Published in final edited form as:

Crit Care Med. 2013 July ; 41(7): 1679–1685. doi:10.1097/CCM.0b013e31828a1fc7.

The Influence of Prehospital Systemic Corticosteroid Use on Development of Acute Respiratory Distress Syndrome and Hospital Outcomes

Lioudmila V. Karnatovskaia, MD¹, Augustine S. Lee, MD¹, Ognjen Gajic, MD², and Emir Festic, MD¹ on behalf of U.S. Critical Illness and Injury Trials Group: Lung Injury Prevention Study Investigators (USCIITG-LIPS)

¹Division of Pulmonary and Department of Critical Care Medicine, Mayo Clinic, Jacksonville, FL

²Division of Pulmonary and Critical Care Medicine, Mayo Clinic, Rochester, MN

Abstract

Objective—The role of systemic corticosteroids in pathophysiology and treatment of acute respiratory distress syndrome is controversial. Use of prehospital systemic corticosteroid therapy may prevent the development of acute respiratory distress syndrome and improve hospital outcomes.

Design—This is a preplanned retrospective subgroup analysis of the prospectively identified cohort from a trial by the U.S. Critical Illness and Injury Trials Group designed to validate the Lung Injury Prediction Score.

Setting—Twenty-two acute care hospitals.

Patients—Five thousand eighty-nine patients with at least one risk factor for acute respiratory distress syndrome at the time of hospitalization.

Intervention—Propensity-based analysis of previously recorded data.

Measurements and Main Results—Three hundred sixty-four patients were on systemic corticosteroids. Prevalence of acute respiratory distress syndrome was 7.7% and 6.9% (odds ratio, 1.1 [95% CI, 0.8–1.7]; $p = 0.54$) for patients on systemic corticosteroid and not on systemic corticosteroids, respectively. A propensity for being on systemic corticosteroids was derived through logistic regression by using all available covariates. Subsequently, 354 patients (97%) on systemic corticosteroids were matched to 1,093 not on systemic corticosteroids by their propensity score for a total of 1,447 patients in the matched set. Adjusted risk for acute respiratory distress syndrome (odds ratio, 0.96 [95% CI, 0.54–1.38]), invasive ventilation (odds ratio, 0.84 [95% CI, 0.62–1.12]), and in-hospital mortality (odds ratio, 0.97 [95% CI, 0.63–1.49]) was then calculated from the propensity-matched sample using conditional logistic regression model. No significant associations were present.

Conclusions—Prehospital use of systemic corticosteroids neither decreased the development of acute respiratory distress syndrome among patients hospitalized with at one least risk factor, nor affected the need for mechanical ventilation or hospital mortality.

Keywords

acute lung injury; acute respiratory distress syndrome; invasive ventilation; mortality; steroids; systemic corticosteroids

One of the most controversial issues in the development and treatment of acute respiratory distress syndrome (ARDS) is the effect of systemic corticosteroids (SCS). Physiologically, exposure to infectious or noninfectious insults elicits a host defense response aimed at containing and destroying the injurious agents via activation of inflammation, coagulation, and tissue repair pathways (1). In ARDS, dysregulated inflammation from either direct or indirect stimulus leads to a disruption of the alveolar-capillary membrane resulting in edema and filling of the pulmonary lobules with the protein-rich neutrophilic exudate (1, 2).

Animal studies appear to support a protective role of exogenous SCS on lung function: dexamethasone alleviated meconium-induced airway hyperreactivity and attenuated endotoxin-induced lung injury by inhibition of inducible nitric oxide expression at the very early stage of ARDS (3, 4). However, studies investigating the role of SCS in humans yielded equivocal results. Trials incorporating high doses of methylprednisolone in mechanically ventilated patients at high risk for ARDS (5), patients with established ARDS (6, 7), or patients just diagnosed with sepsis (8, 9) mostly showed no benefit. Others, however, reported improvements (10), particularly with the use of lower doses of corticosteroids in earlier stages of ARDS (11, 12) and even in management of unresolving ARDS (13).

Despite extensive research into management of ARDS and the use of protective modes of ventilation, overall associated hospital and ICU mortality remains high (14). Therefore, the task of the U.S. Critical Illness and Injury Trials Group: Lung Injury Prevention Study investigators has been to identify modifiable risks for ARDS and to seek strategies to prevent its occurrence. Given encouraging results of trials that used low-dose cortico-steroid administration early in the course of ARDS, we hypothesized that patients who take SCS prior to hospital admission might be protected against the development of ARDS.

METHODS

The original investigation by the U.S. Critical Illness and Injury Trials Group: Lung Injury Prevention Study was designed to validate the Lung Injury Prediction Score (LIPS) and included 5,584 patients from 22 hospitals (15). Data were collected prospectively in 19 and retrospectively in three centers, and the study protocol was approved by the Institutional Review Board at each participating location. The current study is a preplanned subgroup analysis of the prospectively identified LIPS cohort.

Study Population

Details of the study population have been previously described (15). Inclusion criteria were adult patients (> 18 yr) who had at least one major risk factor for ARDS, including sepsis, shock, pancreatitis, pneumonia, aspiration, high-risk trauma, or major cardiac and lung surgery. Exclusion criteria were acute lung injury (ALI) at the time of admission, transfer from an outside hospital, death in the emergency department, comfort or hospice care, or hospital readmission during the study period (15). In addition, we excluded patients on inhaled corticosteroids (ICS), because a previous study from our group suggested potential protective effect of inhaled steroids on the development of ALI (16).

Predictor Variables

The exposure of interest was SCS therapy documented in the medical record at admission; details pertaining to dose or duration of therapy were not collected. Demographic and clinical information was obtained at the time of hospital admission or preoperatively at the time of surgery. These data were used to calculate the LIPS as a measure of the baseline risk of developing ARDS and the Acute Physiology and Chronic Health Evaluation (APACHE)-II score as a measure of disease severity (15).

Outcome Variables

The main outcome was the development of ARDS during the hospitalization. At the time of data collection, the presence of ALI/ARDS was determined by the Standard American-European consensus conference criteria (17): development of acute, bilateral pulmonary infiltrates and hypoxemia (ALI: $\text{PaO}_2/\text{FIO}_2 < 300$, ARDS: $\text{PaO}_2/\text{FIO}_2 < 200$) in the absence of clinical signs of left atrial hypertension. However, since the recent Berlin definition removed the term of ALI and reclassified hypoxemia in the range of $\text{PaO}_2/\text{FIO}_2 < 300$ as ARDS (18), we used that term in reporting our results. Secondary outcomes included the need for invasive ventilation and in-hospital mortality. Patients were followed for the duration of their hospital stay, up to 90 days (15).

Statistical Analyses

Patients were separated into two groups on the basis of whether they were receiving SCS therapy on admission or not. We then performed univariate analyses to compare demographics, comorbidities, and medications between the groups.

However, as associations in unadjusted comparisons in an observational study can be misleading, a propensity score analysis was conducted to minimize biased estimates of the treatment effect. The propensity score is defined as the conditional probability of being treated given the individual's covariates and is calculated from a multiple logistic regression model (19). Unlike logistic regression where number of adjustments is limited by sample size, propensity analysis can incorporate any number of covariates. Therefore, we used all available baseline data, including demographics, comorbidities, medications, LIPS, and APACHE-II score, to essentially simulate randomization and derived a propensity score for each patient. Using a propensity score, we then matched patients on SCS by a Greedy algorithm (within the caliper width of one quarter of the SD of the logit of the propensity score) to identify up to four subjects not on SCS. Matching rather than stratification in this

instance was performed because of the smaller number of treated patients than the number of controls and because of significantly divergent distributions in the propensity scores between those on SCS and those who were not (19). Then, with each matched set as a stratum, a conditional logistic regression model was used to estimate the adjusted association of SCS with ARDS and other secondary outcomes.

Risk assessments are reported as odds ratios (ORs) with 95% CI. A p value of less than 0.05 was considered statistically significant. Contingency variables were compared using a Fisher exact test, and the distribution of continuous variables was assessed with the t test. All statistical analyses were performed using JMP 9.0.1 statistical software and SAS 9.1.3 (SAS Institute, Cary, NC).

RESULTS

As previously described (15), 5,584 patients were enrolled into the LIPS study between March 2009 and August 2009. The median age of the entire cohort was 57 years, and the majority was male Caucasians. At admission, their median severity of illness reflected by the APACHE-II score was 9 (interquartile range, 5–14) and LIPS was 2.5 (interquartile range, 1.5–4.5). As mentioned, 495 patients receiving ICS were excluded from analyses to avoid possible confounding, as secondary analysis of patients using ICS in the LIPS cohort suggested protective effect against ARDS among patients with risk factors for direct lung injury (20). Of the remaining 5,089 patients, 364 were using SCS at the time of hospitalization. Prevalence of ARDS was 7.7% and 6.9% (OR, 1.1 [95% CI, 0.8–1.7]; $p = 0.54$) for patients on SCS and not on SCS, respectively. Univariate analysis showed that patients on SCS were more likely to be older and have chronic pulmonary disease, malignancy, and previous chest radiation. Those patients were also more likely to be on aspirin, inhaled β -agonist, proton pump inhibitor, angiotensin receptor blocker, and insulin. They had a higher APACHE-II score and prevalence of pneumonia, sepsis, and shock. They were also less likely to undergo cardiac surgery, have brain injury, have bone fractures, were less frequently abusing alcohol and tobacco, and had a lower body mass index (Table 1).

Following derivation of the propensity score, covariates were well balanced (Table 1). The final analysis set of 1,447 patients comprised 354 patients (97%) on SCS who were matched to 1,093 not on SCS. Adjusted risk for ARDS, invasive ventilation, and in-hospital mortality was then calculated from this propensity-matched sample using a conditional logistic regression model with each matched set as a stratum. Following this comprehensive adjustment, there were no significant associations between prehospital use of SCS and primary or secondary outcomes (Table 2).

DISCUSSION

This is the first study that specifically evaluated the role of prehospital SCS use on the in-hospital development of ARDS among at-risk patients. Initial unadjusted analysis revealed no difference in prevalence of ARDS but suggested a decreased need for the mechanical ventilation and increased mortality among patients on SCS prior to hospitalization. Following propensity score-matched analysis on the basis of all available covariates, we

found that prehospital SCS intake neither reduced the prevalence of ARDS nor significantly affected the need for mechanical ventilation or mortality.

Due to their potent anti-inflammatory effect, the role of corticosteroids in the development and management of ARDS has been investigated for several decades. Corticosteroids were shown to switch off genes responsible for the synthesis of pro-inflammatory cytokines, chemokines, adhesion molecules, inflammatory enzymes, and receptors. Furthermore, they activate genes encoding anti-inflammatory mediators, such as interleukin-10- and interleukin-1-receptor antagonist (21). Patients with ARDS also manifest enhanced coagulation and diminished fibrinolysis. Infusion of methylprednisolone in early ARDS was previously shown to restore protein C levels in those with infectious/pulmonary causes (22). Additionally, corticosteroids have been shown to attenuate lung injury via inhibition of inducible nitric oxide expression (4). Nonetheless, there still exists an equipoise regarding the role of corticosteroids in ARDS.

To the best of our knowledge, no previous studies looked at the effect of prehospital corticosteroids on the development of ARDS, need for invasive mechanical ventilation, or hospital mortality. In fact, a few early randomized trials examining the role of corticosteroids in prevention of ARDS among septic patients used high-dose regimens and showed no significant role in prevention or survival benefit but rather potential harm due to increased infectious complications and mortality (5, 6, 9, 23). Of note, these studies employed varying definitions of ARDS and were conducted prior to the era of lung protective ventilation and early goal-directed therapy.

In an attempt to find a more definitive answer regarding the role of SCS in management of ARDS, several meta-analyses have been conducted. Agarwal et al (24) concluded that the evidence did not support a role for corticosteroids in the management of ARDS in either early or late stages, whereas Tang et al (25) reported that the use of low-dose corticosteroids was associated with improved mortality and morbidity without increased adverse effects. However, these meta-analyses included both randomized and observational studies, thus introducing the risk of bias associated with observational design into the overall analysis. Any direct comparison of observational data with a randomized trial should be done with caution as obtained results may not be attributable to the treatment effect alone.

A meta-analysis of randomized controlled trials using prolonged glucocorticoid treatment concluded that longer treatment duration substantially improved gas exchange, resulting in reduction in markers of inflammation, decreased duration of mechanical ventilation, and decreased ICU stay when initiated before day 14 of ARDS (26). Peter et al (27) concluded that although there was a possibility of reduced mortality and increased ventilator-free days when steroids were started after the onset of ARDS, preventive steroids appeared to increase the prevalence of ARDS in critically ill adults. Most recent work by Lamontagne et al (28) concluded that low-dose corticosteroids given within 14 days of disease onset may reduce all-cause mortality in patients with ALI, ARDS, and severe pneumonia, but that the quality of the evidence underlying the pooled estimate of effect was low, precluding definitive conclusions.

Overall, given the facts that ARDS represents a very heterogeneous syndrome and that treatment trials generally enrolled patients with varying disease etiologies and at different points in the disease course into one group representing “ARDS,” it is hardly surprising that the use of SCS has not shown consistent effects. Lack of significant effect of prehospital corticosteroids on ARDS prevalence, mechanical ventilation, and hospital mortality from our study, therefore, fits into the existing body of literature.

Our study has several important limitations. Although a secondary analysis, it was preplanned at the time of conception of the LIPS cohort. We decided to do separate analyses for SCS and ICS as a previous study from our group suggested protective effect of inhaled steroids on the development of ALI (16). Notably, by excluding the patients on ICS, we excluded some patients requiring the use of both ICS and SCS, limiting generalizability of obtained results. More importantly, data on the indication for SCS therapy, its duration, dose, patient compliance, and administration following hospital admission were not available. However, to address these limitations, we calculated a propensity score for each patient that included demographics, comorbidities (e.g., lymphoma, leukemia, chronic obstructive pulmonary disease, and asthma), and concurrent medications (e.g., chemotherapy, β -agonists, and insulin) and through matching approximated those on SCS to those not on SCS by a comprehensive propensity score. With this methodology, all potential imbalances in up to 50 clinical covariates were adjusted for, and those on SCS were very similar to the matched patients not on SCS based on the assigned propensity score. While propensity score matching partially addressed hidden biases, potential for unmeasured effects remains. Although, from the methodology standpoint, a prospective trial would be the option, at this time, it does not appear to be feasible.

Nonetheless, this study adds to the body of extensive research into the role of SCS on prevention and treatment of ARDS, specifically with regard to the effect of prehospital SCS use. The strengths of the study include its multicentered design and a large number of patients at risk for ARDS, as well as a comprehensive propensity score-matched analysis.

In conclusion, prehospital use of SCS neither prevented the development of ARDS among patients with at least one predisposing condition for ARDS nor affected the need for mechanical ventilation or hospital mortality.

Acknowledgments

Supported, in part, by KL2 RR024151 and the Mayo Clinic Critical Care Research Committee.

Drs. Lee and Gajic received funding from the National Institutes of Health.

We acknowledge help and support of Rob Taylor (Vanderbilt University, Nashville, TX) and Joseph J. Wick (Mayo Clinic) for the availability and maintenance of REDcap database.

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APPENDIX 1. U.S. Critical Illness and Injury Trials Group: Lung Injury Prevention Study Investigators 1 Participating Centers and Corresponding Investigators

Mayo Clinic, Rochester, MN: Adil Ahmed, MD; Ognjen Gajic, MD; Michael Malinchoc, MS; Daryl J. Kor, MD; Bekele Afessa, MD; Rodrigo Cartin-Ceba, MD; Departments of Internal Medicine, Pulmonary and Critical Care Medicine, Health Sciences Research, and Anesthesiology. University of Missouri, Columbia: Ousama Dabbagh, MD, MSPH, Associate Professor of Clinical Medicine; Nivedita Nagam, MD; Shilpa Patel, MD; Ammar Karo; and Brian Hess. University of Michigan, Ann Arbor: Pauline K. Park, MD, FACS, FCCS, Co-Director, Surgical Intensive Care Unit, Associate Professor, Surgery; Julie Harris, Clinical Research Coordinator; Lena Napolitano, MD; Krishnan Raghavendran, MBBS; Robert C. Hyzy, MD; James Blum, MD; Christy Dean. University of Texas Southwestern Medical Center in Dallas, TX: Adebola Adesanya, MD; Srikanth Hosur, MD; Victor Enoch, MD; Department of Anesthesiology, Division of Critical Care Medicine. University of Medicine and Dentistry of New Jersey: Steven Y. Chang, PhD, MD, Assistant Professor, MICU Director, Pulmonary and Critical Care Medicine; Ameer Patrawalla, MD, MPH; Marie Elie, MD. Brigham and Women's Hospital: Peter C. Hou, MD; Jonathan M. Barry, BA; Ian Shempp, BS; Atul Malhotra, MD; Gyorgy Frendl, MD, PhD; Departments of Emergency Medicine, Surgery, Internal Medicine and Anesthesiology Perioperative and Pain Medicine, Division of Burn, Trauma, and Surgical Critical Care. Wright State University Boonshoft School of Medicine & Miami Valley Hospital: Harry Anderson III, MD, Professor of Surgery; Kathryn Tchorz, MD, Associate Professor of Surgery; Mary C. McCarthy, MD, Professor of Surgery; David Uddin, PhD, DABCC, CIP, Director of Research. Wake Forest University Health Sciences, Winston-Salem, NC: James Jason Hoth, MD, Assistant Professor of Surgery; Barbara Yoza, PhD, Study Coordinator. University of Pennsylvania: Mark Mikkelsen, MD, MSCE, Assistant Professor of Medicine, Pulmonary,

Allergy and Critical Care Division; Jason D. Christie, MD; David F. Gaieski, MD; Paul Lanken, MD; Nuala Meyer, MD; Chirag Shah, MD. Temple University School of Medicine: Nina T. Gentile, MD, Associate Professor and Director, Clinical Research; Karen Stevenson, MD; Brent Freeman, BS, Research Coordinator; Sujatha Srinivasan, MD; Department of Emergency Medicine. Mount Sinai School of Medicine: Michelle Ng Gong, MD, MS, Assistant Professor, Pulmonary, Critical Care and Sleep Medicine, Department of Medicine. Beth Israel Deaconess Medical Center, Boston, MA: Daniel Talmor, MD, Director of Anesthesia and Critical Care, Associate Professor of Anesthesia, Harvard Medical School; Stephen Patrick Bender, MD; Mauricio Garcia, MD. Massachusetts General Hospital Harvard Medical School: Ednan Bajwa, MD, MPH, Instructor in Medicine; Atul Malhotra, MD, Assistant Professor; Boyd Taylor Thompson, MD, Associate Professor; David C. Christiani, MD, MPH, Professor. University of Washington, Harborview: Timothy R. Watkins, MD, Acting Instructor, Department of Medicine, Division of Pulmonary and Critical Care Medicine; Steven Deem, MD; Miriam Treggiari, MD, MPH. Mayo Clinic Jacksonville: Emir Festic, MD; Augustine Lee, MD; John Daniels, MD. Akdeniz University, Antalya, Turkey: Melike Cengiz, MD, PhD; Murat Yilmaz, MD. Uludag University, Bursa, Turkey: Remzi Iscimen, MD. Bridgeport Hospital Yale New Haven Health: David Kaufman, MD, Section Chief, Pulmonary, Critical Care & Sleep Medicine, Medical Director, Respiratory Therapy. Emory University: Annette Esper, MD; Greg Martin, MD. University of Illinois at Chicago: Ruxana Sadikot, MD, MRCP. University of Colorado: Ivor Douglas, MD. Johns Hopkins University: Jonathan Sevransky, MD, MHS, Assistant Professor of Medicine, Medical Director, JHBMC MICU.

TABLE 1

Group Characteristics, Univariate, and Propensity-Matched Adjustment

Variable	SCS (<i>n</i> = 364)	No SCS (<i>n</i> = 4,725)	Univariate, <i>p</i>	Propensity-Matched Set, <i>p</i> (<i>n</i> = 1,447)
Age ^a	57.6 + 17	55.4 + 19	0.03	0.49
Gender (male)	54%	58%	0.13	0.64
Caucasian	64%	60%	0.15	0.67
Body mass index > 30	19%	25%	0.02	0.67
Active smoking	12%	25%	< 0.001	0.81
Alcohol use	5%	9%	0.002	0.64
Acute Physiology and Chronic Health Evaluation II ^a	13.9 + 0.3	9.1 + 0.1	< 0.001	0.75
Lung injury prediction score ^a	2.9 + 1.9	3.1 + 2.1	0.2	0.80
Comorbidities				
Cardiac surgery	3.6%	10.1%	< 0.001	0.93
Aortic surgery	0.8%	2.4%	0.05	0.90
Thoracic surgery	1.4%	3.2%	0.05	0.91
Emergency surgery	3.3%	6.7%	0.01	0.99
Acute abdomen	4.4%	5.6%	0.3	0.50
Spine surgery	6%	9.2%	0.04	0.98
Bone fractures	2.2%	6.7%	< 0.001	0.86
Brain injury	1.4%	10.1%	< 0.001	0.74
Smoke inhalation	0.3%	0.6%	0.5	0.33
Lung contusion	0.3%	3.9%	< 0.001	0.33
Congestive heart failure, New York Heart Association IV	4.1%	2.9%	0.2	0.69
Sepsis	57.7%	29.9%	< 0.001	0.62
Shock	11.3%	6.9%	0.002	1.0
Diabetes	26.7%	22.3%	0.06	0.57
Pneumonia	33.5%	18.8%	< 0.001	0.85
Chronic obstructive pulmonary disease	10.7%	6.9%	0.006	0.38
Asthma	8.2%	5.5%	0.03	0.50
Interstitial lung disease	3.3%	0.5%	< 0.001	0.94
Gastroesophageal reflux disease	13.2%	11.1%	0.2	0.99
Aspiration	2.8%	4%	0.23	0.84
Pancreatitis	2.5%	6.2%	0.003	0.93
Sleep apnea	5.5%	3.7%	0.05	0.97
Chest radiation	2.5%	1%	0.009	0.97
Solid cancer	11%	4.8%	< 0.001	0.94
Leukemia	3.3%	0.8%	< 0.001	0.50
Lymphoma	4.4%	1.3%	< 0.001	0.91

Variable	SCS (<i>n</i> = 364)	No SCS (<i>n</i> = 4,725)	Univariate, <i>p</i>	Propensity-Matched Set, <i>p</i> (<i>n</i> = 1,447)
Hemodialysis	8%	3.6%	< 0.001	0.67
Cirrhosis	2.8%	2.2%	0.5	0.87
Medications				
Angiotensin-converting enzyme inhibitor	22.5%	19.3%	0.1	0.80
Angiotensin receptor blocker	7.4%	4.8%	0.03	0.72
Statin	27.8%	23.6%	0.08	0.45
Aspirin	32.1%	25.9%	0.009	0.47
Amiodarone	1.7%	0.8%	0.07	0.75
Proton-pump inhibitor	37.9%	19.5%	< 0.001	0.84
Histamine receptor 2 blocker	6%	5.1%	0.4	0.90
Insulin	16.2%	9.2%	< 0.001	0.77
Oral hypoglycemic	7.4%	11%	0.03	0.65
Inhaled β -agonist	16.2%	7.7%	< 0.001	0.50
Chemotherapy	11%	2.4%	< 0.001	0.69
Admission from home	84%	79%	0.04	0.48

SCS = systemic corticosteroids.

^aMean + SD.

TABLE 2

Association of Systemic Corticosteroids and the Outcomes in the Entire Cohort and in the Propensity-Matched Subset

Outcome	SCS (<i>n</i> = 364), %	No SCS (<i>n</i> = 4,725), %	Univariate, OR (CI), <i>p</i>	Propensity-Matched Set OR (CI), <i>p</i>
Acute respiratory distress syndrome	7.7	6.9	1.1 (0.8–1.7), 0.54	0.96 (0.54–1.38), 0.53
Mechanical ventilation	23	36	0.54 (0.42–0.7), < 0.001	0.84 (0.62–1.12), 0.24
Mortality	9.9	4.6	2.26 (1.56–3.27), < 0.001	0.97 (0.63–1.49), 0.89

SCS = systemic corticosteroids.