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Role of inhaled corticosteroids/formoterol in relieving acute asthma as compared to traditional salbutamol in children 6 to 11 years old on maintenance and reliever therapy step 3 and above as per the Global Initiative for Asthma guideline

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Abstract

The recent Global Initiative for Asthma (GINA) guidelines offer two reliever therapy options for patients on step 3 and above: the more popularly used short-acting β-agonists (SABA) and the newly introduced inhaled corticosteroids (ICS)-formoterol combination. Our aim was to assess the effectiveness of the ICS/formoterol combination in comparison to the traditional SABA offered to patients aged 6-11 years old following step 3 and above of the GINA guidelines. A retrospective study was conducted at a tertiary care facility in Karachi, Pakistan. The study involved children aged 6-11 years old who were admitted with an asthma exacerbation and were subsequently discharged on step 3 and above as per the GINA guidelines for 3 months. The patients were then categorized into two groups depending on the type of reliever used (ICS/formoterol or salbutamol). There were 80 pediatric patients enrolled in our study. The emergency room visits with asthma exacerbation in 3 months following discharge were significantly lower in the ICS/formoterol reliever group (1.27±0.83) than in the salbutamol reliever group (1.93±1.36) (p=0.01). Mean admission with asthma in 6 months post-discharge was significantly higher in the salbutamol group (2.18±0.82) as compared to the ICS/formoterol group (1.24±0.83). Moreover, the number of patients requiring step-up control within 3 months of discharge was also significantly lower in the ICS/formoterol group, with 2 patients, than the salbutamol group, with 10 patients (p=0.02). The forced expiratory volume in 1 second value 3 months after discharge was significantly greater in the ICS/formoterol group (91.27±8.32) than in the salbutamol group (84.58±10.44) (p=0.02). Through our analysis, we were able to highlight the superiority of ICS/formoterol as a reliever compared to SABA for moderate asthma.

Key words: acute asthma exacerbation, reliever, inhaled corticosteroids, formoterol, short acting β-agonists.

Introduction

Asthma exacerbations are a major cause of disease morbidity and increases health care costs. Consequently, it is important to have a plan of management that improves disease control and patient well-being [1]. The Global Initiative for Asthma (GINA) was established in 1993 in collaboration with the World Health Organization (WHO) and U.S NHLBI. It aims to improve the diagnosis, management and prevention of asthma by providing an up-to-date evidence-based strategy and tools and practical resources for physicians globally [2]. In children aged 6-11 years following step 3 as per the 2023 GINA guidelines have the option of choosing between two reliever therapies. The most common and widely used short-acting beta agonist or the more recently introduced low-dose inhaled corticosteroids (ICS) and formoterol combination for patients already on maintenance ICS/formoterol [3].

This alternative ICS/formoterol reliever therapy was offered due to the recognition that SABA overuse and ICS underutilization was resulting in poor control outcomes such as hospitalizations and possibly death. While SABA can provide rapid relief of asthma symptoms, it does not treat the underlying inflammatory process and thus does not protect the patient from exacerbations. Patients who rely solely on SABA are at a higher risk of asthma related death [4]. Formoterol is a long-acting beta-agonist (LABA) that causes rapid bronchodilation within 1-3 minutes of inhalation that is similar to that of salbutamol -a SABA. High dose of formoterol is as effective and well tolerated as high doses of SABA in treating patients with acute asthma. Inhaled corticosteroids also provide anti-inflammatory effects [5].

The autonomy provided by the GINA guidelines allows physicians and patients the freedom of choice to choose their preferred reliever therapy. We organized a study to assess the effectiveness of the two reliever options offered in patients aged 6-11 years old following step 3 and above of the GINA guidelines. Our hypothesis is that ICS/formoterol reliever is superior at achieving optimal asthma control as compared to salbutamol. This study was conducted to promote the usage of ICS/formoterol reliever therapy over the more widely used salbutamol in our population.

Materials and Methods

Our study was conducted at a tertiary care facility in Karachi, Pakistan from January 1, 2022 to December 31, 2023. Ethical approval was taken from institution ethics review committee (2024-10088-29895) before commencement of the study. The study involved children aged 6-11 years old who were admitted with an asthma exacerbation and were subsequently discharged on step 3 and above as per the GINA guidelines for 3 months. The patients were then categorized into two groups depending on the type of reliever used- ICS/formoterol or

salbutamol. The patients were categorized into two groups using their electronic medical records that document every patients' hospital visits as well as their treatment plans. All the patients divided into the two groups were on ICS/LABA maintenance therapy. This was possible due to the freedom of choice offered to physicians by the GINA guidelines.

We collected the patients' information regarding demographics- age, gender, BMI. Moreover, we also noted the average duration of diagnosis with asthma and the average use of reliever per month. The patients were followed post-discharge for ER visits with asthma exacerbation and number of patients needing step-up therapy within 3 months, as well as mean admission with asthma within 6 months (Figure 1). Lung function tests were also collected of patients - FEV1 and FEV1/FVC ratio- 1 week and 3 months after discharge.

The patients who were managed on any step below step 3 as per GINA guidelines upon discharge were excluded from the study. Those who were lost to follow-up, didn't have lung function tests done, or had an incomplete medication history were not included in the study. Additionally, patients admitted with bronchiolitis, bronchopneumonia, upper airway obstruction, cystic fibrosis, and tuberculosis were also excluded from the study.

Asthma exacerbation is defined as an acute or subacute episode of worsening symptoms of asthma- wheezing, cough, and chest tightness-, worsening of lung function tests, or an increase in bronchodilator use for at least two days [6,7].

Lung function tests were done using easy-On-PC® device and interpretations of FEV1 readings, ratio of FEV1 and forced vital capacity (FVC) and other parameters were performed using American thoracic Society Guideline and European Respiratory Society Technical Statement [7].

This study was conducted using patients' electronic medical records system available at the hospital that contains information pertaining to patient demographics, medical history, medication use, and clinical outcomes. Approval for exemption was obtained from the Ethics Review Committee; reference number: 2024-10088-29895. Pharmacy data provided information on medication prescriptions and duration of treatment allowing for the categorization of the patients into two reliever groups. The data collected was carefully selected and validated to ensure accuracy and completeness. The sample size was determined using non-probability continuous sampling through medical records.

The use of electronic medical records also allowed for improved accuracy rather than relying on patient recall. Furthermore, we utilized our inclusion and exclusion criteria in order to have a better representative sample for our study. We also followed a standardized data collection protocol and used validated measures to ensure consistency.

Statistical analysis

The data was analyzed using IBM Corp. released 2020, IBM SPSS Statistics for Windows, Version 27.0. Armonk, NY: IBM Corp. Categorical variables were expressed using frequency and percentages and continuous variables were described as mean and standard deviation. ANOVA test and paired T-test was used for means and Chi-square test was used for categorical data to assess significant difference between groups. A p-value of 0,05 was considered significant with a type I error of 5%.

Results

There was a total of 80 pediatric patients enrolled in our study. These patients were divided into 2 groups, 38 (47.50%) patients and 42 (52.50%) patients were categorized into the ICS/formoterol reliever group and salbutamol reliever group respectively. It was noted that there was no significant difference in the age, gender, and body mass index between the two groups. The average use of reliever per month was also similar in both groups- 2.56±0.86 in the ICS/formoterol group and 2.46±0.73 in the salbutamol group- with no significant difference.

The ER visits with asthma exacerbation in 3 months following discharge were significantly lower in the ICS/formoterol reliever group (1.27±0.83) than the salbutamol reliever group (1.93±1.36) (p=0.01). Mean admission with asthma in 6 months post discharge was significantly higher in the salbutamol group (2.18±0.82) as compared to the ICS/formoterol group (1.24±0.83) with p<0.001 (Figure 2). Moreover, the number of patients requiring step-up control within 3 months of discharge was also significantly lower in the ICS/formoterol group with 2 (5.26%) patients than the salbutamol group with 10 (23.81%) patients (p=0.02) (Table 1).

The lung function tests 1 after discharge of the two groups in FEV1 and FEV1/FVC ratio were quite similar with no significant differences. Three months after discharge, there was an improvement in the pulmonary function tests of both groups. The FEV1 value three months after discharge was significantly greater in the ICS/formoterol group (91.27±8.32) than the salbutamol group (84.58±10.44) (p=0.02) (Table 2). Moreover, the FEV1/FVC ratio was also significantly greater in the ICS/formoterol reliever group (90.72± 10.1) as compared to the salbutamol reliever group (82.74±9.17) (p<0.01).

Discussion

In our study, we wanted to highlight the shifting trend of reliever use from SABA to ICS/formoterol in children 6-11 years old following step 3 as per the GINA guidelines. Hence,

we conducted a retrospective analysis of the different outcomes possible when using either reliever therapy. Through this study, we noted that ICS/formoterol is a superior reliever therapy as compared to the more traditional SABA. Through this study, we can promote the usage of ICS/formoterol over SABA in our population, informing both physicians and patients of its benefits.

We found that the ER visits with asthma exacerbation in 3 months was significantly lower in the ICS/formoterol reliever group than the salbutamol reliever group. The number of patients needing step-up on control in 3 months was also significantly reduced in the ICS/formoterol group than the salbutamol group. Moreover, the mean admission with asthma in 6 months was also significantly decreased in patients using ICS/formoterol reliever than the ones using salbutamol reliever. Both reliever groups exhibited an improvement in lung function tests from 1 week to 3 months. However, the lung function tests parameters after 3 months- FEV1 and FEV1/FVC ratio- was significantly greater in the ICS/formoterol reliever group than the salbutamol reliever group. The average use of reliever per month was similar in both groups with no significant difference.

Asthma is prevalent chronic inflammatory airway disease that is marked by reversible airway obstruction, airway hyperresponsiveness, and structural changes in the airways. In 2019, death cases for asthma were estimated to be 461.07 thousand [8]. The GINA guidelines offer two possible reliever options for 6-11 years old children on step 3 – ICS/formoterol or SABA. Short-acting beta-agonists are rapid onset bronchodilators that are effective for symptom relief but offer no anti-inflammatory properties. Patients using SABA alone are at an increased risk of asthma relate mortality and emergency even in the presence of good symptom control [9]. The over-reliance on SABA for symptom control in asthma leads to SABA overuse and ICS underutilization resulting in an increased of asthma exacerbations and mortality [10].

Therefore, the GINA guidelines recommend low dose ICS/formoterol reliever therapy over SABA reliever therapy across a spectrum of asthma severity. The ICS/formoterol reliever is expected to have greater efficacy with reduced severe exacerbations and a better safety profile due to a reduced risk of reliever overuse episodes leading to delay in seeking medical treatment [11]. In contrast to SABA, the long-term use of ICS improves lung-function and decreases asthma-relate mortality. The addition of a fast-acting LABA, formoterol, to the ICS allows for quick symptom relief [12]. ICS/formoterol reliever has anti-inflammatory properties, hance it is described as ‘anti-inflammatory reliever’ (AIR) [13].

In a study by *Beasley et al.*, it was noted that the greater efficacy was due to budesonide/formoterol as compared to SABA reliever therapy, rather than the specific ICS/LABA used for maintenance therapy for patients on step 3 of the GINA guidelines [14].

Moreover, another study by *Lazarinis et al.* demonstrated that ICS/formoterol as needed was superior at reducing exercise induced bronchoconstriction in comparison to as needed SABA [15].

Pauwels et al. conducted a study to explore the effectiveness of formoterol as a reliever in comparison to salbutamol. Through this study, it was found that formoterol as a reliever reduced the risk of all types of asthma exacerbations by 12-16% as compared to salbutamol which is similar to our study where the ER visits with asthma exacerbation in 3 months was less in the ICS/formoterol reliever group than the SABA reliever group. It was also noted that the formoterol reliever group exhibited longer times to first exacerbation as compared to the salbutamol. This study was a prospective study that was conducted among 24 countries, in contrast to our study which is a single-center retrospective study. In this study the investigators were not blinded to treatment and may have influenced the study outcomes, however, our study does not have this issue since it is a retrospective study using hospital electronic records [16]. Another study by *Tattersfield et al.* compared the effectiveness of formoterol and terbutaline as needed. This study found that the time to first severe exacerbation was longer in the formoterol group than in the terbutaline group ($p=0.013$). Moreover, the relative risk ratio of having a first exacerbation in the formoterol group compared to the terbutaline group was 0.55 (95% CI 0.34-0.89) [17].

A review conducted by *Beasley et al.* also found that budesonide/formoterol reliever therapy has greater potency and efficacy than budesonide/formoterol fixed dose maintenance plus SABA reliever therapy at reducing the risk of severe exacerbations [18]. In a study by *O'Byrne et al.,* it was noted that budesonide/formoterol maintenance and reliever therapy had prolonged time to first severe exacerbation as compared to budesonide/formoterol maintenance plus SABA reliever and budesonide maintenance with SABA reliever (both $p<0.001$) [19]. Our study showed that the mean admission with asthma in 6 months was less in the ICS/formoterol reliever group as compared to the SABA reliver group (1.24 ± 0.83 vs. 2.18 ± 0.82, $p<0.001$). Additionally, another study by *Kuna et al.* also found that there was a 26% reduction in the hazard ratio for a first severe reduction in budesonide/formoterol maintenance and reliever therapy as compared to the maintenance budesonide/formoterol plus terbutaline group. The total number of severe exacerbations was also reduced by 28% in the budesonide/formoterol maintenance and reliever group as compared to the budesonide/formoterol maintenance plus terbutaline reliever group [20].

Limitations

Limitations of study is the retrospective design making it difficult to measure the compliance of the pediatric population. This study is a single-center study design therefore limiting generalizability. It is also difficult to assess whether the results noted are due to the reliever therapies or possibly due to the differing maintenance therapies. The differing maintenance therapies may be a potential confounding factor in our result. More studies should be conducted to further solidify our findings.

Conclusions

The aim of our study was to demonstrate the effectiveness of ICS/formoterol reliever therapy over that of SABA reliever therapy in children 6-11 years old following step 3 of the GINA guidelines. Through our analysis, we were able to highlight the superiority of ICS/formoterol as a reliever compared to SABA for moderate asthma. We recommend more prospective studies to add further weightage to our study and aid in validating our findings.

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Table 1. Demographics and variables.

	ICS/formoterol group	Salbutamol group	P-value
Patient n (%)	38 (47.50%)	42 (52.50%)	
Age (Years)	7.20 ±2.40	6.8±2.80	0.171
Male: Female	1.3: 1	1.4:1	
Body Mass Index (BMI)	18.67±2.36	17.23±1.94	0.145
Average duration on diagnosis with asthma (Years)	6.84±1.67	5.93±1.40	0.187
Average Use of Reliever per month	2.56±0.86	2.46±0.73	0.56
ER visit with Asthma Exacerbation in 3 months	1.27 ±0.83	1.93±1.36	0.01
Number of patients needing Step-up on control in 3 months	2 (5.26%)	10 (23.81%)	0.02
Mean Admission with Asthma in 6 months	1.24± 0.83	2.18±0.82	<0.001

Table 2. Lung function tests.

	ICS/formoterol group	Salbutamol group	P-value
FEV1 (%) at discharge	74.75±7.03	77.64±6.48	0.19
FEV1 (%) at 3 months interval	91.27±8.32	84.58±10.44	0.02
FEV1/FVC (%) at discharge	77.91±6.89	78.06±7.20	0.49
FEV1/FVC (%) at 3 months interval	90.72±10.1	82.74±9.17	<0.01

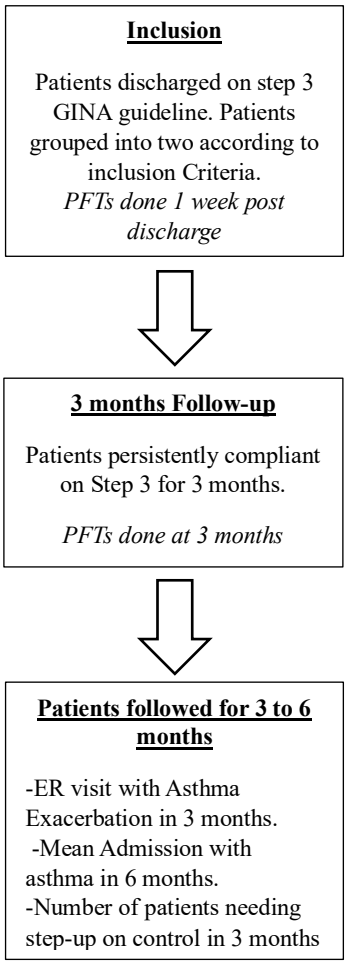

Figure 1. Study design.

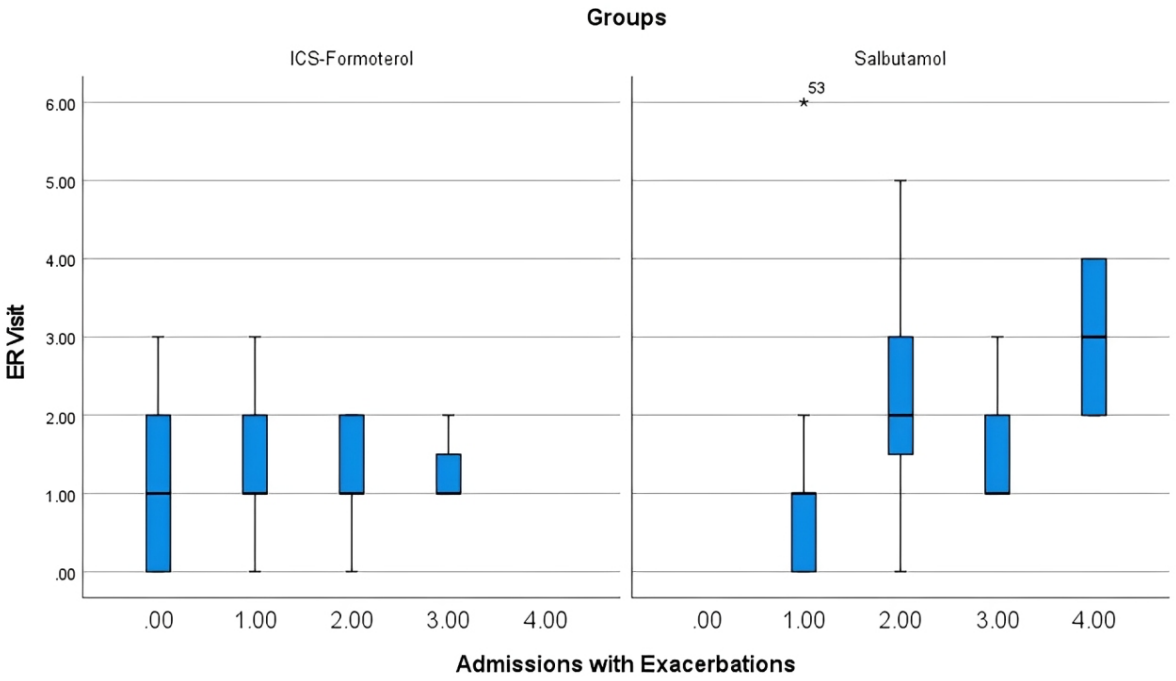

Figure 2. Comparison of ER visits and Admissions with Exacerbations between the groups. ICS, inhaled corticosteroids; ER, emergency room.