Indian Academy of Pediatrics (IAP)

nRICH

Newer **R**esearch and recommendations **I**n **C**hild **H**ealth

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UNDER THE AUSPICES OF THE IAP ACTION PLAN 2023

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Dear fellow IAPans,

nRICH

Newer **R**esearch and recommendations **I**n **C**hild **H**ealth-aims to bring you the abstracts of some of the breakthrough developments in pediatrics, carefully selected from reputed journals published worldwide.

Expert commentaries will evaluate the importance and relevance of the article and discuss its application in Indian settings. nRICH will cover all the different subspecialities of pediatrics from neonatology, gastroenterology, hematology, adolescent medicine, allergy and immunology, to urology, neurology,vaccinology etc. Each issue will begin with a concise abstract and will represent the main points and ideas found in the originals. It will then be followed by the thoughtful and erudite commentary of Indian experts from various subspecialties who will give an insight on way to read and analyze these articles.

I'm sure students, practitioners and all those interested in knowing about the latest research and recommendations in child health will be immensely benefitted by this endeavor which will be published online on every Monday.

Happy reading!

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Evidence for the Use of Dexamethasone in Critical Asthma.

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BASED ON ARTICLE

Roddy MR, Sellers AR, Darville KK, et al. Dexamethasone versus methylprednisolone for critical asthma: a single centre, open-label, parallel-group clinical trial. Paediatric Pulmonology. 2023;58:1719-1727. doi:10.1002/ppul.26386

SUMMARY

Up to 10% of paediatric asthma exacerbations across various studies need paediatric intensive care unit (PICU) admission. These cases are termed as" critical asthma".

Systemic glucocorticoids and nebulized bronchodilators are primary therapeutic agents for acute management of asthma exacerbations .

Since decades , systemic corticosteroids have been the cornerstone therapy for acute severe asthma. In general, mild asthma exacerbations are managed with enteral prednisolone and severe exacerbations with IV methylprednisolone, where respiratory failure ,altered mentation or other clinical situations necessitate parenteral therapy.

Dexamethasone is a promising agent for severe exacerbations given its long half Life and potent glucocorticoid activity. In the emergency department and general paediatric wards, observational data and systematic reviews suggest Dexamethasone as an alternative to methylprednisolone. Various studies have noted reductions of inpatient length of stay (LOS), hospital relapse rates, gastrointestinal side effects, and direct costs. Yet, data reveals that most paediatric intensivists report prescribing IV methylprednisolone, using clinical experience as the basis for preferred drug and dosage in this context.

To date, few clinical trials have compared IV methylprednisolone to dexamethasone among children with critical asthma in the PICU setting.

This prospective clinical trial is one of the first to assess clinical efficacy and safety endpoints among children hospitalized in the PICU setting for critical asthma comparing groups allocated to receive Dexamethasone (intervention group) versus methylprednisolone (standard care group).

Materials & Methods

The Ideal STeroids for Asthma Treatment in the PICU (iSTAT PICU) trial was an investigator initiated, single centre, open Label, non-randomized, two arm, parallel Group trial conducted at Johns Hopkins All Children's Hospital from April 2019 through December 2021.

Children 5 through 17 years of age with a primary diagnosis of critical asthma admitted to the PICU were included. Otherwise eligible children less than 5 years of age were excluded to avoid inadvertent inclusion of children with bronchiolitis or wheezing difficult to distinguish from critical asthma .

For the intervention arm, IV dexamethasone was started on PICU admission dosed at 0.25 mg/kg/dose (maximum dose of 15 mg) every 6 h to complete a 48 h course. If the participant began tolerating enteral medications ,or was deemed fit for hospital discharge before 48 h, IV dexamethasone was changed to enteral dosing of 0.5 mg/ kg (max 16 mg dose) every 24 h to start 6 hrs after the preceding IV dose and to complete a total of 48 h of dexamethasone.

For the standard care arm, IV methylprednisolone was initiated upon PICU admission using standard dosing at 1 mg/kg/dose (maximum dose of 60 mg) every 6 h to complete a 5day course. If participants began to tolerate enteral medications or were fit for hospital discharge earlier, IV methylprednisolone was changed to prednisolone or prednisone 2mg/kg/day divided twice daily to complete a 5 day course following enrolment.

Endpoints

(1). The primary endpoint was hospital LOS

(2). Secondary endpoint was duration of continuous nebulized Salbutamol (defined as the time between continuous initiation of , and first intermittent Salbutamol administration)

(3) Tertiary endpoint was the composite outcome of exposure to adjunctive asthma pharmacologic or respiratory based interventions (like non-invasive ventilation, invasive mechanical ventilation, Heliox, terbutaline, aminophylline, ketamine, inhaled anaesthetic gases, or extracorporeal life support.)

The safety endpoint was the cumulative rate of known corticosteroid related adverse events including clinically relevant gastrointestinal bleeding, gastritis, ventilator associated pneumonia, necrotizing enterocolitis, hypertension, hyper- glycemia, altered mentation (including hallucinations and delirium), and adrenal insufficiency before hospital discharge.

Of the 92 participants enrolled into study, 61 were allocated to the standard care arm and 31 the intervention arm

For the overall sample, mean age was 9.6 ± 3.8 years, 53.3% were male participants, and median admission paediatric asthma severity scores were 11. These were matched in their clinical and demographic profiles.

Sixty-three percent of study participants including 45.9% of the standard care arm and 100% of the interventional arm were given dexamethasone in the emergency department before enrolment (mean dose, 0.44 ± 0.15 mg/kg). The remaining 54% in the standard care arm were given methylprednisolone in the emergency department (mean dose, 1.65 ± 0.65 mg/kg).

Following enrolment, the intervention arm received IV dexamethasone as per protocol (mean dose, 0.25 ± 0.05 mg/kg/dose) and the standard care arm IV methylprednisolone (mean dose, 0.9 ± 0.3 mg/kg/dose). Most participants in the standard care arm (91.8%) were switched to enteral prednisolone/prednisone and 72.1% required a prescription upon discharge to complete a 5day course. In contrast, 74.2% ($p = 0.029$) of participants in the intervention arm were switched to enteral dexamethasone and only 12.9% ($p < 0.001$) were provided a prescription at discharge to complete a 48 h course. In both arms, the frequency of need to extended steroid tapers was similar.

This prospective clinical trial found no difference in clinical efficacy between 2 days of dexamethasone at 0.25 mg/kg/dose every 6 h (intervention group) versus 5 days of methylprednisolone at 1 mg/kg/dose every 6 h (standard care group) as measured by hospital LOS, duration of continuous Salbutamol, and frequency of adjunctive asthma interventions.

No children suffered serious adverse events and corticosteroid related adverse events were rare, with the most frequent being transient hyperglycaemia (9.8% of participants). Those receiving dexamethasone more frequently completed corticosteroid dosing without transition to enteral formulations and less frequently required a prescription at discharge.

These findings reflect an apparent clinical efficacy and relative safety for dexamethasone in paediatric critical asthma as compared to methylprednisolone. Potential advantages also exist in discharge prescription compliance

This data suggests two daily doses of dexamethasone may be equivalent to a 5-day course of prednisone or methylprednisolone. In the context of hospital discharge, this may represent an advantage in the form of post discharge patient compliance that contributes to emergency department relapse rates, same Cause hospitalizations, and asthma related mortality.

Limitations:

The study analytic plan was powered to assess differences in hospital LOS as the primary clinical endpoint. Other important endpoints such as the risk reduction for life- threatening asthma and hospital readmission were not studied. Also, this study was not designed to detect non inferiority, so it does not tell us about drug superiority between the two regimens.

Research was conducted at a quaternary referral centre and study findings may not be generalizable across all other healthcare settings.

COMMENTARY

Systemic glucocorticoids are an important component of the management of asthma exacerbations due to their ability to decrease airway inflammation and secretions by reducing the production of inflammatory mediators, capillary permeability, and the activity of lymphocytes. In acute severe asthma (ASA) the administration of glucocorticoids also enhances the bronchodilator response to beta agonists by reversing desensitization and downregulation of beta receptors.

Glucocorticoids may be given as prednisone, prednisolone, methylprednisolone, Hydrocortisone or dexamethasone, all of which have been shown to decrease inflammation in asthma[1]. They are similar in how well and how quickly (one to two hours after an enteral dose) they decrease asthma symptoms. The plasma half-life, which correlates with the anti-inflammatory potency of glucocorticoids, is longer for dexamethasone than either prednisone or prednisolone and dexamethasone can be given intravenously, or intramuscularly.

However, in the case of hydrocortisone, special attention needs to be given to the risk for higher blood pressure, due to its higher mineralocorticoid effects. In a PICU setting most patients need parenteral glucocorticoids as oral administration is difficult.

Dosing varies from institution to institution but is typically1- 2 mg/kg/day of prednisone, prednisolone, or methylprednisolone orally in divided doses given twice daily for a total of five days

(with a maximum dose of 60 mg per day)[2]. An alternative is to administer as a single dose given once daily. Dexamethasone dosing is typically 0.3 to 0.6 mg/kg (maximum daily dose of 8 to 16 mg), given as a single daily oral dose, a twice-daily split oral dose, or a single daily intramuscular dose for a total of two days.

In the current study IV dexamethasone was given on PICU admission in the dose of 0.25 mg/kg/dose (maximum dose of 15 mg) every 6 h for 48 h and IV methylprednisolone for the standard arm was given at 1 mg/kg/dose (maximum dose of 60 mg) every 6 h for a 5day course. The above study suggests two daily doses of dexamethasone may be equivalent to a 5 day course of prednisone or methylprednisolone.

This study uses higher dose of dexamethasone for a shorter duration and demonstrates similar clinical efficacy and safety compared to IV Methylprednisolone. The added advantage includes- no need for oral corticosteroids post discharge , hence improving compliance.

To date, however there is no objective evidence of the superiority of one IV corticosteroid over the other and this study compares the use of 2 day course of dexamethasone with methylprednisolone with good efficacy and safety. Based on another study [3] IV methylprednisolone, dexamethasone and hydrocortisone are safe and have equivalent efficacy when used at the appropriate doses, but with a higher risk of mineralocorticoid side effects with hydrocortisone. GINA 2023 mentions the use of oral dexamethasone for an exacerbation in the dose of 0.6mg/kg given once daily for 1-2 days with no difference in relapse rates when compared to prednisolone and lower risk of vomiting. GINA cautions about the use of oral dexamethasone over 2 days due to the risk of metabolic side effects.

The choice of which of these IV corticosteroids are to be used in the treatment of ASA at present continues to be based on the physician's preference.

Given common practice, it is likely that methylprednisolone, and dexamethasone to a lesser extent, will continue to be the preferred choices for the management of ASA in the PICU setting. Larger studies with a more diverse population are needed to compare the effectiveness of IV corticosteroids in the management of ASA in the PICU setting.

Comparison of systemic glucocorticoid preparations

	Equivalent doses (mg)	Antiinflammatory activity relative to hydrocortisone*	Duration of action (hours)
Glucocorticoids			
Short acting			
Hydrocortisone (cortisol)	20	1	8 to 12
Cortisone acetate	25	0.8	8 to 12
Intermediate acting			
Prednisone	5	4	12 to 36
Prednisolone	5	4	12 to 36
Methylprednisolone	4	5	12 to 36
Triamcinolone	4	5	12 to 36
Long acting			
Dexamethasone	0.75	30	36 to 72
Betamethasone	0.6	30	36 to 72

From: Up to Date

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