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Original Article

Use of corticosteroids in acute respiratory distress syndrome: Perspective from an Indian intensive care unit

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ARTICLE INFO

Article history:

Received 9 December 2015

Accepted 23 October 2016

Available online 16 December 2016

Keywords:

Acute respiratory distress syndrome

Corticosteroids

Sepsis

Mortality

Intensive care unit

ABSTRACT

Background: Acute respiratory distress syndrome (ARDS) causes overwhelming inflammation, which serves as a potential target for corticosteroids. Despite extensive Western literature, there are no Indian studies evaluating steroids in ARDS.

Methods: This was a retrospective study at an Indian intensive care unit (ICU) on ARDS patients. Demographic, clinical, laboratory, and imaging parameters were collected. Patients were divided into cohorts based on steroid use, and some received high-dose (2 mg/kg/day), whereas others received low-dose (1 mg/kg/day) steroids. Primary outcomes were in-hospital mortality and secondary outcomes included need for and duration of invasive mechanical ventilation (IMV), IMV-free days, ICU length of stay (LOS), and total LOS. Two-tailed $p < 0.05$ was considered statistically significant.

Results: During the 20-month period, 95 patients [median age 37 (30–47) years; 48 (50.5%) males] met our inclusion criteria. Steroid use was noted in 48 (50.5%) patients [11 (22.9%) low-dose and 37 (77.1%) high-dose]. Baseline characteristics of the cohorts, including ARDS severity indices, were comparable. Of these 95 patients, 70 (73.7%) had sepsis, but microbiological diagnosis was positive only in 17 (17.9%) patients. Steroid use did not significantly influence mortality [odds ratio (OR) 0.6 (0.3–1.4)] or need for IMV [OR 1.0 (0.4–2.6)]. There were no differences in outcomes of IMV-free days, ICU LOS, or total LOS. These outcomes were comparable between the high-dose and low-dose steroid users.

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<http://dx.doi.org/10.1016/j.mjafi.2016.10.012>

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Conclusions: Steroid use and comparison of low-dose vs. high-dose steroids did not influence outcomes associated with ARDS in the Indian population.

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Introduction

Acute respiratory distress syndrome (ARDS) is characterized by inflammatory injury of the lungs progressing through early exudative phase, fibroproliferative phase, and late fibrotic phase.¹ The evolution of this systemic and pulmonary inflammation serves as a determinant of outcomes in the disease process.² Clinically, ARDS has a high-mortality rate of 40–60%, and multiple studies have evaluated newer targets for therapy for this life-threatening disease process.^{2,3} Glucocorticoids gained prominence as a therapeutic strategy in the late 1990s⁴ following which the National Heart, Lung and Blood Institute (NHLBI) ARDS Clinical Trials Network conducted a randomized controlled trial in 2006,⁵ which did not demonstrate efficacy in ARDS.

Over the last 10 years since the publication of the NHLBI study, there has been a renewed interest in corticosteroids with multiple studies and meta-analysis published in literature.^{1–3,6–9} However, there are no documented studies in the Indian population evaluating the efficacy of this group of medications. The Indian ARDS population^{10,11} is clinically distinct from reports published by our Western colleagues prompting us to evaluate the role of corticosteroids in ARDS in an Indian intensive care unit (ICU).

Material and methods

This was a retrospective cohort study at the medical ICU of a tertiary care academic medical center in southern India from September 2006 to April 2008. The procedures followed were in accordance with the ethics standards as detailed in the Helsinki Declaration. The Institutional Ethics Committee permission was sought and obtained for this study. All patients who met the inclusion criteria of ARDS as per the revised American/European consensus statement,¹² including (a) acute onset, (b) bilateral infiltrates on chest radiography, (c) Carrico index or P/F ratio [ratio of partial pressure of arterial oxygen (PaO_2) and fraction of inspired oxygen (FiO_2)] ≤ 200 , and (d) absence of clinical signs of left atrial hypertension, left heart failure, or pulmonary capillary wedge pressure < 18 mmHg (if pulmonary artery catheter is present in situ), were included in our study. Patients with significant underlying lung disease, age < 16 years, active pregnancy, and those discharged against medical advice were excluded from our study. Patient details related to the index admission were collected, including demographic information, comorbidities, clinical data, laboratory parameters, and imaging studies, and were assessed. Severity of illness was measured using Acute Physiology and Chronic Health Evaluation 2 (APACHE-2) score, and presence of sepsis was documented using the American College of Chest Physicians/Society

of Critical Care Medicine consensus definition¹³ on the day of ARDS onset. Patients were retrospectively followed for the duration of their hospital stay and treatment regimens, including sources of infection, microbiological etiology, antimicrobial use, and invasive mechanical ventilation (IMV), were documented. Methylprednisolone use was divided into low-dose and high-dose categories defined as 1 mg/kg/day and 2 mg/kg/day respectively for 3–5 days followed by tapering over 48 h. Steroids were initiated within 72 h of ARDS diagnosis during the hospital stay. We assessed the role of steroid therapy and low- vs. high-dose of steroids on the primary outcome of in-hospital mortality. Secondary outcomes assessed included need for IMV, duration of IMV, IMV-free days, ICU length of stay (LOS), ICU-free days, and total LOS.

Statistical analysis

Statistical analysis was performed with JMP version 9.0.1 (SAS Institute, Cary, NC). Descriptive data are detailed as median $\pm$ interquartile range (IQR) or number (percentage). Chi-square test or Fisher's exact test was used to compare categorical variables, and unpaired t-test or Mann–Whitney U test was used for continuous variables. Outcomes are presented as odds ratio (OR) with 95% confidence interval (CI) for categorical variables. Multiple regression analysis was performed for dependent variable of in-hospital mortality. Independent variables of age, gender, APACHE-2 score, and P/F ratio were selected after univariate and correlational analysis. OR with their corresponding 95% CI was used to report categorical variables in univariate and multiple analyses. Two-tailed *p*-value of < 0.05 was considered statistically significant.

Results

During the period between September 2006 and April 2008, 95 patients with ARDS were admitted to the ICU with median age of 37 (30–47) years and 48 (50.5%) males. Of the 95 patients, corticosteroids were administered to 48 (50.5%) patients of whom 11 (22.9%) received low-dose and 37 (77.1%) high-dose therapy. Baseline patient characteristics between steroid users and non-users were not significantly different (Table 1). Baseline characteristics were not different within the steroid group between low- and high-dose steroid users (not detailed). Only 60 (63.2%) had an obvious etiology for the ARDS as follows: leptospirosis 15 (15.7%), dengue 14 (14.6%), community-acquired pneumonia 11 (11.5%), and falciparum and mixed malaria 8 (8.4%). Minor causes included pancreatitis, drowning, organophosphate poisoning, cholangitis [2 patients (2.1%) each] and Fournier's gangrene, postpartum intra-abdominal infection, appendicular abscess rupture/peritonitis, and femoral venous catheter tip infection [1 patient (1.1%) each].

Table 1 – Baseline patient characteristics.

Characteristics	Steroid users (n = 48)	Steroid nonusers (n = 47)	p-Value
Age	36 (28.5–45)	38 (30–52)	0.32
Male gender	23 (47.9)	25 (53.2)	0.68
Hypertension	1 (2.1)	3 (6.4)	0.36
Diabetes mellitus-2	2 (4.2)	4 (8.5)	0.44
CKD	1 (2.1)	1 (2.1)	1.00
Alcohol abuse	3 (3.2)	3 (3.2)	1.00
Tobacco abuse	4 (8.3)	5 (10.6)	0.74
APACHE-2 score	10.5 (8–17.8)	13 (9–20)	0.28
PaO ₂ /FiO ₂ ratio	135 (104.8–169.5)	106 (83–183)	0.09
Sepsis diagnosis	34 (70.8)	36 (76.6)	0.64
Positive cultures	5 (10.4)	12 (25.5)	0.06
Etiology known	27 (56.3)	30 (63.8)	0.53

Represented as: Median (interquartile range) or number (%).

Abbreviations: APACHE-2, Acute Physiology and Chronic Health Evaluation 2; CKD, chronic kidney disease; FiO₂, fraction of inspired oxygen; PaO₂, partial pressure of arterial oxygen.

Table 2 – Univariate analysis of outcomes.

Parameter	Steroid users (n = 48)	Steroid nonusers (n = 47)	p-Value
Mortality	23 (47.9)	28 (59.6)	0.31
Need for IMV	36 (75.0)	35 (74.5)	1.00
Duration of IMV	1.5 (0.3–5.8)	2 (0–5)	0.99
IMV-free days	0 (0–2)	0 (0–7.5)	0.51
ICU LOS (days)	3 (2–6.8)	4 (2–6)	0.88
ICU-free days	6 (4.5–8)	6 (4–7.3)	0.91
Total LOS (days)	6 (2–11)	8 (2–12.8)	0.63

Represented as: Median (interquartile range) or number (%).

Abbreviations: CI, confidence interval; ICU, intensive care unit; IMV, invasive mechanical ventilation; LOS, length of stay.

Specific microbiological diagnosis was possible only in 17 (17.9%) of the cases with sterile cultures in all other patients. Endotracheal tube secretion cultures were positive in 11 (11.6%) patients – *Pseudomonas aeruginosa* 6 (33%), *Klebsiella pneumoniae* 3 (17%), *Staphylococcus aureus* 1 (6%), *Escherichia coli* 2 (11%), and *Acinetobacter baumannii* 6 (33%). Blood cultures were positive in 6 (6.3%) patients – 3 (50%) for *S. aureus* and 1 (17%) each for *K. pneumoniae*, *E. coli*, and *P. aeruginosa*. Additional cultures included were the following: peritoneal for *E. coli*, pleural fluid for *A. baumannii*, and skin abscess for methicillin-resistant

S. aureus (MRSA) in 1 (1.1%) patient each. Antimicrobial therapy was used in all patients irrespective of etiology, with piperacillin/tazobactam, penicillin, doxycycline, and cephalosporins being the most commonly used in 56, 39, 37, and 24 patients, respectively.

Of the 95 patients, 71 (74.7%) needed IMV with median duration of 3 (2–6) days and median IMV-free days of 0 (0–5) days. ICU LOS was 3 (2–6) days and median ICU-free time was of 6 (4–8) days in the survivors. Total LOS was 7 (2–12) and mortality was noted in 51 (53.7%) patients. Detailed univariate analysis of outcomes based on steroid use is detailed in Table 2. Steroid use did not significantly influence mortality (OR 0.6, 95% CI 0.3–1.4) or need for IMV (OR 1.0, 95% CI 0.4–2.6). In a univariate analysis of the steroid group, there were no differences in outcomes in patients receiving low- and high-dose steroids (not detailed). In a multiple regression analysis evaluating the influence of steroid use on mortality, they were not an independent predictor (OR 0.9, 95% CI 0.2–3.1, p-value 0.84) (Table 3).

Table 3 – Multiple regression analysis for in-hospital mortality.

Parameter	OR (95% CI) or Est. (SE)	p-Value
Steroid use	0.9 (0.3–3.1)	0.84
Age	0.05 (0.03)	0.87
Gender	1.1 (0.3–3.8)	0.89
APACHE-2 score	–0.38 (0.09)	<0.001
PaO ₂ /FiO ₂ ratio	0.01 (0.00)	0.17

Represented as: Odds ratio (95% confidence interval) or estimate (standard error).

Abbreviations: APACHE-2, Acute Physiology and Chronic Health Evaluation 2; CI, confidence interval; Est., estimate; FiO₂, fraction of inspired oxygen; OR, odds ratio; PaO₂, partial pressure of arterial oxygen; SE, standard error.

Discussion

The major findings of our study are as follows: (a) ARDS is etiologically and demographically different in the Indian population as compared to published Western literature; (b) sepsis is a leading diagnosis in ARDS with specific

microbiological etiology diagnosed in less than one-fifth of the population; (c) use of corticosteroids did not influence outcomes in our study; and (d) low- vs. high-dose corticosteroids did not influence outcomes within the steroid group.

Inflammation is a key pathophysiological mechanism in ARDS and involves the epithelial and endothelial spaces with the degree of inflammation (measured by serum and bronchoalveolar cytokines) correlating with the severity of the disease.^{1,2,8} The release of cytokines and chemokines is responsible for the alveolar-capillary membrane damage, increased vascular permeability, and fibroblast proliferation resulting in ventilation constraints.^{2,8} If unchecked, these fibroproliferative changes progress to fibrosis and reduced compliance resulting in long-term changes and worse outcomes.^{2,8} Glucocorticoids are anti-inflammatory medications and are commonly employed in high inflammatory conditions, including rheumatoid arthritis, systemic lupus erythematosus, vasculitis, etc. In addition to decreasing inflammatory mediators, glucocorticoids act on the cardiovascular system counteracting the changes of systemic inflammation by increasing cardiac contractility, vasoconstriction, and augmentation of cardiac output.^{1,2,8} These actions are well documented in septic shock and have shown to decrease mortality by downregulation of systemic inflammation as documented by decreased circulating inflammatory cytokines and C-reactive protein.^{1,2}

However, these sound pathophysiological mechanisms did not yield the expected response in clinical trials in ARDS. In the NHLBI ARDS Network study,⁵ use of 2 mg/kg methylprednisolone for 14 days was associated with no difference in mortality at 60 or 180 days; however, it demonstrated higher ventilator-free days, higher cardiovascular failure-free days, and decreased ICU LOS at 60 days. However, the patient population in the steroid group experienced higher reintubation rates likely due to abrupt steroid withdrawal vs. increase in neuromuscular weakness from steroid use.^{5,8} This study was offset by a randomized trial published in 2007, where a longer course of steroids (starting at 1 mg/kg/day) over 28 days showed decreased duration of MV, shorter ICU LOS, and decreased mortality.² However, a major criticism of this study is the baseline differences in catecholamine-deficiency shock contributing to differential outcomes.^{7,8} Unlike these studies, patients in our study did not show positive outcomes with steroid use. Use of steroids in ARDS is often a fine balance between therapeutic advantages and surveillance for complications.⁶ Considerations for timing of initiation, dosage, frequency, and duration of therapy are still actively debated in literature.^{6,8} The American College of Critical Care Medicine gives steroids a grade II-B recommendation for severe ARDS (P/F ratio <200).¹⁴ Mean P/F ratios in our steroids and nonsteroid groups were consistent with these guidelines; however, the timing of 7–13 days was not adhered to.^{5,8} The 'optimal' time period of 7–13 days post-ARDS diagnosis was not validated in a meta-analysis study, including a meta-regression calculation for initiation time.^{1,3} Additionally, our patient population did not receive a prolonged tapering dose of steroids that had demonstrated benefit in prior literature.^{2,9} However, often times, prolonged duration of therapy has to be balanced against the risk of infection, increased neuromuscular weakness, and costs of surveillance, all of which are pragmatic issues in a developing nation.⁶ Additionally, the absence of

ventilatory parameters, lack of confirmation of low-tidal volume strategy, and logistic constraints with implementation of early goal-directed sepsis therapy could be potential confounders to the applicability of our results. The steroid group in our study did not demonstrate any difference in mortality, and more importantly no increase in mortality that is presumed to be due to the release of macrophage migration inhibition factor.^{3,5}

The presentation of ARDS in India is distinct from the published Western literature. Patients are frequently younger and with lesser comorbidities.^{10,11,15} Sepsis continues to be the leading cause of ARDS and is often associated with tropical illnesses, including malaria, leptospirosis, dengue, etc., seen in a predominantly male population with occupational exposure to unsanitary environmental conditions.^{10,11,15,16} Consistent with these studies,^{10,11,16} our patients too showed similar demographic and etiological characteristics, but the microbiological yield of our patients was significantly lesser (17.9%) vs. the 40–50% range noted by our Indian colleagues. This can partially be explained by the nature of patients presenting to our tertiary referral center who have often times been admitted at other centers and received multiple doses of antimicrobials. The mortality in our patients was 53.7%, which, despite being comparable to other Indian studies,^{10,11,15–17} is significantly higher than the 15–30% noted in Western literature.^{2,5}

Our study had certain limitations as well. We performed a single-center study using a retrospective study design with inherent selection and informational biases. Our sample size was limited by the duration of study and was not powered to detect differences, which may be reflected in our outcomes. We were also limited by the absence of detailed ventilator parameters, assessment of shock, and vasopressor use, all of which could have influenced the choices of therapy, including use and dose of steroids. The role of adrenal insufficiency was not evaluated with a cosyntropin stimulation test due to financial constraints and lack of standardized guidelines in ARDS.^{2,6,8} Being a referral center for a predominantly rural Indian population, our study may not be generalizable to a pan-Indian population due to the complex socioeconomic dynamics. Despite ARDS being a clinical diagnosis, it has different pathological phenotypes with recent literature documenting differential outcomes in these populations.¹⁸ Tissue diagnosis of ARDS, however, is not a part of standard clinical practice in our institution, thereby potentially resulting in an admixture of various phenotypes and impacting our clinical outcomes.

In summary, our study is the first to evaluate the role of corticosteroids in ARDS in the Indian population. These patients are often demographically and etiologically different from the presentations in the western world, where the majority of the literature originates. Our study did not show any benefit from the use of steroids in the Indian population, but as enlisted above, we had certain limitations. This hypothesis-generating study needs further validation in more large scaled trials in the Indian and Asian populations to help develop individualized consensus guidelines.

Conflicts of interest

The authors have none to declare.

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