air entry	0	0	0
3. **Baseline PEFR (L/min)**	135.78 ± 51.808	147.78 ± 48.78	0.261
4. **Baseline PASS score**	6.09 ± 0.668	6.20 ± 0.726	0.452

Table 2: Baseline variables with present illness and examination

Symptomatic Improvement: At 5 minutes, 77.7% in Group A improved vs. 46.6% in Group B (p=0.002). Subsequent intervals showed no difference (Figure 2).

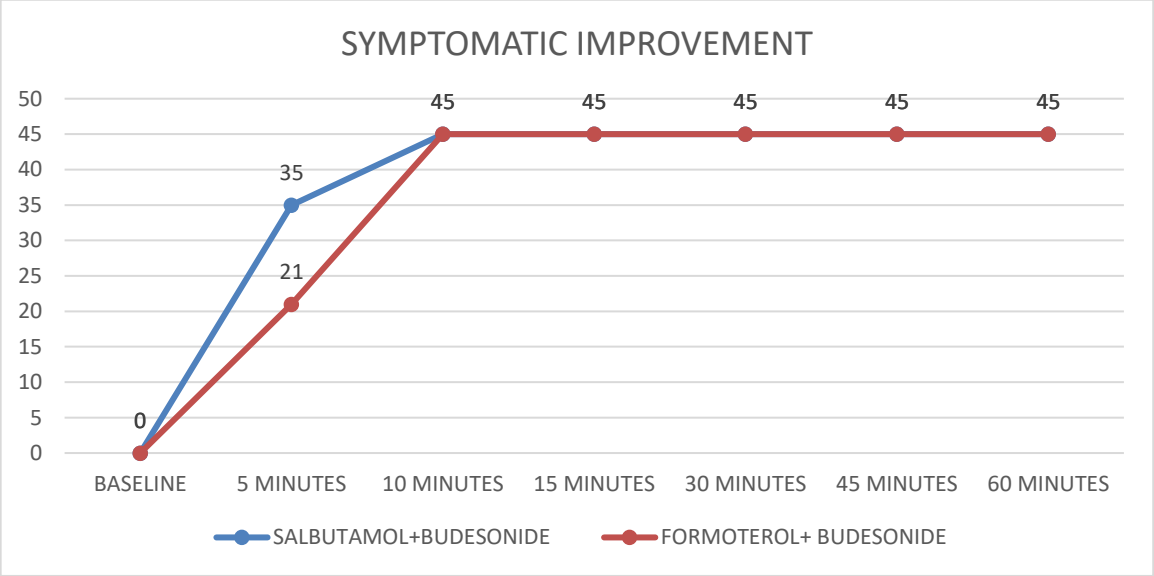

Figure-2: Symptomatic Improvement In The 2 Groups At Different Time Intervals Post Intervention

Both the salbutamol+budesonide and formoterol+budesonide groups showed similar improvements in PASS scores over time, with no significant differences between them at any point (Figure 3).

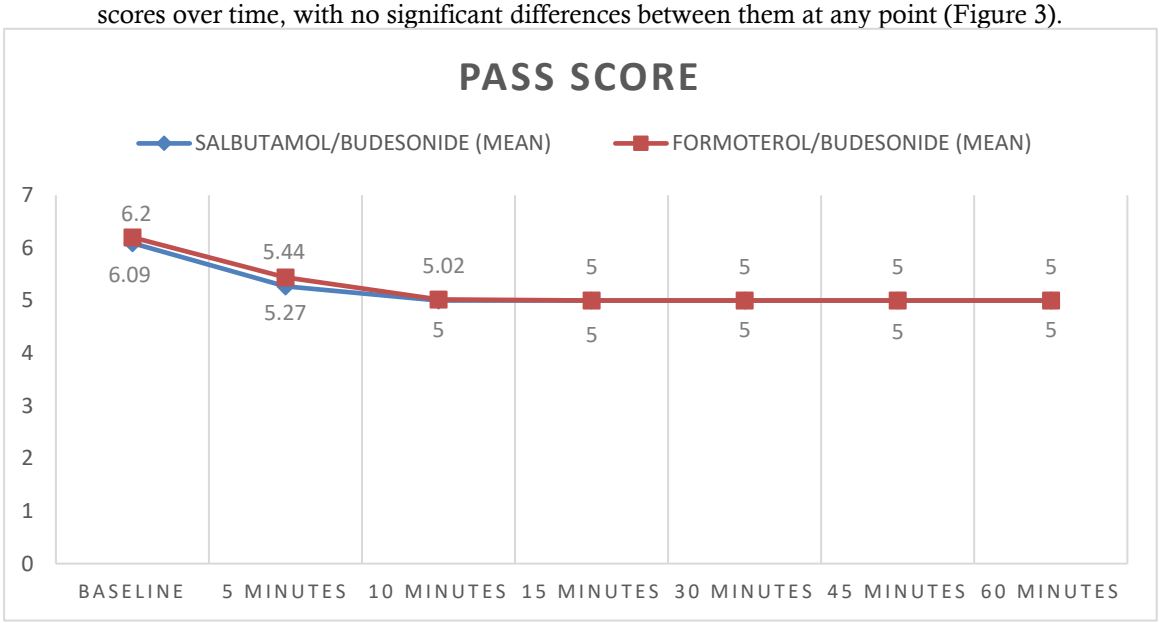

Figure-3: Pass Score In The 2 Groups At Different Time Points Post Intervention

Across all measured time points (baseline, 5, 10, 15, 30, 45, and 60 minutes), there was no statistically significant difference in PEFR scores between the Salbutamol+Budesonide and Formoterol+Budesonide groups. Mean PEFR values were comparable throughout, with both interventions yielding similar improvements over time (all p values > 0.1). (Figure 4)

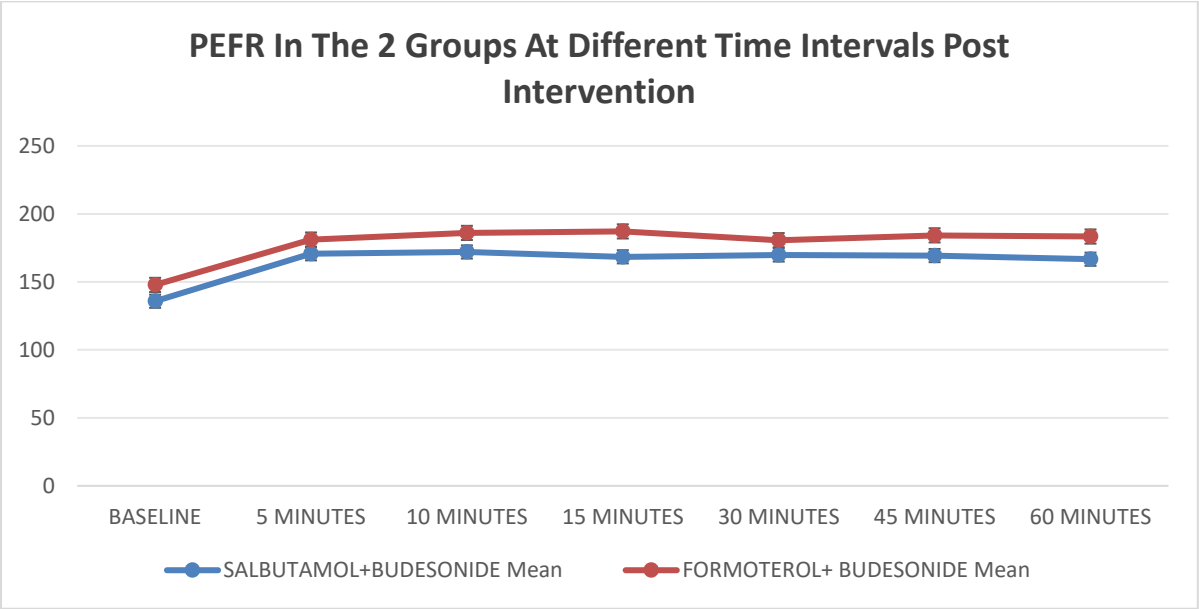

Figure-4: PEFR In The 2 Groups At Different Time Intervals Post Intervention

After 5 minutes, mean percentage improvement in PEFR in Salbutamol+Budesonide group was 28.42% whereas 24.31% improvement was noted in PEFR value in Formoterol+Budesonide group from baseline. At the end of 1 hour, improvement of 26.04% was noted in PEFR value in salbutamol+ budesonide group whereas, 27.4% improvement in PEFR value was noted in Formoterol+Budesonide group, with no statistical significance (Figure 5).

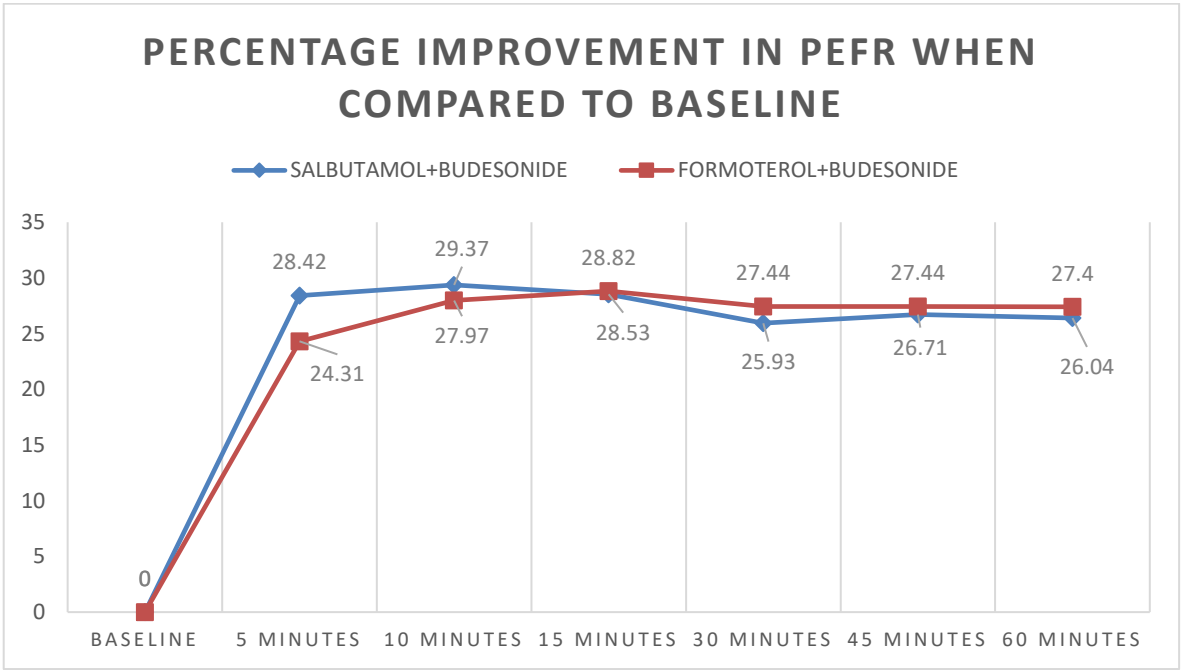

Figure 5: Percentage Improvement In PEFR After The Intervention

A total of 103 children between 6 to 12 years of age, with acute exacerbation of asthma presenting to Pediatric department in MVJMC&RH were enrolled in our study conducted over a period of 2 years from January 2023 to January 2025. Thirteen of them were excluded from the study, as they were unable to do PEFR or had associated pneumonia or congenital heart disease. Ninety children were enrolled in the study and randomized to 2 groups- 45 to salbutamol+ budesonide group and 45 in formoterol+budesonide group. All children were hemodynamically stable throughout the study period.

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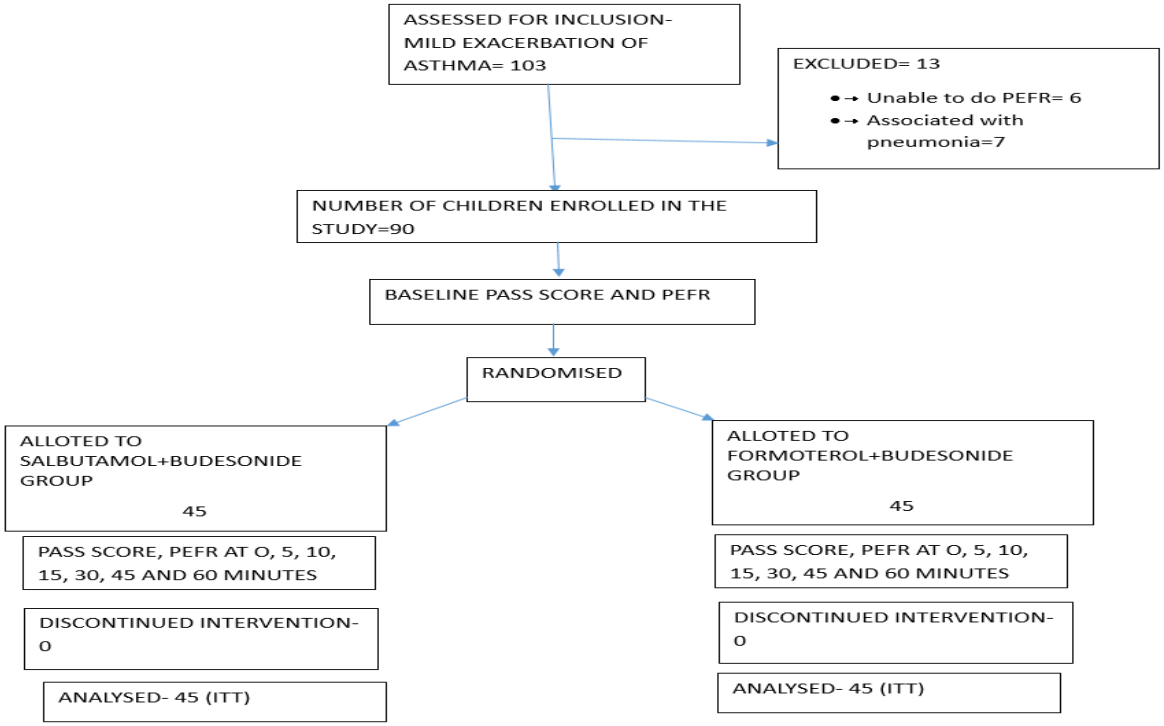

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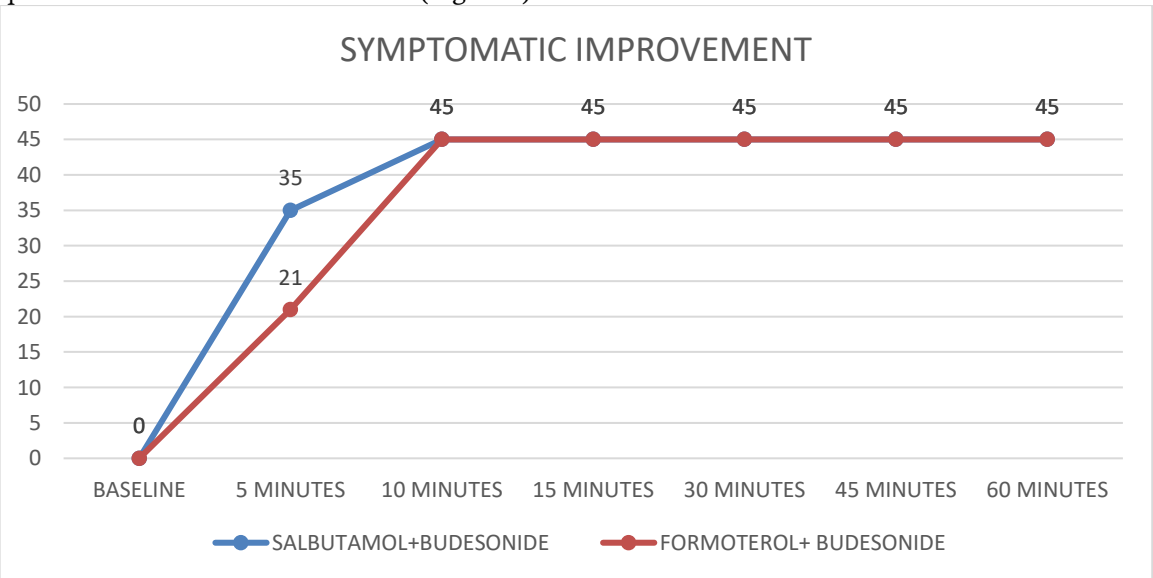

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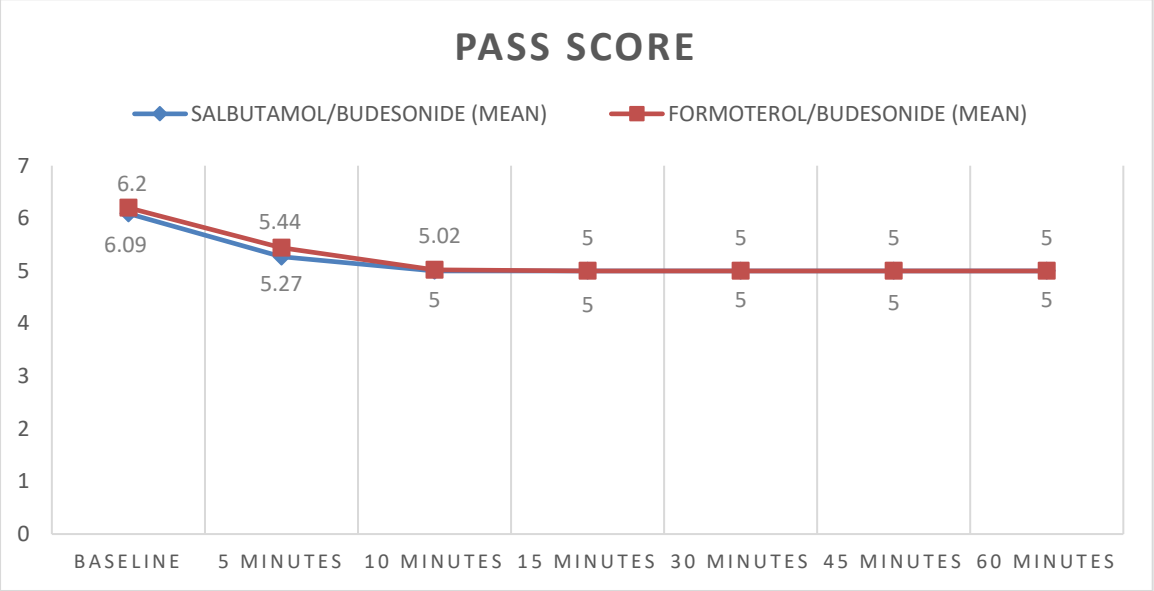

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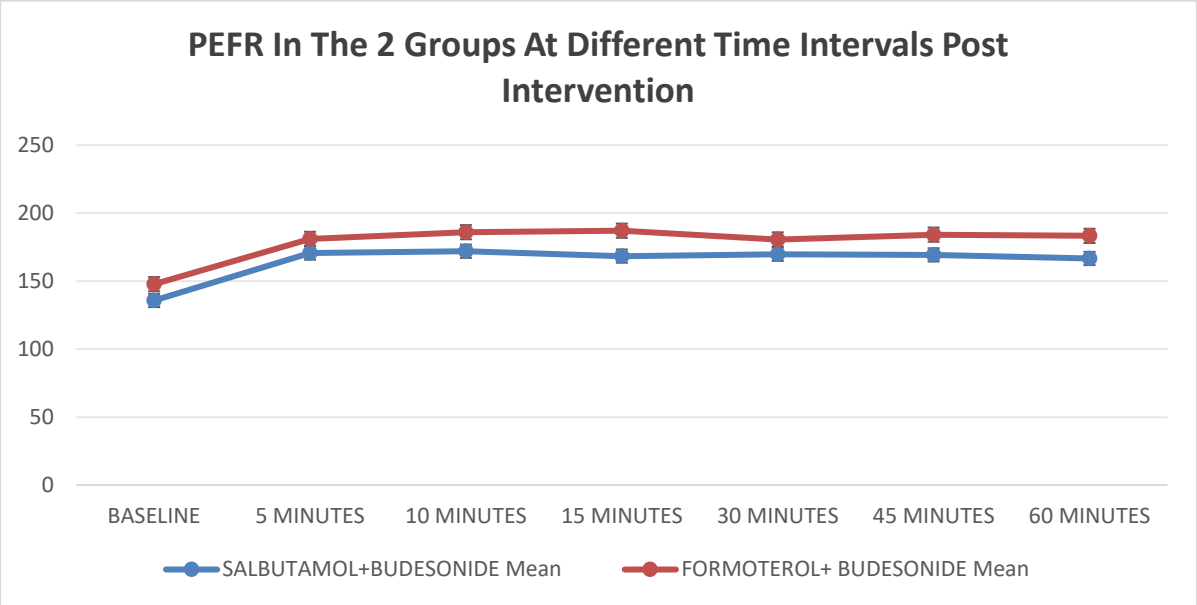

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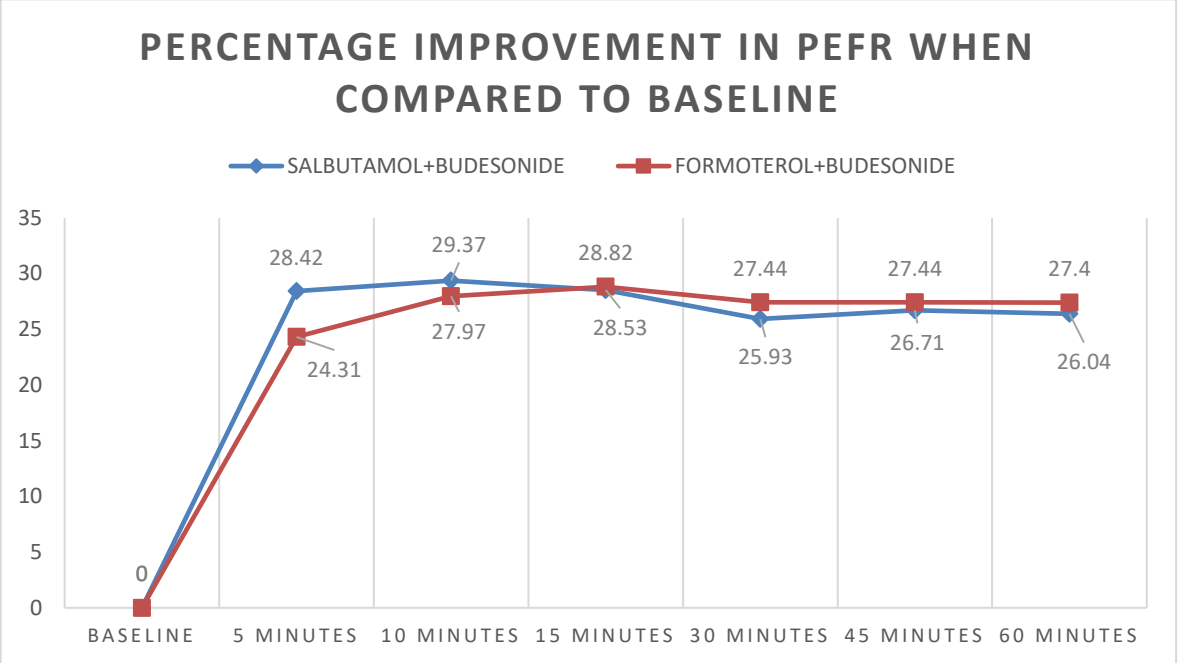

Figure 5: Percentage Improvement In PEFR After The Intervention

Time Point	Symptomatic Improvement (%)		P value (Symptoms)	PASS Score (mean ± SD)		P value (PASS)	PEFR (mean ± SD)		P value (PEFR)	% Improvement in PEFR (mean ± SD)		P value (% PEFR)
	Salbutamol/Budesonide	Formoterol/Budesonide		Salbutamol/Budesonide	Formoterol/Budesonide		Salbutamol/Budesonide	Formoterol/Budesonide		Salbutamol/Budesonide	Formoterol/Budesonide	
Baseline	0%	0%	0	6.09 ± 0.668	6.20 ± 0.726	0.452	135.78 ± 51.808	147.78 ± 48.78	0.261	–	–	–
5 min	35 (77.7%)	21 (46.6%)	0.002	5.27 ± 0.495	5.44 ± 0.586	0.124	170.67 ± 55.74	181.11 ± 53.39	0.366	28.422 ± 14.54	24.311 ± 10.97	0.134
10 min	45 (100%)	45 (100%)	0.041	5.0 ± 0	5.02 ± 0.149	0.32	172 ± 57.07	186 ± 51.89	0.227	29.378 ± 16.07	27.978 ± 11.79	0.639
15 min	45 (100%)	45 (100%)	0.041	5.0 ± 0	5.0 ± 0	–	168.44 ± 60.6	187.11 ± 53.37	0.125	28.533 ± 16.29	28.822 ± 13.14	0.926
30 min	45 (100%)	45 (100%)	0.041	5.0 ± 0	5.0 ± 0	–	169.78 ± 56.06	180.67 ± 50.69	0.336	25.93 ± 10.72	27.44 ± 14.45	0.508
45 min	45 (100%)	45 (100%)	0.041	5.0 ± 0	5.0 ± 0	–	169.33 ± 54.58	184.22 ± 52.37	0.19	26.711 ± 10.70	27.44 ± 14.85	0.79
60 min	45 (100%)	45 (100%)	0.041	5.0 ± 0	5.0 ± 0	–	166.67 ± 54.020	183.33 ± 52.223	0.14	26.044 ± 11.38	27.4 ± 14.85	0.628

Table 3: Results

The only observed side effect was tachycardia. Tachycardia was noted in 20% of children who received salbutamol/budesonide and in 8.8% of children in formoterol/budesonide group (p value 2.25). No child was noted to have either hypertension/ tremor in both the groups.

PARAMETER	SALBUTAMOL+BUDESONIDE	FORMOTEROL+ BUDESONIDE	P VALUE
	N (%)	N (%)	
TACHYCARDIA	9 (20)	4 (8.8)	2.25
HYPERTENSION	0 (0)	0 (0)	0
TREMORS	0 (0)	0 (0)	0

TABLE 4- ADVERSE EVENTS

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	N (%)	N (%)	
TACHYCARDIA	9 (20)	4 (8.8)	2.25
HYPERTENSION	0 (0)	0 (0)	0
TREMORS	0 (0)	0 (0)	0

TABLE 4- ADVERSE EVENTS

DISCUSSION

Asthma is a chronic disease impairing daily life which is characterized by chronic airway inflammation. Management of asthma is continuously evolving for better control and quality of life.

According to latest GINA guidelines 2025,(8) inhaled corticosteroid-formoterol can be used as reliever in acute exacerbations of asthma in adults and children more than 12 years, and in children of age 6 to 12 years only when on maintenance Formoterol+ Budesonide combination.

In this randomized controlled trial, we investigated and compared the onset and efficacy of formoterol with budesonide versus salbutamol with budesonide in children of 6-12 years of age, experiencing a mild acute asthma exacerbation. Baseline characteristics were similar between both groups: mean ages were 9.2 years (Salbutamol+Budesonide) and 10.16 years (Formoterol+Budesonide), with a male predominance consistent with higher asthma rates among boys as suggested by previous study done by Chowdhury et al.(9) Chronic cough was the most frequent symptom depicting bronchial hyper

responsiveness in children with chronic cough during the childhood period is a strong risk factor for the development of asthma. (10) Both daytime and night-time symptoms, exercise-induced triggers, and seasonal variations in severity showed similar distribution across treatment arms. In a similar study done by Koster ES et al in Netherlands in children between 4 to 12 years of age, the prevalence of wheeze ranged from 32% in summer to 56% in autumn.(11)

Comorbid allergic conditions such as rhinitis, conjunctivitis, and atopic dermatitis were reported in varying proportions, aligning with existing data on their prevalence and age-related trends as shown in the study done by Soyoung Hong et. al.(12) Asthma control levels (controlled, partially controlled, uncontrolled) and absence of long-term maintenance therapy were also comparable between groups.

In our study, symptomatic relief in terms of decrease in cough, wheeze and chest tightness at 5 minutes post intervention was significantly more in the Salbutamol + Budesonide group (77.7%) compared to the Formoterol + Budesonide group (46.6%, p = 0.002). However, both groups showed equal improvement by 10 minutes and subsequently.

PASS scores and percentage change in PEFR improved similarly in both groups, with no statistically significant differences at any time point. After 10 minutes, the pattern of improvement was same in both the groups.

The pharmacodynamics of both medications reveal they are β2-adrenergic agonists, but while salbutamol acts quickly and briefly for acute relief, formoterol has a similarly rapid onset but with prolonged action, making it suitable for both maintenance and rescue therapy. (13)

These findings are consistent with a double blinded randomized control trial done by Jenish et.al.(14) They compared the bronchodilatory effects of inhaled formoterol+ budesonide (dose: 200µg and 12µg respectively) combination with salbutamol (200µg)+ budesonide (200µg) administered by metered dose inhaler and spacer in children of 5-15 years with mild acute exacerbation of asthma with Modified Pulmonary Index Score (MPIS) between 6-8. The Modified Pulmonary Index Score (MPIS) is a clinical scoring system (range 0–12) that assesses acute asthma severity based on respiratory rate, oxygen saturation, accessory muscle use, wheeze, inspiratory–expiratory ratio, and heart rate. FEV_1 (% predicted) and Modified Pulmonary Index Score (MPIS) improved significantly from baseline in both groups as early as 1 minute post-administration, with no significant differences observed between the two treatments at any time point.

Findings from adult studies by Chew et al.(15) comparing inhaled budesonide/ formoterol with inhaled budesonide showed comparable improvements in oxygen saturation, PEFR (p value 0.4) in both the groups at 1 minute. Another study done by Lai et al.(16) comparing inhaled budesonide/formoterol with salbutamol showed similar improvement in post treatment outcomes (in terms of respiratory rate, oxygen saturation and PEFR) in both the groups except that tachycardia was noted in salbutamol group (p value- 0.001).

Study done by David S Pearlman et al.(17) showed that in children aged 6 to <12 years with asthma who remained symptomatic on ICS monotherapy, the combination of formoterol and budesonide (pMDI 9/160 µg) produced significant and clinical improvements in lung function compared to budesonide alone (p value <0.015). This supports the efficacy of adding a long-acting β2-agonist to ICS in achieving better symptom control and lung function in pediatric patients not adequately controlled on monotherapy.

Adverse events were infrequent and mild, with tachycardia occurring slightly more often in the salbutamol + budesonide group, though not statistically significant, and no cases of hypertension or tremors were reported. These findings align with Jenish et al.,(17) who observed tremors in two children receiving salbutamol and one receiving formoterol, highlighting the favorable safety profile of both regimens in acute asthma.

The findings from our study, supported by evidence from previous research, indicate that formoterol Budesonide combinations exhibit a rapid bronchodilatory effect which is comparable to that of short-acting β_2-agonists such as salbutamol Budesonide combination. This suggests its potential utility as a rescue medication during acute exacerbations in children. The rationale for ICS/formoterol therapy is based on concerns about the risks of SABA reliever therapy, and the potential benefit of titrating additional ICS through the same vehicle of bronchodilator reliever use.

The study's findings are limited by its small sample size, single-centre study, short observation period, focused on children with mild asthma, and the use of PEFR instead of spirometry for assessing airway function.

CONCLUSION

Inhaled Formoterol+Budesonide combination has rapid onset of action within 5 mins and similar efficacy as bronchodilator as inhaled Salbutamol+Budesonide combination, traditionally used as reliever in children 6-12 years of age. Inhaled formoterol+ budesonide combination also found to be safe and can be used as reliever in acute asthma exacerbation in children of age 6 -12 years of age, taking into consideration long term risks associated with repeated use of SABA. Further large-scale, longitudinal studies are warranted to assess the sustained efficacy and long-term safety profiles of these therapeutic combinations.

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Conflict of Interest

The authors declare no conflicts of interest.

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Ethical Approval

Approved by the Institutional Ethics Committee of M.V.J. Medical College & Research Hospital. Written informed consent obtained from guardians.

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