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Intravenous methylprednisolone versus intravenous methylprednisolone combined with inhaled budesonide in acute severe pediatric asthma

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ABSTRACT

Introduction: Corticosteroids are important part of acute severe asthma (ASA) management in pediatric intensive care units. Few studies look at the efficacy of inhaled corticosteroids (ICS) in critical care settings. We aimed to investigate the potential beneficial effects of ICS when added to intravenous corticosteroids in pediatric patients with ASA admitted to the pediatric intensive care unit (PICU)

Methods: This was a randomized controlled trial involving pediatric patients aged 1–21 years admitted to PICU with ASA. Patients were randomized into 2 groups using block randomization. Patients in Group A received intravenous methylprednisolone (2 mg/kg/day) alone and patients in Group B received intravenous methylprednisolone (2 mg/kg/day) plus budesonide nebulization (0.5 mg every 12 h). Main outcomes were duration of continuous albuterol treatment, PICU and hospital length of stay (LOS), and need and duration of respiratory support. Kruskal-Wallis and Chi-square tests were used for statistical analysis, in which a p -value < 0.05 was considered statistically significant.

Results: Duration of continuous albuterol treatment was not different between the 2 groups median/(QR), 30/(18–51) vs. 25/(14–49). ($p = 0.38$) PICU and hospital LOS between the 2 groups was similar, median/(QR), 44/(30–64) vs. 46/(30–62), ($p = 0.75$) and 78/(65–95) vs. 72/(58–92), ($p = 0.19$). Number of patients requiring respiratory support was 22(58%) in Group A and 25(64%) in Group B ($p = 0.19$).

Conclusions: In critically ill children with ASA, intravenous methylprednisolone combined with inhaled budesonide did not shorten the duration of continuous albuterol inhalation treatment, the PICU and hospital LOS, and the need for respiratory support.

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Introduction

Asthma is a reversible, heterogeneous obstructive airway disease with bronchoconstriction and inflammation of peripheral airways resulting in air trapping and mucus production. Acute severe asthma (ASA) also known as status asthmaticus is an acute exacerbation of asthma that is unresponsive to initial management including bronchodilators, corticosteroids, and magnesium sulfate. Patients with ASA who fail to respond to initial intensification therapy are admitted to the Pediatric Intensive Care Unit (PICU).

Corticosteroids stimulate cytosolic glucocorticoid receptors that decrease inflammatory leukocytes and increase anti-inflammatory mediators (1,2). Corticosteroids can be given systemically or through a local inhalation. The National Heart, Lung, and Blood

Institute Expert Panel Report-3 (EPR3) Asthma guidelines recommend using systemic corticosteroids for patients with ASA who have an incomplete or poor response to initial treatment (3). Inhaled corticosteroids (ICS) are mainly used for long term management of asthma to prevent episodes of exacerbations. The efficacy of ICS in ASA has not been well studied. Several studies evaluated the use of ICS exclusively in the emergency department. A Cochrane systematic review showed promising benefits of using ICS, resulting in a decrease in hospital admissions when compared to placebo (4). Despite the promising results, the use of ICS in ASA is not recommended in EPR3 due to limited evidence of efficacy. There are no studies that investigated the impact of ICS in pediatric patients with ASA in intensive care settings.

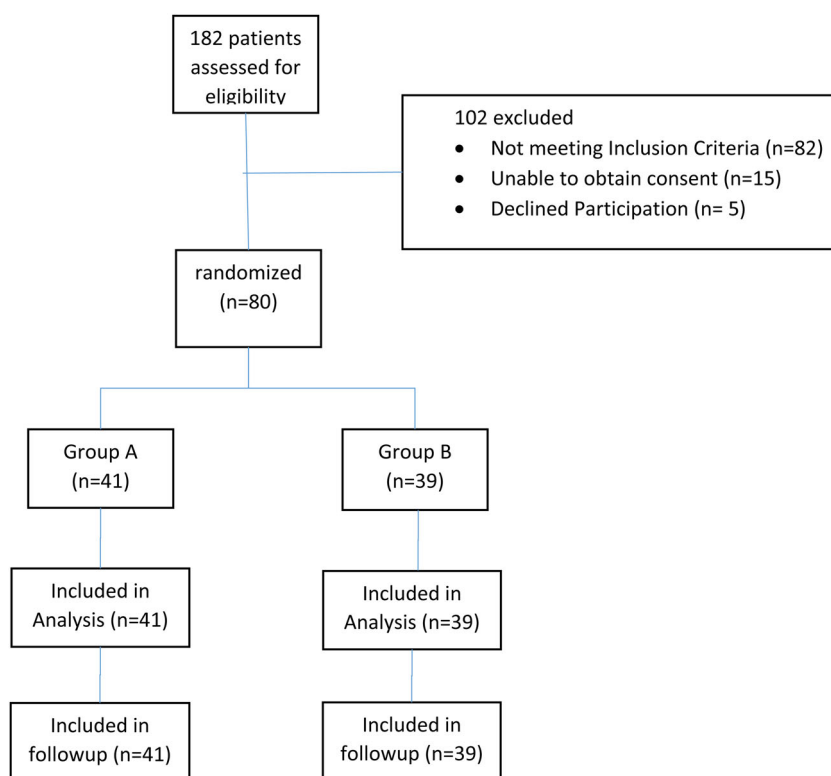


Figure 1. Study enrollment chart.

Our randomized controlled study was conducted to evaluate the benefits of incorporating inhaled budesonide to intravenous IV methylprednisolone, as compared to IV methylprednisolone alone, in children admitted to PICU with ASA. We hypothesize that the addition of inhaled budesonide will reduce the duration of continuous albuterol nebulization treatment, the PICU and hospital length of stay (LOS), and the need for respiratory support in pediatric patients admitted to PICU

Methods

This study was approved by our institution's review board (#855093–5). It is a randomized non-blinded clinical trial that includes pediatric patients aged 1 to 21 years, admitted to the PICU at our institution for ASA from May 2017 to February 2019. Written consent and assent forms were obtained from patients and their families. Subjects with history of prior cardiovascular disease, neurological disease, neoplastic disease, renal disease or pregnancy were excluded from the study (Figure 1). Demographic data was collected from all patients including their age, gender, race, and body mass index (BMI). Patients' baseline asthma severity was assessed using the Global

Initiative for Asthma guidelines, their prior use of ICS, and their number of prior hospitalizations for asthma. History of allergic rhinitis, eczema, and environmental and food allergies were also assessed for all patients. Participants were randomized for treatment allocation into two groups (Group A: Control and Group B: Intervention) using block randomization with a block size of two. Patients assigned to the treatment group received inhaled budesonide (0.5 mg/2 ml twice daily) by nebulizer with a facemask, combined with IV methylprednisolone (2 mg/kg/day). The control group received only IV methylprednisolone (2 mg/kg/day). The group assignment was provided in sequentially numbered opaque sealed envelopes to the PICU team member to be revealed at time of enrollment. Patients were enrolled in the study within 12 h of admission to the PICU. All study participants received continuous beta-2 agonist treatment titrated to effect (minimum dose: 5 mg/kg/hour and maximum dose: 20 mg/kg/hour) and ipratropium bromide nebulization (250 mcg/dose) every 6 h for the first 24 h, as the standard treatment of ASA in our PICU. Duration of continuous beta-2-agonist was measured in hours and collected by the PICU team. Total duration in hours, including continuous and intermittent doses,

was measured until discharged from the hospital. The use of other treatment modalities in the PICU were also collected, including the number of treatments of magnesium sulfate, intravenous fluids, epinephrine, and terbutaline. Terbutaline was either given as bolus or intravenous continuous medication. Respiratory support was given to patients based on their clinical condition, including noninvasive and invasive respiratory support modalities. The duration in hours, the type of maximum respiratory support, the fraction of inspired oxygen (FiO₂), the PICU and hospital LOS in hours were also collected for all the subjects. Pediatric asthma severity scores (PASS) were measured by PICU team at 0, 6, 12, 18, 24 and 48 h respectively in both groups (5). Patients were contacted 6 months following discharge to inquire if they required readmissions, and the duration of readmission. The main outcome measures were the duration of beta-2 inhalation treatment, the PICU and hospital LOS, and the duration of respiratory support.

Statistical analysis

Descriptive analyses including mean, median, and standard deviation, and 25th–75th inter quartile ranges (IQR) were used to compare groups. T-test and Mann Whitney U test was used to compare parametric and non-parametric continuous data including age, BMI, PICU and hospital LOS, PASS, duration of continuous albuterol treatment, and duration of maximum respiratory support. Chi-square testing was used to analyze nominal data including number of prior PICU and hospital admissions, gender, race and need for respiratory support.

Sample size calculation for the study was based on the primary outcome. Based on previous studies, we expected the mean (SD) of the duration of the bronchodilator therapy to be 48(±4.8) hrs in the control group. A 5% difference in the mean duration therapy between the two study groups was selected as the smallest effect that would be of clinical importance. Assuming the same variability in both groups, we assumed that a sample size of 64 patients in each of the two groups would have 80% power to detect a statistically significant difference, using a p values < 0.05. However, we were only able to enroll 80 patients in total to both groups during the study period due to a period in which there was a national shortage of the concentrated albuterol solution required for continuous nebulization protocols.

Results

We screened 182 patients who were admitted with a diagnosis of ASA to our PICU. One hundred patients were eligible for enrollment. Reasons for non-enrollment were use of levalbuterol due to the shortage of concentrated albuterol solution for 4 months during the study period, patients being non-English speakers (consent and assent forms available in English only), patients having cerebral palsy, patient being less than a year old, patients having wheezing secondary to bronchiolitis rather than asthma, and patients having a history of congenital heart disease. Eighty patients were enrolled with ages ranging from 18 months to 18 years, with a mean (SD) of 7.9 (±4.39) years. Sixty-eight (85%) patients were African American. 49 patients were enrolled in Group A and 39 patients were enrolled in Group B. All enrolled subjects completed the trial and were included in the final data analysis (Figure 1). The baseline characteristics were similar in both groups in terms of age race and sex. Patient in group A had higher BMI and BMI percentile for age and sex compared to those in Group B ($p=0.008$). Between the two groups, there was no significant difference in patient baseline asthma severity, their PASS score at admission, their use of ICS prior to admission, their history of hospitalization, prematurity, eczema, smoke exposure, aeroallergen sensitization, or food allergies (Table 1).

There were no statistical differences in the duration of continuous albuterol nebulization treatment, or in the duration of PICU and hospital LOS between the two groups (Table 2). 58% of the patients enrolled in the trial were treated with noninvasive ventilation. One patient in each group needed invasive mechanical ventilation. The mean duration of respiratory support was higher in Group B, although not statistically significant (median (IQR); 6 (0–19) vs. 9.25 (0–28); $p=0.327$). We also noted that the mean fraction of inspired oxygen was similar between the two groups. The use of ipratropium bromide nebulization, IV magnesium sulfate boluses, epinephrine, and parenteral terbutaline were not different between the two groups during the enrollment period. (Table 2). Pediatric asthma severity scores were comparable for the two groups throughout hospital stay. 24h PASS scores showed a significant difference in favor of group B (median (IQR); 11(9–12) vs 9 (7–11); $p=0.02$) (Figure 2). Number of readmissions at six months follow up after discharge was statistically similar between the two groups. (Table 2).

Table 1. Comparison of the baseline demographics and clinical characteristics of Group A (intravenous methylprednisolone) versus Group B (intravenous methylprednisolone and inhaled Budesonide), n = number of patients, n (%) = number of patients in percentage, PICU = Pediatric intensive care unit, SD = Standard deviation, BMI percentile calculated using CDC growth for age and sex chart.

Groups (Number of patients)	A (n = 41)	B (n = 39)	p-value
Age in years, median (IQR)	8 (5–11)	5 (4–9)	0.052
Female, n (%)	22 (54.7)	12 (30.8)	0.065
Race: African American, n (%)	39 (95.1)	29 (74.4)	0.079
BMI, median (QR)	20(17–24)	16.6 (15–21)	0.008
BMI percentile, median (IQR)	91.6 (67–98.7)	52.7 (31.4–93.9)	0.017
Types of asthma, n (%)			0.109
• Mild intermittent asthma	13 (31.7)	22 (56.4)	0.208
• Mild persistent asthma	4 (9.8)	2 (5.1)	1
• Moderate persistent asthma	23 (56.1)	13 (33.3)	0.326
• Severe persistent asthma	1 (2.4)	2 (5.1)	1
Pediatric Asthma Severity Score at admission	13.36 (1.99)	13.05 (2.48)	0.99
Inhaled corticosteroid use, n (%)	26 (63.4)	19 (48.7)	0.272
Previous PICU admission, n (%)	22 (53.7)	20 (51.3)	1
Previous hospital admissions, n (%)	34 (82.9)	24 (61.5)	0.058
Allergic rhinitis, n (%)	24 (58.5)	16 (41)	0.180
Eczema, n (%)	19 (46.3)	21 (53.8)	0.655
Smoke exposure, n (%)	8 (19.5)	8 (20.5)	1
Prematurity, n (%)	8 (19.5)	8 (20.5)	1
Aeroallergen sensitization, n (%)	2 (4.9)	7 (17.9)	0.135
Food allergy, n (%)	9 (22)	11 (28.2)	0.698

Table 2. Measured outcomes in the study, IQR = Quartile range 25–75 percentile, n = Number of patients, n (%) = Number of patients in percentage.

	Group A	Group B	p value
PICU LOS in hours, median (IQR)	44 (30–64)	46 (29.5–62)	0.751
Hospital LOS in hours, median (IQR)	78 (65–95)	72 (57.5–92)	0.190
Duration of continuous albuterol in hours, median (IQR)	30 (18–51)	25 (14–49)	0.386
Total duration of albuterol treatment in hours, median (IQR)	76 (68–90)	72 (57–94.5)	0.363
Duration of respiratory support in hours, median (IQR)	6 (0–19)	9.25 (0–28)	0.327
Maximum FiO ₂ , median (IQR)	0.3 (0.25–0.4)	0.3 (0.3–0.4)	0.416
Number of patient require Oxygen Support, n(%)	32 (78)	33 (84.6)	0.642
Maximum dose of continuous albuterol treatment, n (%)			0.53
5 mg/hour	0	1 (2.5)	0.30
10 mg/hour	14 (34.1)	15 (38.5)	0.69
15 mg/hour	14 (34.1)	15 (38.5)	0.69
20 mg/hour	13 (31.7)	8 (20.5)	0.26
Other Medications			
Number of intravenous magnesium sulfate boluses, median (IQR)	1 (1–2)	1 (1–2)	0.35
Number of subcutaneous epinephrine given, median (IQR)	1 (1–2)	1 (1–2)	0.60
Number of fluid boluses given in the emergency department (20 ml/kg), median (IQR)	1 (1–2)	2 (1–2)	0.46
Use of Terbutaline, n (%)	9 (22)	5 (12.8)	0.435
Readmission			
Patients requiring re-admissions, n (%)	16 (39)	9 (23.1)	0.195
Time to readmission in months, median (QR)	4.5 (1.8–6.3)	4.5 (3–6)	0.690
Maximum Respiratory Support, n (%)			0.752
No respiratory support	18 (43.9)	12 (30.8)	0.23
High Flow Nasal Canula	1 (2.4)	2 (5.1)	0.53
Bi-level positive airway pressure	20 (48.8)	22 (56.4)	0.49
Continuous positive airway pressure	1 (2.4)	2 (5.1)	0.52
Invasive mechanical ventilation	1 (2.4)	1 (2.5)	0.97

Discussion

Corticosteroids are an important part of acute and chronic asthma treatment due to their potent anti-inflammatory effects. The choice and dose of systemic corticosteroid agent for the treatment of ASA is variable among pediatric intensive care and inpatient units (3,6,7). EPR3 Asthma guidelines recommends the use IV route for corticosteroid therapy in critically

ill asthmatic children with ASA (3). However, the use of ICS for ASA is not supported by clinical guidelines and is dependent on the intensivist experience. In our institution there is variability among the use of ICS in patients admitted to the PICU for ASA.

In the recent years, nearly all studies that reported clinical benefits of ICS in management of pediatric acute asthma were done in the emergency department

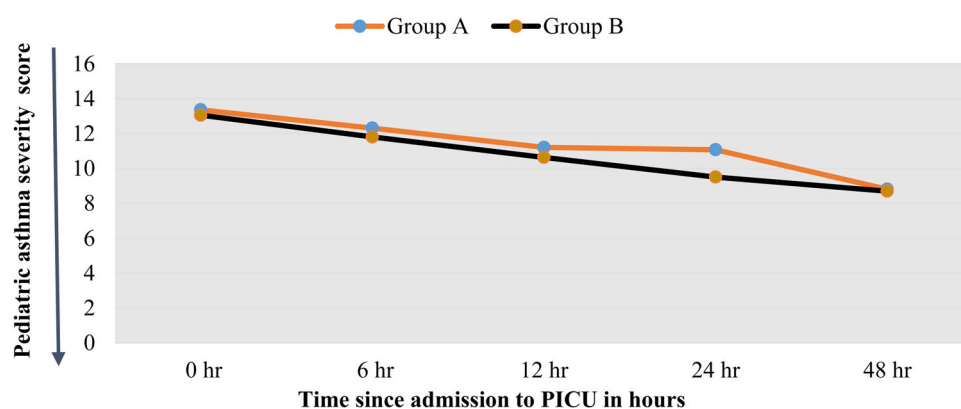


Figure 2. Pediatric asthma Severity score (PASS) changes with time.

(8–11). Our knowledge is limited regarding the use of ICS in the pediatric critical care setting. At our institution, treatment of ASA consists of continuous beta-2 agonist treatment combined with IV corticosteroids. Based on their prior experiences and knowledge of our patient population, some of the intensivists in our PICU have added ICS to IV corticosteroid therapy and noted beneficial effects on asthma outcomes anecdotally. Our facility provides care for an underserved, urban patient population with a very high (23%) childhood asthma rate, and the PICU staff utilizes the critical care stay as an opportunity to educate parents on the need for ICS as a daily controller as well as to demonstrate proper medication delivery technique(s). No one formally examined if there are any beneficial acute effects of this practice, which lead us to conduct this research study. In our study, we added inhaled budesonide (1 mg/day) to IV methylprednisolone in group B patients with the intent to enhance the effect of corticosteroid therapy in children with ASA. However, there was no significant improvement in the group B in the duration of continuous beta-2 agonist treatment, and the PICU and hospital LOS. Our results showed a significant 24 h PASS scores in favor of group B which might indicate initiation of ICS in the first 24 h might be beneficial. Larger study with more patients is needed to investigate this finding further.

Razi et al. compared the effects of inhaled budesonide (2 mg/day) versus placebo with normal saline inhalation added to IV methylprednisolone (1 mg/kg/day) in children aged 7–72 months who were admitted to pediatric ward for acute asthma exacerbation. Patients in the inhaled budesonide group had a shorter hospital LOS after 36 h ($p=0.02$) and lower clinical asthma scores compared to the placebo group. Inhaled budesonide dose used in the Razi et al. study

was higher compared to our study (2 mg/day vs. 1 mg/day). Differences in our results may be due to the dose difference of inhaled budesonide (12). EPR3 Asthma Guidelines consider 2 mg/day of inhaled budesonide to be high dosage for term control of asthma and prevention of asthma exacerbation (3). Future studies investigating higher dose of ICS may show better outcomes of ASA during pediatric critical care.

Asthma is well studied in the literature for white patient populations. However, there is scarcity of asthma studies in the African American population. Majority of the patients (85%) enrolled in our study were African American. A prior study showed African American children exhibited a better response to higher doses of ICS (13). In our study, we used low doses of ICS, which could explain why our patients did not show better response compare to the no ICS group. In future studies, we could investigate the effect of higher doses of ICS in African American children who require PICU admission for ASA.

We had some limitations in our study. Our sample size was small with a predominantly African American and underserved population, which include patients with low family income, recent immigrant status, or poor access to health care. Enrollment did not reach the desirable number to achieve statistical significance. We also did not include non-English speakers due to the lack of consent forms translated to other languages. The study characteristics and outcomes were limited to duration of continuous albuterol treatment and PICU and hospital length of stay. Further studies can be done to investigate the response of critical ill asthmatic children with high BMI to ICS. Additionally, It would have been beneficial if the patients were randomized in the ED room setting prior to admission to PICU thereby optimizing

the frequency of budesonide inhalation so it could be started immediately upon admission to PICU. Perhaps higher doses of inhaled budesonide (2 mg/day) would be more effective in ASA, which we will include in future studies involving ASA patients in the PICU setting. Additionally, physicians determining the outcomes were not blinded to the treatment given.

Conclusion

Based on our results, we did not find any benefit to providing critically ill children with ASA inhaled budesonide at a dose of 1 mg/day combined with IV methylprednisolone, when compared to IV methylprednisolone therapy alone. Future studies with a larger number of patients and higher doses of inhaled budesonide might be needed to validate our results. More research is required to fully investigate the benefits of ICS as an adjunct to systemic corticosteroids in patients with ASA in the PICU.

Declaration of interest

Authors have no conflicts of interest to disclose.

Funding

Authors have no financial relationships relevant to this article to disclose.

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