SYNOPSIS

ON

COMPARISON OF EFFICACY OF HYDROCORTISONE AND METHYLPREDNISOLONE IN ACUTE SEVERE ASTHMA

Presented By

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COVERING LETTER FOR RESEARCH PROTOCOL

The Dean,
PG committee
Ziauddin University Hospital
Karachi, Pakistan

Respected Sir,

Please find enclosed herewith a copy of synopsis titled "*COMPARISON OF EFFICACY OF HYDROCORTISONE AND METHYLPREDNISOLONE IN ACUTE SEVERE ASTHMA.*"

Prepared by Dr. Inayat as a prerequisite for MD in EMERGENCY MEDICINE. Details of candidate and supervisor are given below.

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This is certified that this study is not being duplicated in the same institute.

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Supervisor's sign with stamp Co: Supervisor's sign with stamp

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Sincerely

COMPARISON OF EFFICACY OF HYDROCORTISONE AND METHYLPREDNISOLONE IN ACUTE SEVERE ASTHMA

INTRODUCTION

BACKGROUND:

Asthma is one of the commonly reported chronic, heterogeneous and non-communicable disease of airways, diagnosed in both adults and in children. Asthma is characterized with airflow obstruction, bronchial hyperresponsiveness and inflammatory changes (Hsieh A et al., 2023, Guida G et al., 2023). Global Initiative for Asthma (GINA) defined the asthma on presence of different respiratory symptoms including wheezing, shortness of breath, chest tightness and cough along with expiratory airflow limitation (GINA, 2021).

Asthma is significantly associated with increased rate of morbidity and mortality among the population of world (Guida G et al., 2023, Jarab AS et al., 2023). Global report of asthma, includes the asthma among leading cause of morbidity, life-long disability and mortality and ranked asthma as sixteen leading cause of life-long disability and twenty eight among the diseases which put extra burden on patients and health care system (GINA 2021). Currently, more than three hundred million people of world are living with asthma and further one hundred million will be affected with asthma till 2025 (Dharmage SC et al., 2019). World Health Organization (WHO) reports 455,000 deaths due to asthma in year 2019 that makes 0.8% of total deaths among which 97.46% were reported among the asthma patients with age of ≥ 15 years (WHO 2020).

Acute severe asthma is a very common and sudden onset of severe asthma in which asthmatic patient does not recover even after taking the medicine and has to be hospitalized in emergency, which can sometimes be fatal (Bosi A 2021 and Guilleminault L et al., 2023). Early diagnosis followed by intervention is very important in appropriate management of acute severe asthma before it becomes severe and life threatening (Ramsahai JM et al., 2019 and Cevhertas L et al., 2020). Asthma exacerbations of asthma are responsible for more than 1.8 million admissions in hospitals per year throughout the world (Zaidan MF et al., 2020).

In order to lower ICS dosages, control asthma symptoms, and lower the risk of exacerbation for asthma patients, leukotriene receptor antagonists and other controller therapies—mostly long-acting b2-agonists (LABAs) and ICS—are now the main therapeutic interventions for persistent asthma (GINA 2019). Patients with asthma who are not controlled by medium- to high-dosage inhaled corticosteroids plus controller medications are advised to receive add-on treatments, which were traditionally long-acting muscarinic antagonists or low-dosage oral corticosteroids (prior to the introduction of targeted biologics) (GINA 2019).

Consequently, benralizumab, an anti-IL-5 receptor-directed cytolytic therapy, and mepolizumab and reslizumab, anti-IL-5 treatments, were licenced for the management of severe eosinophilic asthma(Langton D et al., 2023). Dupilumab, an anti-IL-4 and anti-IL-13 therapy, was most recently approved by the FDA in 2019 to treat moderate-to-severe eosinophilic asthma or asthma dependent on oral corticosteroids (FDA 2019). In their respective target patient populations, these targeted biologic treatments have shown improved specificity for attaining disease control by lowering the risk of exacerbations and the need for rescue medication and oral corticosteroids, with minimal adverse events. (Shah PA et al., 2023)

Glucocorticoids are the drugs used for inhibiting inflammatory processes and are most commonly utilized in management of asthma exacerbations (McDowell PJ et al., 2021). Early and appropriate use of glucocorticoids including hydrocortisone and methylprednisolone is very important and can be considered for short and long term asthma treatment (Price D et al., 2020, Matsumura Y, 2023 and Bourdin A et al., 2019).

Due to their anti-inflammatory properties, inhaled corticosteroids (ICS) have long been the cornerstone of asthma treatment. Acute asthma exacerbations are also treated with systemic and ICS. The use of systemic corticosteroids in the early management of moderate-to-severe acute asthma upon ED presentation is advised by a number of international guidelines for asthma management. On the other hand, the use of ICS in the treatment of acute asthma has been investigated in a variety of settings, with mixed results. (Bigoni T et al., 2023).

STATEMENT OF THE PROBLEM:

In our population, lack of education, poverty, expensive medications and lack of health care facilities are important aspects that leads towards the poor control of sign and symptoms of asthma, It reduces the adherence of asthmatic patients towards medications and improper utilization of healthcare services that increases the morbidity and mortality in asthmatic patients. Lack of researches on asthma, its appropriate management with available drugs is also very important issue that should be resolved, and researches should be conducted.

RESEARCH QUESTIONS:

Is hydrocortisone more efficacious then methylprednisolone in the management of acute severe asthma?

RESEARCH OBJECTIVE:

To compare the efficacy of hydrocortisone v/s methylprednisolone among patients with acute severe asthma presenting at tertiary care hospital, Karachi.

NULL HYPOTHESIS:

There is no difference in efficacy of hydrocortisone and methylprednisolone in the management of acute asthma.

ALTERNATE HYPOTHESIS:

There is a difference in efficacy of hydrocortisone and methylprednisolone in the management of acute asthma.

RATIONALE:

The study will compare the efficacy of hydrocortisone v/s methylprednisolone in management of patients presented with acute severe asthma in emergency. A local study was conducted by Ali L et al., in 2009, after that there is a big research gap exists at national level although international literature is available on the same but it can not be generalized to our population due to socio, geographic and economic differences so there is dire need to conduct this study this gives a strong rationale to implement it in our settings.

SIGNIFICANCE OF STUDY:

As we know that, patients presented with severe acute asthma are at a higher risk of asthma exacerbation with poor control over respiratory symptoms, decreases the adherence towards medications as well as improper utilization of healthcare services,

that increases the risk of morbidity, life-long disability and mortality. So, management of acute severe asthma in emergency with appropriate drug either hydrocortisone or methylprednisolone is very important, and it can decrease the risk of morbidity, life-long disability and mortality.

OPERATIONAL DEFINITION:

1. **ACUTE SEVERE ASTHMA:** A patient presented with sudden onset of severe asthma symptoms including wheezing, shortness of breath, dyspnea, or coughing bouts and confirmed on PEFR <40% on spirometry at the time of presentation.
2. **HYDROCORTISONE:** A drug used in dose of 200 mg bolus followed by three doses of 100mg at six hour interval for next 24 hours given intravenously for treatment of acute severe asthma.(Ali L et al., 2009)
3. **METHYLPREDNISOLONE:** A drug used in dose of 125 mg single dose will be administered intravenously within half an hour of admission for treatment of acute severe asthma.(Ali L et al., 2009)
4. **EFFICACY:**

   Outcome variable efficacy will be evaluated as follows:

   a. **Improved PEFR:** PEFR > 65% will be labeled as improved PEFR.

   b. **Time to achieve improved PEFR:** Time taken from baseline (first PEFR at the time of admission) to achieve improved PEFR.

REVIEW OF LITERATURE

Gillani et al. (2022) conducted a study comparing nebulized corticosteroids (Group I) and systemic corticosteroids (Group II) in asthmatic patients. After two weeks, Group I showed a shorter mean hospitalization (1.5±3.14 days) and reduced disease severity by 4.1±5.14, while Group II had 2.8±9.31 days of hospitalization and a decrease of 5.1±5.12 from 8.3±6.31 in disease severity. The study concluded that nebulized steroids were more beneficial and effective in reducing disease severity and hospital stay. (Gillani S et al., 2022)

Doymaz et al. (2022) conducted a randomized trial on three asthmatic drugs (methylprednisolone, dexamethasone, and hydrocortisone). Among 61 patients aged 1 to 21 years, all three drugs demonstrated equal efficacy with standard doses. (Doymaz S et al., 2022).

Bleecker et al. (2020) highlighted in a review that oral and systemic corticosteroids are overused in treating asthma, especially in severe cases. The study emphasized the need for a shift to biologic treatments, such as omalizumab, to reduce the risk of adverse events associated with corticosteroid use. (Bleecker ER et al., 2020)

Hall et al. (1995) conducted a randomized prospective study on the management of acute severe asthma, comparing hydrocortisone and methylprednisolone. The research concluded that hydrocortisone was more effective, showing faster time to achieve maximum peak expiratory flow rate (PEFR) at 19 versus 23 hours, higher maximum PEFR at 81.5 ± 20.3 versus 81 ± 21.6%, and a shorter hospital stay at 30 versus 36 hours. (Hall CM et al., 1995).

Aggarwal et al. (2010) conducted a randomized prospective study on the management of acute exacerbation of asthma in the emergency department, comparing

hydrocortisone and methylprednisolone. The research concluded that both drugs significantly increased PEFR at six hours, with group A at a mean PEFR of 160.0±40.44 L/min and group B at 167.6±33.39 L/min. (Aggarwal P et al., 2010).

Trevor et al. (2021) conducted a real-world cohort study on adults with Severe Asthma in the United States receiving specialist treatment. The study revealed a high rate of exacerbations and health care resource utilization, with a lower burden of exacerbations observed in patients receiving biologics. (Trevor J et al., 2021)

Ali et al. (2009) conducted a quasi-experimental interventional study on asthma patients, comparing hydrocortisone and methylprednisolone in the management of acute severe asthma. The research concluded that hydrocortisone is more effective in achieving improved peak expiratory flow rate (PEFR), with 86.7% of patients in the hydrocortisone group achieving improvement compared to 40.0% in the methylprednisolone group. (Ali L et al., 2009).

Price et al. (2020) emphasize the critical role of systemic corticosteroids in managing acute asthma exacerbations but highlight the need to avoid inappropriate use due to the associated morbidity. The balance between efficacy and safety is crucial to prevent steroid-related morbidities in asthma patients. (Price D et al., 2020).

Chipps et al. (2020) found that a high starting dose of inhaled corticosteroids (ICSs) for moderate to severe asthma did not provide additional clinical benefit in three of four efficacy parameters compared to low or moderate ICS doses. However, safety risks associated with high starting doses are noted. (Chipps, B et al., 2020)

McKeever et al. (2018) conducted a randomized trial, demonstrating the effectiveness of a temporary 4-fold increase in ICS dose in reducing severe asthma exacerbations. This approach aims to reduce systemic steroids and flare-ups in asthma patients, with a

decrease in the frequency of severe exacerbations and oral corticosteroid use. (McKeever T at al., 2018)

Waljee et al. (2017) conducted a retrospective cohort study, revealing a high prevalence of short-course systemic corticosteroid (SCS) prescriptions, especially in patients with respiratory conditions. Patients receiving short-course SCS had a significantly higher prevalence of sepsis, venous thromboembolism, and fractures compared to those who did not receive SCS. (Waljee AK et al., 2017).

Lee et al. (2020) suggest that high-dose inhaled corticosteroids can benefit children experiencing asthma exacerbations, with effects apparent as early as four hours. The initial effects are attributed to the suppression of Cys-LTs production, and later effects may be influenced by the suppression of both Cys-LTs and oxidants. (Lee YJ et al., 2020)

Demarche et al. (2017) found that in a previous study, inhaled corticosteroids (ICS) were beneficial specifically for eosinophilic asthmatics, supporting their real-world efficacy against eosinophilic inflammation. The study also suggests the possibility of attempting ICS tapering in non-eosinophilic asthmatics. (Demarche, S.F et al 2017)

Marghli, S., et. Al. 2022 concluded that combining nebulized budesonide with hydrocortisone hemisuccinate does not provide any extra benefits compared to using hydrocortisone alone for the management of acute asthma in adults within the Emergency Department. (Marghli, S., et. Al. 2022)

Inayat et al. (2016) assessed the effectiveness of magnesium sulfate as an alternative therapy for severe acute asthma. The addition of magnesium sulfate to the treatment regimen significantly improved FEV1, enhancing pulmonary function in patients who did not respond to standard care. (Inayat, N., Khan et al., 2016)

In the management of acute asthma exacerbations, the crucial role of corticosteroids, especially in the emergency setting and post-discharge, has been emphasized. However, there is a need for more research to understand the optimal dosage and duration of inhaled corticosteroids (ICS) and their concurrent use with systemic corticosteroids. Additionally, the safety of administering oral corticosteroids at home during asthma attacks requires further investigation (Bigoni T et al., 2023).

In patients with moderately symptomatic asthma, the addition of tiotropium once daily to medium-dose inhaled corticosteroids has shown benefits in reducing airflow obstruction and enhancing asthma control. Tiotropium is considered a safe and effective bronchodilator that may serve as a replacement for salmeterol (FitzGerald JM et al., 2020).

A study on corticosteroid prescription practices in the intensive care setting revealed that IV methylprednisolone is widely prescribed, with the majority of intensivists opting for methylprednisolone. The chosen dosage is often based on clinical experience, and factors such as PICU size, years of experience, and country of practice do not significantly influence the preferred corticosteroid dosage (Giuliano Jr, J.S et al., 2013).

Comparing hydrocortisone and dexamethasone in the management of acute pediatric asthma, a 2007 study by Sarkari, S.E.B., found that children receiving dexamethasone had a considerably shorter mean hospital stay than those receiving hydrocortisone. (Sarkari, S.E.B., 2007).

For asthma and COPD treatment, the novel inhaled combination of fluticasone furoate/vilanterol, administered once daily, offers multiple advantages, including improved outcomes, enhanced quality of life, better compliance, a significant reduction in exacerbation rate, effective symptom control, and a favorable safety profile (Antonio Buendía J et al., 2023).

Understanding the impact of circadian rhythm disruptions on respiratory disorders is crucial for choosing effective chronotherapy. Administering drugs at specific times aligning with circadian oscillations of disease-related proteins, genes, and enzymes can optimize efficacy and manage side effects. Chronotherapy holds potential superiority over routine therapy in treating various illnesses, including respiratory disorders. However, empirical research is needed to validate chronotherapy as a therapeutic option compared to traditional methods (Paudel, K.R., 2021).

Combining oral and intravenous corticosteroids proves equally effective in treating acute asthma in hospitalized adults (Cunnington D et al., 2005).

In the management of persistent asthma, inhaled corticosteroids are established as the primary therapy, showing efficacy across age groups and asthma severity. While most patients respond well, a small percentage may require more targeted anti-inflammatory medications with fewer systemic effects (Bigon T et al., 2023).

Research suggests that high doses of systemic corticosteroids do not offer additional benefits over low doses in the treatment of severe acute asthma (Marquette, C.H., 1995).

For acute severe asthma, a study concludes that hydrocortisone 50 mg intravenously given four times a day for two days, followed by low-dose oral prednisone, is as effective as higher doses of hydrocortisone followed by higher prednisone doses (Bowler, S.D et al., 1992).

In a study comparing high and moderate doses of IV hydrocortisone in adult patients with acute severe asthma, no discernible differences were found in spirometric analysis between the two groups (Raimondi AC et al., 1986).

RESEARCH METHODOLOGY

SETTING: Emergency department of Ziauddin University Karachi.

TARGET POPULATION: Acute Asthma patients

STUDY DESIGN: Randomized control trial.

DURATION OF STUDY: Six months or till desired sample obtained after approval of synopsis.

SAMPLE SIZE:

Software: Open EPI

Proportion: Ali L, et al. who reported the 86.7% improved PEFR in hydrocortisone group and 40.0% improved PEFR in methylprednisolone group. The sample size of 48 is calculated. To attain the normality assumption sample size of 60 (30 in each group) will be taken (Ali L et al., 2009).

Confidence Level: 95%

Power: 90%

Sample Size: 60 (30 in each group)

- **Group A:** 30 patients will be treated with hydrocortisone.
- **Group A:** 30 patients will be treated with methylprednisolone.

SAMPLING TECHNIQUE: Convenience sampling.

SAMPLE SELECTION:

- **INCLUSION CRITERIA:**
    - Either gender.
    - Patients aged 18 to 50 years.
    - Patient with acute severe asthma presenting to emergency department.
- **EXCLUSION CRITERIA**
    - Diagnosed COPD, life threatening asthma and near fatal patients.
    - Patients with critical illness or pregnant females.
    - Patient treated other than hydrocortisone and methylprednisolone.
    - Patients not willing to participate in study.

DATA COLLECTION PROCEDURE: Research permission will be obtained from hospital research committee and ethical committee of Ziauddin University Karachi. A written informed consent will also be taken from patient after explaining the study purpose. Asthmatic patients who fulfilled the study inclusion criteria will be enrolled from emergency department of Ziauddin hospital, Karachi. Performa will be used for data collection. Demographics, Medical history of each patient including asthma duration, allergic details (allergic rhinitis, atopic dermatitis, dust allergy, smoke allergy and fragrance allergy) and current treatment will be obtained. Vital signs of each asthmatic patient will also be measured. Presenting complaints including wheezing, shortness of breath, dyspnea, or coughing bouts will be asked from patient. Spirometry of each patient will be performed by placing asthmatic patient at upright position and

at least three maneuvers will be obtained. Findings of spirometry will be interpreted by experienced consultant pulmonologist. Forced vital capacity (FVC), forced expiratory volume in one second (FEV_1) and PEFR will be measured at baseline. Data will be collected by principal investigator. Patients will be enrolled into study by using convenience sampling. Later lottery method will be used to make groups A and B. Among Group A; patients will be treated with hydrocortisone (200 mg bolus followed by three doses of 100mg at six hour interval for next 24 hours) will be administered intravenously). Among group B patients will be treated with methylprednisolone (125 mg single dose) will be administered intravenously within half an hour of admission. Outcome variables efficacy will be measured in terms of improved PEFR and time from baseline to achieve improvement among groups. PEFR will be measured after every 6 hours for 24 hours. At 24 hours PEFR will be recorded for improved PEFR (PEFR > 65%). Moreover time taken from baseline (first PEFR at the time of admission) to achieve improved PEFR will also be recorded for both groups.

DATA ANALYSIS PROCEDURE: Data will be analyzed with statistical package for social sciences version 25. Quantitative data includes age , duration of disease, spirometry(FVC,FEV1, PEFR) at admission and at 24 hours and outcome variable time to achieve improved PEFR will be presented as mean and standard deviation in both groups. Qualitative data includes a gender, allergic rhinitis, atopic dermatitis, dust allergy, smoke allergy, fragrance allergy, previous treatment, vital signs (Heart Rate BP Respiratory rate O_2 Saturation), presenting complain(wheezing, shortness of breath, dyspnea, coughing bouts) and outcome variable improved PEFR will be presented in frequency and percentages in both groups. Independent sample t-test/chi-square test will be used for parametric data by using p-value ≤ 0.05 as significant.

ETHICAL CONSIDERATIONS: Approval of study will be obtained from ethical committee of hospital.

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APPENDICES-I INFORMED CONSENT

Comparison of efficacy of hydrocortisone and methylprednisolone in acute severe asthma.

- **Name of Research Scholar: Dr. Inayat Ur Rehman** confirm that I have understood the information regarding the study.
- I confirm that I had the opportunity to ask the questions about the study and the investigator has answered my queries.
- I confirm that my participation is voluntary, and I can withdraw from the study at any time.
- I am satisfied that my data will be confidential.
- I give consent to use my data in research, publications, sharing and archiving.
- I agree to participate in the study.

Name of the participant	Date	Signature

APPENDICES-II PROFORMA

Hospital Registration # _____ Case # _____

STUDY GROUP:☐Group A (Hydrocortisone)☐Group B (Methylprednisolone)

DEMOGRAPHICS:

- Name: _____
- Gender: ☐ Male ☐ Female • Age (Years): _____

MEDICAL HISTORY:

- Duration of Disease (Months): _____ • Allergic rhinitis: ☐ Yes ☐ No
- Atopic dermatitis: ☐ Yes ☐ No • Dust Allergy: ☐ Yes ☐ No
- Smoke Allergy: ☐ Yes ☐ No • Fragrance Allergy: ☐ Yes ☐ No
- Treatment: ☐ No ☐Montelukast☐Inhaled steroid☐ LABA

☐ Any other: _____

VITAL SIGNS:

- Heart Rate (beats/min): _____ • BP (mm/Hg): _____
- Respiratory rate (breaths/min): _____ • O_2 Saturation (%): _____

PRESENTING COMPLAINTS:

- Wheezing: ☐ Yes ☐ No • Shortness of breath: ☐ Yes ☐ No
- Dyspnea: ☐ Yes ☐ No • Coughing bouts: ☐ Yes ☐ No
- Any other: _____

SPIROMETRY:

VARIABLES	AT ADMISSION	AT24 HOURS
• FVC		
• FEV1		
• PEFR		

OUTCOME:

- Improved PEFR: ☐Yes☐No
- Time to achieve improved PEFR: _____