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High-dose of intravenous methylprednisolone versus oral in treatment of acute asthmatic patients: a cohort study

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Abstract

Currently, the recommended first-line treatment for an acute asthma attack (in the emergency department or urgent care setting) is an inhaled short-acting beta-2 agonist. If the patient does not respond well to treatment or has severe asthma, in addition to inhaled β2-agonists, systemic corticosteroids (SCS) could be given to control inflammation and prevent subsequent exacerbations. Although the effectiveness of SCS therapy has been proven, there is controversy concerning the choice of oral or intravenous (IV) routes. Even though IV SCS might control asthma exacerbation more quickly, it is associated with more complications. Thus, the oral route should be considered as a reasonable alternative other than the IV route. Moreover, although systemic dosing of 1-2 mg/kg body weight of oral steroids per day is common in practice, the evidence on the best dose regimen is sparse. A retrospective cohort study was conducted to evaluate the effect of high doses of intravenous methylprednisolone compared with oral methylprednisolone in treating acute asthmatic patients. All patients aged ≥15 years with acute asthma who were treated with systemic corticosteroids in a tertiary care emergency department from January 2013 to December 2015 were reviewed. Based on a chi-squared test for two independent groups, prior to matching, 87 patients in the oral group and 174 patients in the intravenous group met the selection criteria. The mean age was 47.5, with 51% being male. Regarding the presenting vital signs, the IV group had a higher respiratory rate and lower blood pressure at the time of presentation. After conducting a 1:1 match using the nearest-neighbor matching algorithm, 46 pairs were formed, being similar in baseline demographic characteristics, vital signs, and presenting PEF.

Keywords: Asthma; Methylprednisolone; Oral treatment; FEV1

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Introduction

The uncontrolled asthma epidemic in the United States is a troubling public health issue. Current statistics indicate that asthma affects 14% of the adult population and 16% of the pediatric population, with prevalence rates having tripled since the 1980s. Despite the availability of inexpensive and effective asthma control medications, the proportion of patients receiving adequate treatment has not increased, and asthma-related mortality rates have risen sharply for underserved patients. Acute asthma exacerbations, or excursions from established asthma control, can result in hospitalization and can potentially be life threatening.

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Optimal management of acute asthma exacerbations requires the safe and effective use of bronchodilators and systemic corticosteroids to quickly restore lung function. Systemic corticosteroids, the cornerstone of asthma exacerbation treatment, down-regulate the inflammatory response underlying bronchodilator unresponsiveness and status asthmaticus. Their use promotes bronchodilation, hastens recovery, and reduces the need for hospitalization and other medical resources. Recently, there has been considerable interest in how systemic corticosteroids can best be administered to patients with acute asthma. Several studies have examined the feasibility of oral administration versus the more traditional intravenous administration. The outcomes of these studies suggest that oral and intravenous administration result in equivalent recovery, though most of these studies have not been sufficiently powered to detect clinically important differences. Additionally, four of the studies evaluated only relatively low doses of oral corticosteroids (≤150 mg).

At this time, it remains unclear how the absolute dose and route of corticosteroid administration influence clinical outcomes in patients with acute asthma. Because high-dose systemic corticosteroids may limit the duration and extent of the inflammatory response to allergens and irritants, potential for rapid recovery of lung function exists. There are also major logistical and financial advantages to the use of oral versus intravenous corticosteroids. Thus, the purpose of this study was to compare the relative effectiveness of high-dose intravenous and oral methylprednisolone regimens in the treatment of patients with significant acute asthma. A retrospective review of a cohort of matched patients with significant acute asthma treated with one of the two regimens was undertaken and assessment of the clinical course, lung function, and medication use was performed.

Literature Review

Currently, the recommended first-line treatment for an acute asthma attack (in the emergency department or urgent care setting) is an inhaled short-acting beta-2 agonist. If the patient does not respond well to treatment or has severe asthma, in addition to inhaled β2-agonists, systemic corticosteroids (SCS) could be given to control inflammation and prevent subsequent exacerbations. Although the effectiveness of SCS therapy has been proven, there is controversy concerning the choice of oral or intravenous (IV) routes. Even though IV SCS might control asthma exacerbation more quickly, it is associated with more complications. Thus, the oral route should be considered as a reasonable alternative other than the IV route. Moreover, although systemic dosing of 1-2 mg/kg body weight of oral steroids per day is common in practice, the evidence on the best dose regimen is sparse. A retrospective cohort study was conducted to evaluate the effect of high doses of intravenous methylprednisolone compared with oral methylprednisolone in treating acute asthmatic patients. All patients aged ≥15 years with acute asthma who were treated with systemic corticosteroids in a tertiary care emergency department from January 2013 to December 2015 were reviewed. To ensure representation of both groups of interest, WHO's definition of health equity was applied, and the study population was narrowed down to those with no oral systemic steroid treatment within two weeks from presentation. To prevent measurement bias, patients who were discharged directly without any

admission, patients with incomplete medical records, and patients with other comorbidities except upper airway disease or hypertension were excluded.

Based on a chi-squared test for two independent groups, prior to matching, 87 patients in the oral group and 174 patients in the intravenous group met the selection criteria. The mean age was 47.5, with 51% being male. The IV group had a higher rate of intubation and higher peak expiratory flow rate, whereas the oral group had a higher proportion of patients presenting with wheezing. Regarding the presenting vital signs, the IV group had a higher respiratory rate and lower blood pressure at the time of presentation. After conducting a 1:1 match using the nearest-neighbor matching algorithm, 46 pairs were formed, being similar in baseline demographic characteristics, vital signs, and presenting PEF.

Current Treatment Guidelines for Acute Asthma

Acute asthma is defined as an acute onset of shortness of breath, wheezing, cough, chest tightness, or a combination of these symptoms, possibly in a patient with a prior diagnosis of asthma or one with suspected asthma. Common forms of acute asthma are mild exacerbations, moderate exacerbations, severe exacerbations, and life-threatening exacerbations. Treatment is guided by the severity of asthma status. The World Health Organization's Global Initiative for Asthma (GINA) guidelines propose a classification based on severity and an approach generally tailored to it. Short-acting beta-agonists (SABAs) are first-line bronchodilators for acute asthmatic patients, while systemic corticosteroids (CS) are the first-line anti-inflammatory treatment in these cases, and oral methylprednisolone is one of the most commonly prescribed formulations.

All patients treated with systemic CS are often started on a high initial dose regardless of the severity of exacerbation, with high-dose systemic CS commonly recommended. However, studies reported that a low dose of systemic CS (i.e., methylprednisolone 60 mg once daily for 5 days) is equally efficacious as a high dose of systemic CS (i.e., methylprednisolone 125 mg q6h for 3 days) in adults with severe acute exacerbation. No cohort studies have compared a high-dose regimen and a low-dose regimen of oral methylprednisolone. Methylprednisolone can be given orally as well, which would keep patients out of hospitals and works as well as intravenous methylprednisolone. The objective of this study was to compare the efficacy and safety of high-dose intravenous methylprednisolone versus a low-dose oral regimen of methylprednisolone in the treatment of acute asthmatic patients.

Previous Studies on Methylprednisolone in Asthma

Acute asthma exacerbations are medical emergencies that require immediate intervention to restore the normal physiological function of the lungs. Short-acting β_2-agonists are the first choice for bronchodilators and are given through inhaled routes. If there is a lack of response, systemic corticosteroids should be used as an adjunct treatment.

The optimal route and form of administration of systemic corticosteroids are still being investigated and debated. Methylprednisolone can be administered orally or through intravenous routes. Oral methylprednisolone has to go through the gut and hepatic metabolism, resulting in a 50% reduction in

bioavailability. On the contrary, intravenous administration bypasses the gut and liver, increasing the bioavailability of methylprednisolone. It is shown that high-dose intravenous methylprednisolone administration would result in a higher plasma concentration of methylprednisolone than oral administration in the first few hours after treatment.

Several studies have compared the efficacy of intravenous and oral methylprednisolone administration in the treatment of acute asthmatic patients. found that intravenous methylprednisolone was more effective than oral in decreasing the more pronounced clinical symptoms of wheezing and shortness of breath. Both studies were conducted in patients with severe acute asthma and thus response bias is highly probable because severe asthmatic patients would be more prone to have a better response to intravenous administration than patients with moderately acute asthma. found that although intravenous methylprednisolone administration was more effective than oral at 24 hours after treatment in improving respiratory rates in patients with moderate acute asthma, both routes were equally effective in improving PEF. However, the sample size for this study was small, which might not represent the patients' population accurately. In general, the previously conducted studies have a highly biased population responses to treatment. All studies were conducted in developing countries where modern rescue inhalers might not be available, and where patients might not have access to adequate and on-time treatment prior to hospital visits. Due to these facts, many of the patients studied in previous studies were rate ill and severe asthmatics, which might lead to different treatment efficacy than those studied in developed countries where modern asthma treatments are widely available.

The treatments used in the previous studies also vary widely, from younger and older age groups to different medications used in addition to methylprednisolone, which make patient condition before treatment initiation impossible to replicate. Moreover, none of these studies reported the plasma concentration or profile of treatment drugs, failing to establish a clear pharmacological relationship driving treatment efficacy. Despite the inconsistencies and limitations of the previous studies, the findings are still clinically relevant in that they encourage studies with higher-quality designs to further investigate methylprednisolone treatment route comparison in acute asthmatic patients.

Research Design

In one of the government hospitals affiliated with the Ministry of Health and Medical Education in southeastern Iran, a cohort study was conducted. The research setting and study period were determined based on the arrival of patients with acute asthma attacks at the emergency room. Then, using systematic sampling, patients who met the inclusion criteria were randomly selected from all patients encountered with the research setting. Finally, data collection was conducted using a checklist developed by the researcher. To increase the reliability of the researcher-made checklist, the validity and reliability of its items were determined based on the experts' opinion, and an acceptable CVI index and correlation coefficient were achieved.

A total census was conducted for the patients who entered the hospital and received intravenous medications in a 15-day period. Consequently, a total of forty patients were entered in the intravenous group of medications and received high-dose medications. In the next 15 days, all asthmatic patients

in the hospital who received oral medications entered the study. There was mutual exclusivity between treatment methods, and no person was entered to both medication groups. The patients in both groups received medications based on the global initiative for asthma recommendations. Oxygen supply was performed for all patients with a mask at 4-6 L/min. In the intravenous group, 1 gram of methylprednisolone was administered as a bolus (before 30 min) and then as an infusion (over 4 hours) 2 times daily; additionally, 15 mg of salbutamol salin was nebulized, and ipratropium bromide was 500 mcg nebulized bi-dose. In the oral group, 48 mg of metoprednisolone was prescribed daily (each dose with 16 mg) and salbutamol was 8 puffs every 4 hours.

As for the research variables, the age, sex, marital status, type of asthma, and admission time were demographic and background characteristics. The study variable was the response to treatment, operationally defined based on the clinical measures of patients by physicians including no more wheezing, normal respiratory rate, no retraction, SaO2 over 92%, and minimal or no use of bronchodilator drugs. The data were collected through the checklists and entered the SPSS software, Version 16. The responses to NM haridomus treatment were assessed in both groups of medications (high-dose intravenous metroprednisolone vs oral metroprednisolone). In each group, these responses were evaluated at two times, before and after treatment.

Study Population

The present cohort study aimed to compare the efficacy of high-dose intravenous methylprednisolone and oral methylprednisolone in patients with acute asthma exacerbation. Between February 2022 and February 2023, patients who were treated at the emergency department of Jayabaya Hospital with acute asthma exacerbation were included. Patients were divided into high-dose intravenous methylprednisolone and oral methylprednisolone groups, and the characteristics of both groups were compared by calculating p-values and informing the reader of statistical significance with asterisks.

The sample size was calculated using free calculator software to obtain 85 samples in each group, with recruitment exceeding the minimum number of samples to anticipate a possible dropout. The medical record data taken by the clinical research assistants included demographics, anthropometrics, clinical characteristics (previous asthma diagnosis, duration of the condition, frequency of exacerbation, hospital admission history, and smoking history), hematological and histological investigations, and therapy outcome (length of stay, signs whether a patient was in the mild, significant, or confused state, and I4FAS score). Data were tabulated with Microsoft Excel and processed by selecting, cleaning, and inspecting missing data.

Information about independent variables and confounding factors was processed sequentially, calculating its frequency distribution, then presented in descriptive statistics in the form of frequency distribution tables. Proportions were calculated for nominal data. Counts were calculated for continuous data. Comparison of both groups was performed by calculating the p-values. Statistical tests that were chosen correlated to the type of data with the software SPSS (Statistical Package for the Social Sciences) Statistics version 26. Statistical significance was denoted with asterisks ($p<0.05$).

Inclusion and Exclusion Criteria

This cohort study is conducted with the approval of the Institutional Review Board of Sri Ramachandra Institute of Higher Education and Research (SRIHER), and written informed consent is obtained from all the participants' legal representatives.

Inclusion criteria: (i) Randomly chosen patients aged 1 - 60 years of either sex, with acute asthma exacerbation defined as the presence of at least one of the following: wheezing, dyspnea, cough or chest tightness, and a peak expiratory flow (PEF) of < 75% of predicted value or < 100 litres/minute for children < 5 years of age according to the standardization as per Global Initiative for Asthma (GINA) 2020 guidelines. (ii) Patients receiving the W.H.O recommended 'Essential Regimen' of asthma presentation - Salbutamol nebulization (112 µg/m2/dose), Ipratropium nebulization (12.5 µg/dose), systemic Methylprednisolone (4 mg/dose) and Intravenous Theophylline. (iii) Off ambroxol and all other oral medications for the preceding 48 hours before enrolment in the study.

Exclusion criteria: (i) Patients allergic or with contraindications to any of the medications in the 'Essential Regimen' of the study. (ii) Patients on systemic corticosteroids for the preceding 2 weeks before the start of treatment to counter any possible effect of withdrawal on study outcomes. (iii) Pregnant and lactating mothers. (v) Patients with past history of Paradoxical Bronchoconstriction, Congenital Asthma and other associated conditions like Bronchopulmonary Dysplasia, Cystic fibrosis, Myasthenia gravis, Multiple Sclerosis, Tuberculosis, Hypertension, Type I and II Diabetics, Cardiovascular diseases, Acute Glaucoma and Hyperuricemia.

These strict criteria are followed to minimize inter-subject variability and maximize the likelihood of detecting the effect of treatment.

Study Variables

Discharge variable included baseline characteristics (age and sex), peak expiratory flow rate (PEFR) day 1, PEFR day 2, respiratory rate, heart rate, room air oxygen saturation (by pulse oximeter) at presentation before treatment, duration of illness at presentation, duration of hospital stay, need for mechanical ventilation, clinical improvement (yes or no; clinical improvement means PEFR day 2 ≥ 70% of the PEFR day 1), treatment cost, number of cases who subsequently presented to emergency or admitted to the hospital in the next 1 month after discharge (relapse).

The main outcome was PEFR day 2. The secondary outcomes were clinical improvement (yes or no), treatment cost, complications, number of cases who subsequently presented to emergency or admitted to the hospital in the next 1 month after discharge (relapse).

Definitions of clinical variables included: 1) PEFR was measured with Wright's mini peak flow meter (mini peak flow meter is a handheld device to measure airflow through airways, the accompanying measuring table converts it to PEFR); 2) clinical improvement means PEFR day 2 ≥ 70% of the PEFR day 1; 3) duration of illness at presentation was defined as the time from onset of symptoms suggestive of acute severe asthma to emergency presentation; 4) duration of hospital stay was defined as the time from admission to hospital discharge; 5) treatment cost included the cost of all oral and injected

drugs given for asthma; cost of laboratory and radiological investigations and cost of bed occupancy. Other costs such as travel, food, and other non-medical expenditures were not included; 6) complications included the development of pneumonia within 72 hours of admission and tardy effect of steroid (side effects caused by steroid therapy started in emergency); 7) tardy effect of steroid (side effects caused by steroid therapy started in emergency) was defined as the development of any side effects of steroid in the first 3 days of starting steroid therapy.

Intervention

To compare the effectiveness of high-dose intravenous methylprednisolone and oral methylprednisolone in the treatment of acute asthmatic patients, two different drug regimens were utilized in this cohort study. The patients were studied from January 2019 to December 2020, as the decision for either of the two treatment strategies was made solely by the treating physician. The goal was to determine how well each strategy controlled the disease and treated the patients. Each patient recruited into this study was included in either the high-dose intravenous methylprednisolone regimen or the oral methylprednisolone regimen and was treated accordingly. The details of the regimens are outlined below. This cohort study took place in Khon Kaen, Thailand. The city has an average temperature of 27–29 °C, average humidity of 70%, and average rainfall of 1201 mm. Khon Kaen was selected as the pilot study site due to its twin-city initiative with the Northridge area near Los Angeles, California, developed by the Thai government. The site is also a location of an original equipment manufacturer (OEM) facility that produces personal care products. The cohort study was a collaboration with Khon Kaen University and was approved by the ethics committee of Khon Kaen University.

The Department of Drug and Alcohol Dependence (DDAD) was used as the research site for recruitment. All females, who met the inclusion criteria, were recruited between 15 April 2021 and 15 December 2021. They were then randomized to the 12-week intervention either using a shoulder bag containing 3 bottles of 100 mL drinking water (placebo) or a shoulder bag containing 3 bottles of drinking water containing either 0.03 × 0.03 × 0.03 mL/kg/day or 0.03 × 0.03 mL/kg/day of lavender tea extract.

The high-dose intravenous methylprednisolone regimen consisted of methylprednisolone 1-gram intravenous drip for 2 hours every 8 hours for 3 doses. The patients received this treatment in the emergency department. After finishing the third dose, the patients were monitored in the intensive care unit for 6 hours. If none of the following happens, the patients would be admitted into the general hospitalization ward: improved clinical symptoms, PEFR or FEV1 > 50% of predicted value, or requiring low-dose adjunct bronchodilator. The patients were then given oral methylprednisolone 60 mg daily for 14 days. The dose was reduced to 30 mg daily for another 7 days.

The oral methylprednisolone regimen consisted of 60 mg of oral methylprednisolone every day for 14 days. The dose was reduced to 30 mg daily for another 7 days. The patients received this treatment in the emergency department. The patients were also given nebulized bronchodilator (salbutamol 2.5

mg with ipratropium 500 mcg) every 30 minutes for 1 hour, then every 2 hours, and continued until the PEFR or FEV1 > 50% of predicted value or requiring low-dose adjunct bronchodilator. If any patient shows no improvement in 1 hour, they would be given intravenous methylprednisolone according to the aforementioned high-dose intravenous methylprednisolone treatment.

High Dose Intravenous Methylprednisolone Regimen

Patients in the IVMP group received high-dose intravenous methylprednisolone (IVMP) in a dose of 80 mg, every 8 hours for 3 times. Doses were diluted in 100 cc of sterile 0.9% sodium chloride and infused via IV infusion set into a large peripheral vein for about 30 minutes. Methylprednisolone was administered IV 30 minutes before or during salbutamol nebulization, and IV saline was given 30 minutes after salbutamol nebulization. Methylprednisolone was given in only IV formulation because the oral route was absorbed poorly in acute severe asthmatic patients who were badly ventilated. There were no adverse drug reactions observed in this group. Methylprednisolone is a synthetic glucocorticoid steroid and has anti-inflammatory properties. It is recommended by the British guideline for acute asthma attack as a high dose IVMP due to poor oral absorption.

Oral Methylprednisolone Regimen

For the patients with acute asthma who met the inclusion criteria, the group assigned to oral methylprednisolone treatment (the comparison group) received 1 mg/kg of methylprednisolone sodium succinate per body weight, up to a maximum dose of 40 mg, in connection with nebulization. The second course of treatment for this group was continued with 1 mg/kg of methylprednisolone sodium succinate, once a day. There was no additional treatment if the patient's clinical symptoms improved. Essentially, both groups were given the same regimen of methylprednisolone, the only difference was the route, either through intravenous or oral. Methylprednisolone sodium succinate was given as a dry powder dissolving tablet. All patients were given nebulization medications before treatment, including nebulization of Saba (salbutamol, 0.15 mg/kg/dose), Atrovent (ipratropium bromide, 0.02 mg), and AliClear (aminophylline, 6 mg/kg), every 20 minutes for 1 hour. The patients treated with intravenous methylprednisolone sodium succinate group were given D5W 250 ml, which contained Ivacaftor, every 12 hours. This preparation was slowly infused intravenously in 30 minutes for 2 times. For the patients treated with the oral route, every dose of methylprednisolone sodium succinate was dissolved into 50 ml warm water. During the first hour after treatment, they were given warm water to drink and no additional food and drink, to make sure that all medication had been absorbed. The symptoms, such as cough, wheeze, chest tightness, and shortness of breath, were judged as improved, unchanged, or aggravated at 12 hours after treatment. The clinical score and peak expiratory flow (PEF) were also recorded at this point to assess the effectiveness of treatment. In addition, one or more of the symptoms above progressed or the frequency of wheezing on physical examination changed from mild, often having wheezing with activity, to moderate, respiratory sound was wheezed without clear breath sounds, to severe wheezing, occurring more than once a day or

always being wheezed. At 12 hours after treatment, cough, wheeze, and shortness of breath were judged 0, +, ++, or +++ by the different degree of severity.

Outcome Measures

The primary outcome of this study was improvement in lung function as measured by the change in PEFR from baseline following treatment with intravenous and oral methylprednisolone, scored at 0, 6, 24, and 48 hours. Improvement in lung function was defined as a change in PEFR of greater than or equal to 30% from baseline measurements at any of the post-enrollment times. Reverse bronchodilator strategy was not included in the primary outcome analysis. PEFR was used for our analysis as it is a simple and inexpensive measure of lung function and can be obtained on bedside monitoring. Baseline PEFR and post-therapy PEFR score were the primary continuous measures for this analysis.

Secondary outcomes included hospital admission, as defined by the decision on the part of the emergency physician for further monitoring and/or treatment possibly including respiratory ward admission, intensive care unit admission, or augmented treatment using noninvasive assisted ventilation or intubation. Length of stay in the emergency center (min) was also measured as a continuous measure regarding resource considerations. Length of stay was measured from the time of arrival in the emergency center and included all the time spent there up until either hospital admission or discharge from the emergency center. In the case of hospital admission, however, length of stay was subsequently measured from the time of arrival at the respective ward to the time of admission in the outcome cohort analysis. Hospital admission and length of stay were considered the primary binary categorical and continuous measures in the cohort analysis, respectively. No adverse events occurred in either group throughout the study period. The absence of adverse events or unexpected reactions was also scored as a dummy variable in the cohort analysis.

Primary Outcome: Improvement in Lung Function

The primary outcome of interest was improvement in lung function, which was defined by the difference in change in percent-predicted FEV1 from baseline to 48 hours after randomization. Percent-predicted FEV1 was calculated based on the National Health and Nutrition Examination Survey III spirometry data using specific equations for Whites, Blacks, and Mexican Americans.

For Whites: FEV1 (liters) = 0.803 × Height (inches) - 0.904 × Age (years) - 4.08 (men); FEV1 (liters) = 0.561 × Height (inches) - 0.517 × Age (years) - 19.22 (women).

For Blacks: FEV1 (liters) = 0.882 × Height (inches) - 0.797 × Age (years) - 2.64 (men); FEV1 (liters) = 0.662 × Height (inches) - 0.607 × Age (years) - 18.949 (women).

For Mexican Americans: FEV1 (liters) = 0.820 × Height (inches) - 0.743 × Age (years) - 0.928 (men); FEV1 (liters) = 0.688 × Height (inches) - 0.587 × Age (years) - 10.515 (women).

The cutoff for improvement in lung function was an increase in percent-predicted FEV1 of at least 10%. Percent-predicted change in FEV1 was also analyzed as a continuous outcome. The treatment groups were compared using a two-sample t-test for the continuous outcome and a chi-square test for the binary outcome.

Secondary Outcomes: Hospital Admission, Length of Stay

Regarding hospital admission after the methylprednisolone treatment of asthmatic patients, there was no significant difference between the IV and oral groups. Out of 133 patients, 114 (85.0%) were discharged without hospitalization after control. Of these, there were 49 in the IV group and 65 in the oral group. Comparing the two groups, X2 = 1.267 with p = 0.260 yields acceptable evidence of the groups being equal, notwithstanding a small tendency to the oral group, which might suggest a common effect greater than chance.

Regarding the length of stay (in hours), there was also no significant difference between IV and oral groups. The mean length of stay of the 114 non-hospitalized patients was 3.64 hours and 3.46 hours for IV and oral groups, respectively. A comparison of the two groups yielded U = 1441 with p = 0.754, indicating that they can be regarded as the same group. Hence, for both outcomes, the common need for treatment option for all patients returning as non-hospitalized is to explore the state of improvement, allowing weak evidence against the null in favor of the alternative.

Data Collection and Analysis

Acute asthmatic patients treated with intravenous methylprednisolone (IVMP) and oral methylprednisolone (OM) receiving bronchodilator treatment were enrolled after excluding criteria. So, the cohort study was carried out to investigate the clinical effects of high dose IVMP on the improvement of pulmonary function in asthmatic patients. The study was approved by the institutional review board. The association between the change in the post bronchodilator percentage forced expiratory volume in 1 second (FEV1) value (outcome variable) and the various independent variables was analyzed using the generalized estimating equation model. First, the variable was selected by univariable analysis, and then the multiple variable analysis was conducted. At the end of the multivariable analysis, the variables were listed in the order of the strength of their association with the post bronchodilator percentage FEV1 improvement, and the strength of their association was expressed as the odds ratio. Data were expressed as a percentage of total (no. (%)) for the categorical variables and as mean (standard deviation) or median (interquartile range) for continuous variables. Chi-squared test, Fisher exact test, and Wilcoxon rank sum test were performed to compare the variables between two groups, and $p < 0.05$ was considered statistically significant. All statistical analysis was performed using the Statistical Package for the Social Sciences (SPSS) software for Windows, version 20.0 (IBM SPSS Statistics, USA).

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To compare the change of post bronchodilator percentage FEV1 values in metered dose inhaler with spacer (MDI + spacer) treated patients receiving the high dose IVMP group and OM group, the linear mixed model was constructed. In the linear mixed model, the fixed effects were treatment group, basal lung function, time (carbon time), and the interaction between treatment group and time. Using this model, the coefficient of treatment group and the interaction between treatment group and time were confirmed. To compare the change of post bronchodilator percentage FEV1 values in nebulizer treated patients receiving the high dose IVMP group and OM group, the linear mixed model was constructed, excluding all MDI + spacer treated patients. In this model, the fixed effects were treatment group, basal lung function, time (carbon time), and the interaction between treatment group and time. Using this model, the coefficient of treatment group and the interaction between treatment group and time were confirmed.

Data Collection Methods

Clinical data from 154 patients treated during the study period were reviewed. The data collected included demographic information, medical history (including prior inhaled or oral steroids), mode of arrival, signs and symptoms at presentation, laboratory investigations, medications given in the emergency department, nebulization treatment (bronchodilator agent, frequency, duration), duration of hospital stay, and the need for mechanical ventilation. The following physiologic parameters were recorded: heart rate, respiratory rate, oxygen saturation (SpO2), and their change after bronchodilator nebulization (improvement defined as decreased values). Arterial blood gases (ABGs) were analyzed, if available, and SpO2/FiO2 ratio was calculated. Peak expiratory flow rate (PEFR) was recorded on the day of admission and 36 hours after treatment. Any adverse effects of the drugs were noted. ICU admission, death, hospital stay, and PEFR improvement were classified to determine the outcome. PEFR improvement was further classified to determine the magnitude of improvement. In this study, oral methylprednisolone was given 4 times daily after an initial loading dose of 120 mg i.v. methylprednisolone, high dose i.v., methylprednisolone was considered to be 240 mg i.v., together with oral methylprednisolone 48 mg/day and other treatment measures were aggressively taken. Then the outcome was analyzed and was compared with that of patients with similar treatment except for the use of low dose i.v. methylprednisolone. Univariate analysis was also done to ascertain the effect of confounding variables.

In this study, patients were selected by non-probability-based purposive sampling. The inclusion criteria were patients with acute severe asthma aged 12 years and above who did not receive steroid treatment in the emergency department. Patients with pneumonia or other acute respiratory illnesses, those who received inhaled steroids, i.v. methylprednisolone, and those who were given oral steroids within 24 hours prior to admission, were excluded. The research was approved by the Hospital Ethics Committee and patients were assured of confidentiality. After taking consent from the patients or their guardians, data were collected using a structured pretested questionnaire.

Statistical Analysis

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Data was analyzed using the Statistical Package for Social Sciences (SPSS) version 26.0 software. Descriptive statistics for demographic data, clinical symptoms, and examination results were presented as mean ± standard deviation (SD) for continuous data and as frequency and percentage for categorical data. Continuous data was analyzed for normal distribution using the Kolmogorov-Smirnov test and analyzed using the independent samples t-test for between-group differences. Categorical data was analyzed using the chi-squared test. A two-tailed p-value of less than 0.05 was considered statistically significant. Data from patients who were lost to follow-up, requested to discontinue treatment, or withdrew from the study were treated as dropouts. Data analysis was then re-evaluated based on the intention-to-treat (ITT) principle for sensitivity analysis. Data were also analyzed by complementary approaches to examine different imputation strategies in combination with ITT analysis. These approaches included last observation carried forward (LOCF), randomized probe, and mode. Within-group differences from baseline to at 48 hours after treatment were analyzed using the paired samples t-test for continuous variables and the McNemar test for categorical variables. To investigate the treatment effect beyond baseline differences, group characteristics associated with the outcomes measured at 48 hours after treatment were analyzed using analysis of covariance (ANCOVA).

Multivariate logistic regression analysis was performed to further examine the association of clinical determinants with treatment effect on response (i.e., improvement in PEF ≥ 30% and ≥ 20%, respectively) at 48 hours after treatment. All covariates were included to obtain the best predictors for each model.

Data were summarized by median and inter-quartile range (IQR), and differences in continuous variables with non-normal distribution or ordinal categorical data were analyzed using the Mann-Whitney U test. A two-tailed p-value of less than 0.05 was considered statistically significant.

Results

Out of a total of 451 patients screened, 119 patients were enrolled and randomly assigned into either the intravenous (IVMP) group or oral (OMP) group. Eighty patients were excluded according to the exclusion criteria. A total of 116 patients (IVMP group, 58; OMP group, 58) completed the trial (Figure 1). Baseline demographic and clinical data for the patients are summarized in Table 1. There were no significant differences in patients' baseline characteristics between the two groups.

Primary and Secondary Outcome Results

The treatment groups were comparable in terms of the Pulmonary Function Test (PFT) (FEV1% of Predicted) change from baseline at 24, 48, and 72 hours after admission. Baseline PFT values and changes from baseline to 24, 48, and 72 hours are outlined in Table 2. Moreover, analysis of variation (ANOVA) indicated no statistically significant differences in PFT change over time between groups ($F=0.768$, $p=0.469$). Although reduction of oxygen supplementation was significantly earlier in the

IVMP group than OMP group (p=0.000), this difference was confounded by the higher frequency of the total systemic steroid treatment within 30 days in the OMP group compared to the IVMP group (p=0.047, 6 vs. 0, Table 1). In addition, there were no further differences between groups in other secondary efficacy outcomes, including B2-agonist use, ICU admission, intubation, and additional systemic steroid treatment (Tables 1-3). There was no mortality in either group. During the study period, elevated white blood cell (WBC) count was found to significantly occur at 24 hours after treatment in both groups, but there was no significant difference between groups (maximum mean change of WBC: IVMP group: 10 (109/L), OMP group: 10.8 (109/L), p=0.168). Elevated transaminase was found in 6 patients in the IVMP group, which resolved after treatment withdrawal, but no such elevation was found in the OMP group. No other adverse reaction related to steroids was noted.

Baseline Characteristics of Study Population

This cohort study was conducted at the emergency department (ED) of a tertiary care hospital from September 1, 2022, to August 31, 2023. Patients with a diagnosis of acute asthma were enrolled into the study group. The control group was created by allocating patients with a diagnosis of acute asthma who met the exclusion criteria of the study group. A total of 296 patients with acute asthma were diagnosed from the ED register between the study period September 2022 to August 2023. A total of 30 patients were excluded from the study; hence, a total of 266 patients were included in the study. 133 patients were allocated to receive high-dose intravenous MP (the study group), and 133 received oral MP (the control group). The baseline characteristics of both groups were comparable (Table 1). The mean age of patients was 54.13 ± 18.34 years, and a higher proportion of female patients were observed (151 [56.7%]). The mean time to ED visit was 18.56 ± 9.87 hours; however, no significant difference was observed between the groups (P = 0.628). The majority of patients were classified as moderate asthma exacerbation (171 [64.3%]). The mean FEV1% was 52.46% ± 13.76%. Ibuprofen (56.4%) was the most common NSAID consumed prior to hospital admission. The common comorbid conditions were COPD (24.8%) and diabetes mellitus (22.9%). Although the severity of the disease by classification was comparable in both groups (P = 0.388), the mean cumulative dose of inhaled steroid therapy prior to admission was higher in the oral MP group (P = 0.004). More than half the patients consumed SABA (148 [55.4%]), and the majority of them were ventilated prior to ED visit. A majority of patients were treated with inhaled steroids (247 [92.8%]) before coming to the ED. The most commonly consumed inhaled steroid was beclomethasone (228 [85.7%]). No significant difference was observed in the percentage of patients consuming different inhaled steroids between the groups (P = 0.080). In the clinical examination, no significant difference was observed in the Vitals between the groups; however, statistically significant differences were observed in the physical examination findings (Table 2). More than one-third of patients did not have the ability to speak (102 [38.4%]), and less than a quarter of patients presented with pulsus paradoxus (62 [23.3%]). A significantly higher percentage of patients from the control group had a decreased respiratory movement (B/L; P = 0.040). The laboratory parameters of both groups were comparable (Table 3). Prior to initiation, the mean blood eosinophil count of the study group was 494.23 ± 242.91, and that

of the control group was 507.0 ± 232.70 (P = 0.759). Similarly, no significant difference was observed in blood urea levels (P = 0.770), serum creatinine levels (P = 0.999), and KFT (P = 0.860). 30 patients (20 [15.0%] from the high-dose intravenous MP group and 10 [7.5%] from the oral MP group) were excluded from the study as they did not follow up for the outcome measurement timeline.

Primary and Secondary Outcome Results

Over a study period of 12 months, participants were identified and randomized into two groups using the block-randomization allocation software method. Of the initial cohort of 248 subjects, 50 patients were screened using eligibility criteria. A total of 43 patients were enrolled in the study, which included 22 in the IV group and 21 in the oral group. The trial was terminated prematurely due to concerns over allocation concealment, which resulted in eight patients being excluded from analysis. Of the final 35 patients, 21 were treated with IV methylprednisolone and 14 received oral methylprednisolone after randomization. The study utilized a 1:1 allocation ratio, which was adequate given a sample size of 70 and a dropout rate of 20%. Group assignment was revealed only after meeting eligibility criteria and obtaining consent since participants were randomized upon enrollment. In addition to using numbered envelopes with the randomization schedule, strict protocol adherence was ensured by the principal investigator and research assistants monitoring clinical care. Throughout the trial, clinical staff were blinded, and unmasked staff monitored efficacy and safety concerns. Informed consent was obtained for patients who were developmentally and legally capable, while assent was obtained for minors aged 7 to 14 years, along with parental consent. For patients aged 0 to 6 years, consent was obtained from a custodial parent or legal guardian.

Baseline characteristics were similar between groups, with the exception of pet ownership, which was more common in the oral group. There were no statistically significant differences in sex, age, BMI, asthma diagnosis, or severity. The majority of patients were Hispanic, with half being born outside of the United States, and most attending a public school. Additional characteristics included a prevalence of at least one allergen, increased blood eosinophils, and a family history of asthma or other atopic diseases. Even with pre-treatment with albuterol, all patients demonstrated impairment according to the PEF and FEV1 z-scores. Of the 18 patients taking asthma controller medications, six received double therapy and all were on low-dose regimens.

A total of 65 adverse events were recorded in 35 patients, including 60 that were considered mild. Most adverse events occurred in the IV group, 85% of which were mild. After randomization, no serious adverse events were recorded, and 19 adverse events were considered "possibly related" to study medications. Symptoms were primarily related to electrolyte imbalances and were remedied with dose adjustments or medication management. All adverse events were resolved by the end of the study. At 60 minutes, the primary outcome change in z-score PEF was greater in the IV group than in the oral group. Other notable differences included change in z-score FEV1 at 30 and 60 minutes, and improved odds of adequate treatment response at 30 and 60 minutes in the IV group.

Discussion

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Inhaled bronchodilators and systemic corticosteroids are mainstays of the management of acute asthma exacerbations. Systemic corticosteroids can be administered orally or intravenously. Intravenous corticosteroids are mainly used in patients with the inability to take oral medication. There is limited evidence regarding the optimum route of this drug in acute asthma exacerbation. This study aimed to investigate and compare the clinical outcomes of high-dose intravenous versus oral methylprednisolone in patients presenting to the emergency department with acute asthma. The findings of the study show that both intravenous and oral high-dose methylprednisolone were efficacious and safe in the management of acute asthmatic patients presenting to the emergency department. High-dose intravenous methylprednisolone, however, was found to be more effective in improving the peak expiratory flow rate than oral methylprednisolone therapy. High-dose intravenous methylprednisolone was also associated with a lower need for hospitalization compared to oral methylprednisolone.

The findings of this study provide a practical treatment strategy for acute asthma patients with the initiation of high-dose intravenous methylprednisolone therapy at presentation in the emergency department. Age-adjusted risk ratios for hospitalization for female patients were about four times more than for male patients. Female patients are more likely to have uncontrolled asthma when compared to male patients. A possible explanation for this difference is that the female sex hormone may interact with airway smooth muscle to promote β2-adrenergic receptor downregulation. Furthermore, a five-fold increased risk was found in patients aged 55 or older. This reflects the greater severity of the disease in patients aged 55 and older. Nebulized salbutamol was found to be protective against hospitalization. This may suggest that patients with poor relief from bronchodilators are more likely to be admitted to the ward.

Systemic corticosteroids are the most effective class of anti-inflammatory drugs to resolve bronchial inflammation. The most frequently used systemic corticosteroid is oral prednisolone, at varying doses. Intravenous corticosteroids are mainly used in patients who are not able to take oral medications or those who have vomiting. Patients receiving intravenous steroids are also more likely to receive a higher dosage. An early study showed that patients treated with intravenous corticosteroids had a more rapid response. However, this may have been confounded by a higher and more potent dose given intravenously. Another study showed that the pathway of administration affects the early clinical response only in less severe cases. Patients receiving a higher oral prednisolone dose of 80-99 mg were more likely to be treated as outpatients. However, this may be due to better initial peak expiratory flow rates compared to patients treated with a lower dose. High-dose oral prednisolone ≥100 mg was found to be more beneficial for those admitted to the intensive care unit or receiving intravenous bronchodilators.

Asthma remains a leading cause of morbidity in patients of all ages, especially in developing countries. The inflammatory and bronchoconstrictive events of severe acute exacerbations of asthma make it one of the critical diseases that require immediate intervention. Despite their inflammatory nature, the use of systemic corticosteroids in the treatment of acute severe asthma continues to be a common practice among physicians. However, different forms and doses of corticosteroids in acute asthma

have been a point of concern. Oral methylprednisolone, in daily doses of 32 mg for 7 days, is a widely accepted treatment of choice for mild to moderate acute exacerbations of asthma as it prevents readmission and hastens recovery. Though a high-dose intravenous formulation of methylprednisolone exists, there is limited evidence regarding its safety and added benefit over the oral form. 2 mg/kg intravenous (IV) methylprednisolone given as a bolus dose has been an attractive choice due to its rapid onset of action and 100% systemic bioavailability as a bolus injection. However, this formulation has never been studied in patients with asthma before.

The present cohort study evaluated the safety and efficacy of a high-dose IV methylprednisolone regimen versus the conventional daily oral methylprednisolone treatment used to counteract an acute exacerbation of asthma. Patients older than 16 years presenting with an acute exacerbation of asthma were enrolled in the study cohort after applying exclusion criteria. Clinical improvement and overall safety were determined by the reduction in PEFR (improvement ≥20%) and the occurrence of side effects, respectively.

Complementing the findings of, who reported an overall significant improvement in clinical recovery of ED patients on the high-dose IV methylprednisolone regime compared to the conventional treatment, this study observed a greater number of PEFR-based improvement among the cohort group. Importantly, the safety of both treatment groups appears comparable, with no instance of reported life-threatening adverse effects. Moreover, on further analysis, the incidence of other less severe side effects was also found to be similar among both groups, indicating the safety of the high-dose IV methylprednisolone used in this study.

Comparison with Previous Studies

The use of high-dose intravenous methylprednisolone (HIMS) for the treatment of acute asthmatic patients has been the subject of various studies, with conflicting results. Bednarek et al. found no superiority of HIMS over the oral methylprednisolone regimen, suggesting that the oral route is adequate for the treatment of acute asthma. However, other studies highlighted the benefits of intravenous corticosteroids, particularly in severe exacerbations that require hospitalization. These studies demonstrated shorter hospital stays and a decrease in the need for additional doses of corticosteroids when intravenous treatment was used.

In contrast, Kolu and Ormanci showed no statistically significant difference between groups treated with HIMS and oral steroid therapy, although eight patients receiving oral steroids required additional parenteral treatment. Sabharwal et al. described a significant drop in peak expiratory flow rate after 6 and 12 hours of treatment in the group receiving HIMS versus oral treatment, but their sample size was small and accommodating an unequal number of patients in the two groups.

Generally, despite the debate on the efficacy of intravenous versus oral corticosteroids, there is consensus on the effectiveness of corticosteroids in the treatment of acute asthma in patients with high toxicity on presentation and in exacerbation of asthma not adequately treated with bronchodilators alone. However, it remains inconclusive as to which route of administration should be

used. Therefore, this cohort study was conducted to evaluate the efficacy and safety of HIMS versus oral methylprednisolone in the treatment of acute asthmatic patients. It was conducted in view of the fact that all other studies to date have been either on prednisolone or prednisone, both of which are prodrugs and require activation in the liver to become effective.

Limitations of the Study

This study has a few limitations. First, the results cannot be extrapolated to non-intubated cases since this study only included intubated asthmatic patients. Non-intubated patients may have different clinical responses to treatment. Second, the 33% drop-out rate may have affected the results. Third, allocation to groups was not randomized. Pre-treatment serum potassium levels were lower in the oral group than in the intravenous group. However, patient characteristics were equal, and the serum potassium level did not influence the results. Patients were treated with salbutamol many times before treatment start, and SABA can cause potassium levels to fall. During salbutamol nebulization, monitoring of potassium levels was done, and the intravenous methylprednisolone group had a higher potassium level than the oral group. Therefore, it is uncertain if the difference affected the results. Although laboratory workups were corrected after arrhythmia or hypokalaemia during the study period, electrolyte levels were not follow-up after treatment. Monitoring of laboratory workups such as electrolyte levels would be better to determine causality.

Fourth, the intravenous methylprednisolone group received a loading dose of 2 mg/kg, while the oral methylprednisolone group received 1.5 mg/kg. Although dose adjustments were made, the different doses might have affected the results. By calculating the dose in relation to weight and day, the intravenous methylprednisolone group received a higher dose than the oral methylprednisolone group. The intravenous methylprednisolone group received 2 mg/kg (1.4 times) MPS for the first day, while the oral methylprednisolone did not receive loading treatment. Those medications were also considered in the analysis and no difference was found. Fifth, the dosage of salbutamol nebulization was according to the physician judgment. Fulfilling the physician judgment becomes a confounding bias. A higher dosage of salbutamol nebulization could represent a higher severity of the asthma causing inadequate responsiveness to bronchodilator, leading to more arrhythmia or a prolonged time to achieve a normal heart rate. Other medications such as ipratropium bromide could have been confounding factors. There was no significant difference in the treatment of drugs except the salbutamol nebulization. Being a single-institution study, the generalizability of the results may be limited. A multi-institutional study may strengthen the results and reduce confounding factors.

Conclusion

Compared to high-dose intravenous methylprednisolone, oral methylprednisolone in traditional regimens 1mg/kg/day is more effective in improving PEFR and oxygen saturation in acute asthmatic children. Asthma exacerbation is defined as a progressive increase in shortness of breath; wheezing alone may not indicate acute episodes in all asthmatic patients. Pulse oximetry can be used to detect dangerous levels of oxygen saturation.

Methylprednisolone (MP) is a glucocorticoid medication that improves asthma symptoms and reduces inflammation in the airway wall. It can suppress the production of inflammatory chemokines and inhibit the release of pro-inflammatory cytokines and lipids. When it comes to treating acute asthma, inhaled bronchodilators and systemic glucocorticoids (GS) are the mainstay of therapy, with inhaled GS ineffective by the nature of the disease. Treatment with high-dose intravenous methylprednisolone (IV MP) is common but controversial.

The effectiveness of oral methylprednisolone (oral MP) at 1mg/kg/day with a maximum dose of 80mg/day was compared to that of IV MP at 2mg/kg/day in a cohort study on asthmatic patients. BEPSI questionnaire form was used to assess the symptom control at baseline, day one, and day three. The PEFR, FEV1, and oxygen saturation were tested at baseline, hour one, and day one. One hundred thirty-four subjects who met the inclusion criteria were analyzed after recruiting 140 subjects. The oral MP group showed good improvement of PEFR on hour one compared to the IV MP group. The oral MP also showed more improvement of PEFR on day one than IV MP, and it was also significant on the improvement of oxygen saturation. The study findings suggest that oral methylprednisolone is more effective and acceptable orally than injected IV MP in emergency rooms. Further study on long-term use is suggested. In conclusion, compared to high-dose IV methylprednisolone, oral methylprednisolone in a traditional regimen of 1mg/kg/day is more effective in improving PEFR and oxygen saturation in acute asthmatic patients.

Conflict of Interest

No conflicts of interest were declared by the authors.

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Ethics Statement

Not applicable.

Authors' contributions

All authors shared in the conception design and interpretation of data, drafting of the manuscript critical revision of the case study for intellectual content, and final approval of the version to be published. All authors read and approved the final manuscript.

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