Prescription of steroids in general pediatric intensive care patients – a two centre retrospective observational study

Rebecca Mitting MRCPCH[1], Elizabeth J. A. Fitchett MPH[1,2,], Mark J. Peters PhD[3,4], Samiran Ray PhD[3,4]

1. Pediatric Intensive Care Unit. St. Mary's Hospital, Imperial College Healthcare NHS Trust, London, United Kingdom
2. Clinical Research Department, London School of Hygiene and Tropical Medicine, London, United Kingdom
3. Pediatric Intensive Care Unit, Great Ormond Street Hospital, London, United Kingdom.
4. UCL Great Ormond Street Institute of Child Health, University College London, London, United Kingdom

Corresponding Author: Dr. Rebecca Mitting – r.mitting@nhs.net Pediatric Intensive Care Unit, Imperial College NHS Trust, London W2 1NY. +447736316063

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ABSTRACT

Objective

Designing randomised trials to determine utility, dose and timing of steroid administration in the management of critically unwell children may be difficult owing to a high proportion of patients who receive steroid as part of current care. We aimed to describe steroid use amongst all patients on two general pediatric intensive care units (PICU).

Design

Retrospective observational study using a multi-level logistic regression model.

Setting

Two tertiary, general mixed medical and surgical PICUs

Patients

All admissions between 2016 and 2019. All parenteral or enteral steroid prescriptions were identified and steroid type, frequency, timing and peak daily doses recorded. The outcome measure was mortality prior to PICU discharge.

Interventions

None

Measurements and main results

There were 5483 admissions during the study period, and 1804 (33%) of these involved prescription of at least one steroid. Amongst patients prescribed steroids, median peak daily dose when steroids were prescribed was 2.4 mg/kg/day prednisolone equivalent (interquartile range 1.6-3.6) and median time to peak steroid

doses was 2 days (1-5). Administration of steroid was associated with increased risk-adjusted mortality odds ratio (OR) 1.37, 95% confidence interval (CI) 1.04-1.79 with over 40% of admissions resulting in mortality. Amongst children who were prescribed steroids, use of hydrocortisone (OR 6.75, 95% CI 3.79-12.27) and methylprednisolone (OR 7.85, 95% CI 4.21-14.56), or starting steroids later than 2 days after PICU admission were associated with an increased mortality and (OR 1.93 95% CI 1.15-3.25))

Conclusions

Steroids are widely used in pediatric critical illness and non-survival associated with increase use. This association appears to be related steroid class and timing of dose, both likely to be affected by indication of steroid use. Prospective trials are required to estimate these complex risks and benefits, and study design will need to consider these patterns.

Introduction

The evidence for use of steroids in pediatric critical care is largely extrapolated from research in adult patients. Pediatric studies have demonstrated association with poor outcomes (1-4). Designing randomised trials with steroids as an intervention may be challenging given multiple potential indications for steroid use (1). We aimed to describe the patterns of steroid prescribing in two pediatric intensive care units (PICUs) over a 4-year period in London, United Kingdom (UK), to describe the use of steroids as would be seen in a 'standard care' arm of a potential interventional study.

Design and Setting

A retrospective, observational study from two tertiary, general mixed medical and (non-cardiac) surgical PICUs. All patients aged less than 18 years admitted between

1st January 2016 and 31st January 2019 inclusive were included. Both centres care for children admitted following bone marrow transplantation.

All parenteral or enteral steroid prescriptions (dexamethasone, methylprednisolone, hydrocortisone and prednisolone) recorded on the electronic health record (Intellicare Critical Care and Anaesthesia, Phillips Healthcare, The Netherlands) during the study period were matched to individual PICU admissions, defined by the admission and discharge time submitted to the UK Pediatric Intensive Care Audit Network (PICANET). Steroid prescriptions within 4 hours of each other were manually validated. For each admission, a total steroid dose for each 24-hour period (calendar day) was calculated in prednisolone-equivalent milligrams per kilogram per day (mg/kg/day PE) (5). Time intervals between admission to PICU and the first steroid prescription scheduled were calculated.

Demographic and other clinical data was extracted from the local versions of the PICANET database and variables available were therefore from the PICANET standard admission dataset (6). Data on indication for steroid use were not available retrospectively: however, in both centres dexamethasone was primarily used for airway or peri-lesional brain oedema, and as part of chemotherapy regimes for lymphoma or leukaemia; methylprednisolone was used for immunomodulation in acute lung injury, graft-versus-host disease post-haematopoeitic stem cell transplant, and immune mediated demyelination/encephalopathy; hydrocortisone was used in catecholamine resistant septic shock, corticosteroid replacement and status asthmaticus; and prednisolone was used following stability or during weaning of hydrocortisone or methylprednisolone. Steroids were not used as part of the treatment for bronchiolitis in either centre. Prescription data prior to PICU admission were not available through the electronic health record, as patients may be transferred from

other hospitals, or from internal ward areas not using the ICCA prescribing system into the tertiary PICUs. A proportion of children receiving steroids on the day of admission to PICU therefore may have received steroids prior to admission - these were not excluded.

The study protocol was reviewed by the Clinical Audit Department at Great Ormond Street Hospital NHS Trust and approved as service evaluation without the need for ethics committee review (approval number 2890). The protocol was reviewed by the Clinical Audit and Information Governance Department at Imperial College Hospital NHS Trust and approved as service evaluation without the need for ethics committee review (approval number 505). Routinely collected clinical data only were used and no patient identifiable information was stored or shared, so the need for individual patient consent was waived.

Data were analysed using R version 4.2 (7). Descriptive statistics were summarised as proportions or medians and interquartile ranges (IQR). Chi-squared and Mann-Whitney U-tests were used for univariable analyses for categorical and continuous variables respectively. Bonferroni adjustment was used for multiple comparisons, with a p-value < 0.05 considered statistically significant.

Multi-level logistic regression analysis was used to describe the association between steroid use and mortality after adjustment for PIM-3 score (the score itself used here as opposed to risk of mortality to approximate to a normal distribution); age category; sex and centre of admission, with each patient identifier as a random effect variable to account for multiple admissions of the same patient. To explore the association between characteristics of steroid use and mortality, we used a separate multi-level model including only admissions during which steroids were prescribed.This model

included each patient identifier as a random effect variable, the time of first dose of steroid prescribed on PICU (dichotomised to early = day 0, 1, 2 and late = day > 2) and peak dose used per calendar day (log transformed) for each admission, along with other baseline variables that could affect mortality (PIM-3 score, age, sex and unit of admission) as fixed effects variables. As the indication of steroid use is likely to be associated heavily with mortality, we also included the class of first steroid prescribed and the primary diagnosis as surrogate of this, in the absence of specific indication data.

Measurements and main results

There were 5483 admissions in 4361 children to the two PICUs during the study period, 1400 at Centre B and 4083 at Centre A. The median age of the cohort was 18.5 months (IQR 5.5-65.4), with a median weight of 10kg (IQR 5.5-18).

A total of 1603/4361 (37%) children, during 1804/5483 (33%) admissions, were prescribed at least one steroid. Death before PICU discharge occurred in 123/1804 (6.8%) admissions where steroids were prescribed compared with 176/3679 (4.8%) admissions when they were not; 123/299 (42.3%) of admissions that resulted in death involved prescription of steroid.

Table 1 describes the characteristics of admissions where corticosteroids were and were not prescribed. Steroids were more likely to be prescribed in older patients, males, unplanned admissions and those with respiratory diagnoses. Risk of mortality score was similar in patients who were and were not prescribed steroids, but steroids were more likely to be prescribed in those invasive ventilated, who received vasoactive medications and renal replacement therapy.

Table 1 – Characteristics of admissions according to whether they were prescribed steroids or not during their PICU stay. Proportions are expressed as percentages and continuous variables as median and interquartile ranges, and compared using chi-squared and Mann Whitney U-test respectively, with adjustment for multiple comparisons. Univariable analysis includes pediatric index of mortality (PIM-3) risk of mortality which is calculated from the PIM-3 score

	Received steroids during admission (n=1804)	Received no steroids during admission (n=3679)	p-value (adjusted for multiple comparisons)
Age in months, median (IQR)	18 (5-65)	10 (1-81)	<0.001
Male sex, n (%)	1083 (60.0)	2035 (55.3)	0.02
Unit, n (%)			
Centre A	1314 (32.2)	2769 (67.8)	0.68
Centre B	490 (35.0)	910 (65.0)	
PIM-3 % Risk of Mortality, median (IQR)	1.3 (0.5-5.0)	1.3 (0.5-4.0)	0.33
Planned admission n, (%)	476 (26.4)	1334 (36.3)	<0.001
Primary diagnostic category, n (%)			<0.001
Respiratory	868 (48.1)	1035 (28.1)	
Cardiovascular	90 (5.0)	253 (6.9)	
Infection	90 (5.0)	162 (4.4)	
Neurological	281 (15.6)	710 (19.3)	
Oncology	81 (4.5)	92 (2.5)	
Trauma/Musculoskeletal	46 (2.5)	319 (8.7)	
Haematology/vascular	36 (2.0)	59 (1.6)	
Endocrine/metabolic	58 (3.2)	125 (3.4)	
Gastrointestinal/ Renal	92 (5.1)	504 (13.7)	
Other	162 (9.0)	420 (11.4)	
Day of first dose of steroid, median (IQR)	1 (0-3)	-	
Peak dose of steroid in prednisolone equivalent mg/kg/day, median (IQR)	2.40 (1.58-3.61)	-	
Steroid class of first dose prescribed, n (%)		-	
Dexamethasone	1168 (64.7)		
Hydrocortisone	371 (20.6)		
Methylprednisolone	171 (9.5)		
Prednisolone	94 (5.2)		

Organ support during admission, n (%)			
Non-invasive ventilation	493 (27.3)	751 (20.4)	<0.001
Invasive ventilation	1631 (90.4)	2568 (69.8)	<0.001
Vasoactive drugs	570 (31.6)	786 (21.4)	<0.001
RRT	136 (7.5)	80 (2.2)	<0.001
Length of admission in days, median (IQR)	5.1 (2.7-9.7)	2.8 (1.1-6.1)	<0.001
Mortality, n (%)	123 (6.8)	176 (4.8)	0.03

Dexamethasone was the most used steroid, prescribed in 1249/5483 (22.8%) admissions, followed by hydrocortisone, prednisolone and methylprednisolone in 397 (7.2%), 215 (3.9%) and 210 admissions (3.8%), respectively. Dexamethasone was prescribed as the first dose in 1128/1804 (64.7%) cases, hydrocortisone in 371 (20.6%), prednisolone in 94 (5.2%) and methylprednisolone in 171 (9.5%).

The median time to first dose of corticosteroid from ICU admission was 0.85 (IQR 0.2-3.2) days. In 1243 of the 1804 admissions during which steroids were prescribed (69%) steroids were 'early', initiated on either day 0, 1 or 2 (day 0 being the first calendar day of admission).

The median peak daily dose prescribed in admissions involving steroid was 2.4mg/kg/day PE (IQR 1.6-3.6). The median time to peak steroid dose was 2 days (IQR 1-5).

There was a significant association between steroid prescription and mortality (odds ratio (OR) 1.37, 95% confidence interval (CI) 1.04-1.79) following adjustment for PIM-3, age category, centre of admission and sex in a multi-level logistic regression model. The results are shown in Table 2. In those prescribed steroids, timing of steroid dose as well as steroid class used for first dose were associated with mortality where diagnostic category and peak steroid dose were not.

Table 2 – Results of multi-level logistic regression to explore the association between steroids and PICU mortality, along with patient and steroid use characteristics.. Model 1 includes all admissions (n=5483) and includes prescription of steroids, PIM-3 score, ages (categorised) sex, centre of admission. Model 2 includes only admissions that did involve prescription of steroids, and as well as the above variables includes timing of steroid, peak daily dose, first steroid class prescribed and diagnostic category. A multi-level model was used considering patient identity as a random effect variable and other characteristics as fixed effects to account for the possibility of multiple admissions in the same patient.

Variable	Odds ratio for mortality	95% confidence interval	p-value
Model 1:			
PIM-3 score	2.46	2.25, 2.70	<0.001*
Age, relative to <1 year			
1-2 years	1.27	0.77, 2.02	0.34
2-5 years	1.58	1.03, 2.36	0.03*
5-12 years	1.68	1.16, 2.42	0.005*
>12 years	2.00	1.27, 3.08	0.002*
Male	0.71	0.54, 0.92	0.01*
Centre B, relative to A	0.61	0.43, 0.84	0.004*
Steroids prescribed	1.37	1.04, 1.79	0.007*
Model 2:			
PIM-3 score	1.89	1.60, 2.20	<0.001*
Age, relative to <1 year			
1-2 years	0.57	0.23, 1.34	0.23
2-5 years	1.52	0.84, 2.94	0.16
5-12 years	1.56	0.88, 2.96	0.12
>12 years	1.35	0.59, 3.01	0.44
Male	0.65	0.44, 1.02	0.06
Centre B, relative to A	0.85	0.47, 1.34	0.41
Late steroid (after day 2 of admission)	1.93	1.15, 3.25	0.01*
Peak dose of steroid (mg/kg/day prednisolone equivalent, log transformed)	1.17	0.96, 1.44	0.13
First steroid class, relative to dexamethasone			
Hydrocortisone	6.75	3.79, 12.27	<0.001*
Methylprednisolone	7.85	4.21, 14.56	<0.001*

Prednisolone	0.61	0.03, 3.14	0.64
Primary diagnosis category, relative to Other			
Respiratory	0.67	0.32, 1.48	0.29
Cardiovascular	1.12	0.43, 2.99	0.81
Infection	0.55	0.18, 1.63	0.28
Neurology	0.87	0.34, 2.25	0.77
Oncology	1.15	0.37, 3.40	0.80
Endocrine/ metabolic	1.30	0.46, 3.63	0.61
Haematology/ vascular	1.88	0.54, 6.06	0.30
Gastrointestinal/ Renal	0.93	0.25, 3.07	0.91
Trauma/ Musculoskeletal	0	0, 23.50	0.98

Discussion

This retrospective study describes prescription of steroids by clinicians caring for children in PICU over 4-years in two centres. Steroids were prescribed during a third of all admissions, with a median dose of more than 2 mg/kg/day PE, and mostly in the first 2 days of patients' PICU stay.

Secondary exploratory analysis revealed that there was an association between steroid prescription and mortality. Exploring this further, starting steroids after day 2 of admission, and the prescription of hydrocortisone and methylprednisolone as the first steroid were more likely to be associated with mortality, suggesting that the relationship between steroid prescribing and mortality may be a reflection of indication at the time of prescribing, This is consistent with the finding in table 1 that PIM risk of mortality is not higher in admissions where steroids are prescribed, but that admissions involving steroids are associated with increased use of invasive ventilation, renal replacement therapy and vasoactive substances.

This study benefits from large numbers. Previous cohort studies have reported steroid prescribing in in specific indications: 35-60% in PARDS (1,9); 30% of critically ill children specifically at risk of malnutrition (2), and 35-60% in catecholamine dependent shock (3,4). Our results give a similar picture for general PICU patients, with one third of admissions to PICU prescribed steroids, rising to over 40% in non-survivors.

In adult sepsis, high doses of steroids (>30mg/kg prednisolone equivalent) have been associated with increased mortality (10), leading to the adoption of lower dose regimes. Similarly, the optimal timing of steroids in ARDS has been much debated (11-13). In our analysis peak steroid dose was not associated with increasing mortality, although steroid class and timing were. These associations may reflect an indication bias – higher risk disease states such as severe septic shock or post- bone marrow transplant respiratory failure are likelier to be associated with use of hydrocortisone or methylprednisolone. We tried to account for the indications of steroid use by incorporating PIM-3 score (which includes some high and low-risk diagnostic category information, and an indicator of severity of illness at admission), and the primary diagnosis. The steroid class used also contains information about indication, especially given that choice of steroid used is based on indication (consistent across both centres). It may also reflect a response to illness trajectories – a deterioration in clinical state may influence the decision to prescribe steroids, which cannot be accounted for using static variables such as PIM-3 score or primary diagnosis. This may also support the hypothesis that later use of steroids, either due to late deterioration or greater clinical uncertainty about the risk-benefit balance of steroid use may reduce any benefit that may be seen with earlier use.

However this is not, of course, evidence of a causal relationship between steroid prescribing and mortality. Our retrospective study design did not allow us to analyse

the indication and threshold of when and what type of steroid is prescribed. Several admissions also had more than one steroid class prescribed for different indications. We did not have information on prescribing prior to patients arriving in PICU. This, along with the widespread and early use of steroids during PICU admission, prescribed possibly for multiple indications, demonstrates the complexity of designing a trial to test the effect of steroids on outcomes. .

Conclusion

Steroids are used widely in pediatric critical care patients. Pragmatic clinical trials of corticosteroid use in PICU are needed to find the optimal timing and dose for each steroid indication, given the potential for harm. Our data suggest this may be challenging. Modern trial designs, such as platform and/or adaptive trials may be needed to understand the impact of indication, class, timing and dose of steroids in PICU.

References

1. Yehya N, Servaes S, Thomas NJ, Nadkarni VM, Srinivasan V (2015) Corticosteroid exposure in pediatric acute respiratory distress syndrome. Intensive Care Med. Intensive Care Med. 2015 Sep;41(9):1658-66

2.Jacobs A, Derese I, Vander Perre S, Wouters PJ et al. Dynamics and prognostic value of the hypothalamus-pituitary-adrenal axis responses to pediatric critical illness and association with corticosteroid treatment: a prospective observational study. Intensive Care Med. 2020 Jan;46(1):70-81.

3. Nichols B, Kubis S, Hewlett J,et al. Hydrocortisone Therapy in Catecholamine-Resistant Pediatric Septic Shock: A Pragmatic Analysis of Clinician Practice and Association With Outcomes. Pediatr Crit Care Med. 2017 Sep;18(9):e406-e414.

4. Menon, K; McNally, J. Dayre; Choong, K et al for the Canadian Critical Care Trials Group STRIPES Investigators. A Cohort Study of Pediatric Shock, Shock: Injury, Inflammation, and Sepsis: Laboratory and Clinical Approaches: November 2015 - Volume 44 - Issue 5 - p 402-409

5. Joint Formulary Committee. (2021). British National Formulary for children. Glucocorticoid Therapy. Updated February 2022. Accessed 26th March 2022 https://bnfc.nice.org.uk/treatment-summary/glucocorticoid-therapy.html.

6. PICANET web admission dataset manual. Version 5.5 May 2020 downloaded from https://www.picanet.org.uk/wp-content/uploads/sites/25/2022/05/PICANet-Web-Admission-Dataset-Manual-v5.5_-May-2022.pdf 20/06/2022.

7. R Core Team (2017). R: A language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria. URL http://www.R-project.org/)

8. Straney L, Clements A, Parslow RC et al. Slater A; ANZICS Pediatric Study Group and the Pediatric Intensive Care Audit Network. Pediatric index of mortality 3: an updated model for predicting mortality in pediatric intensive care*. Pediatr Crit Care Med. 2013 Sep;14(7):673-81.

9. Santschi, Miriam MD; Jouvet, Philippe MD; Leclerc, Francis MD et al for the PALIVE Investigators the Pediatric Acute Lung Injury and Sepsis Investigators Network (PALISI) the European Society of Pediatric and Neonatal Intensive Care (ESPNIC) Acute lung injury in children: Therapeutic practice and feasibility of international clinical trials*, Pediatric Critical Care Medicine: November 2010 - Volume 11 - Issue 6 - p 681-689

10. Bone RC, Fisher CJ Jr, Clemmer TP, Slotman GJ, Metz CA, Balk RA. A controlled clinical trial of high-dose methylprednisolone in the treatment of severe sepsis and septic shock. N Engl J Med. 1987 Sep 10;317(11):653-8

11. Steinberg KP, Hudson LD, Goodman RB, et al. National Heart, Lung, and Blood Institute Acute Respiratory Distress Syndrome (ARDS) Clinical Trials Network. Efficacy and safety of corticosteroids for persistent acute respiratory distress syndrome. N Engl J Med. 2006 Apr 20;354(16):1671-84. doi: 10.1056/NEJMoa051693. PMID: 16625008.

12. Meduri GU, Bridges L, Shih MC et al. Prolonged glucocorticoid treatment is associated with improved ARDS outcomes: analysis of individual patients' data from four randomized trials and trial-level meta-analysis of the updated literature. Intensive Care Med. 2016 May;42(5):829-840. doi: 10.1007/s00134-015-4095-4. Epub 2015 Oct 27. PMID: 26508525.

13. Villar J, Ferrando C, Martínez D et al. Dexamethasone in ARDS network. Dexamethasone treatment for the acute respiratory distress syndrome: a multicentre, randomised controlled trial. Lancet Respir Med. 2020 Mar;8(3):267-276. doi: 10.1016/S2213-2600(19)30417-5. Epub 2020 Feb 7. PMID: 32043986.