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Prehospital use of inhaled steroids and incidence of acute lung injury among patients at risk☆,☆☆,★

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ABSTRACT

Purpose: Inhaled corticosteroids (ICSs) attenuated lung injury in animal studies. We investigated the association between prehospital ICS and incidence of acute lung injury (ALI) among patients at risk.
Methods: In this ancillary analysis of the large multicenter Lung Injury Prediction Study cohort, we developed a propensity score for prehospital ICS use followed by matching, for all patients and for a subgroup of patients with at least 1 risk factor for direct pulmonary injury. The primary outcome was ALI; secondary outcomes included acute respiratory distress syndrome, need for invasive mechanical ventilation, and hospital mortality.
Results: Of the 5126 patients, 401 (8%) were using ICS. Acute lung injury developed in 343 (7%). The unadjusted incidence of ALI was 4.7% vs 6.9% ($P = .12$) among those in ICS compared with non-ICS group. In the "direct" lung injury subgroup, the unadjusted incidence of ALI was 4.1% vs 10.6% ($P = 0.006$). After propensity matching, the estimated effect for ALI in the whole cohort was 0.69 (95% confidence interval, 0.39-1.2; $P = .18$), and that in the direct subgroup was 0.56 (95% confidence interval, 0.22-1.46; $P = .24$).
Conclusions: Preadmission use of ICS in a hospitalized population of patients at risk for ALI was not significantly associated with a lower incidence of ALI once controlled by comprehensive propensity-matched analysis.
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1. Introduction

Acute lung injury (ALI)/acute respiratory distress syndrome (ARDS) is a heterogeneous syndrome often characterized by early inflammatory dysregulation [1]. Despite significant progress, the mortality and long-term morbidity associated with ALI remain considerable [2,3]. Given the abundance of negative pharmacologic therapeutic trials in established ALI [4,5], the focus has shifted toward the development of preventive strategies [6-8]. The current evidence-based recommendations for ALI prevention are limited to supportive

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measures such as lung-protective ventilation, timely resuscitation, and conservative transfusion practices [9-12].

Owing to their potent anti-inflammatory effects, systemic corticosteroids have been extensively studied for the prevention and treatment of ALI; however, the results have been somewhat discrepant [13-19]. Results of a large multicenter trial suggest that systemic corticosteroids are biologically active in ALI but may have negative systemic effects [18]. Clinical trials of the inhaled corticosteroids (ICSs) in ALI are lacking. However, in animal models of ALI, ICSs have demonstrated consistent attenuation in surrogate measures of ALI severity [20-24]. Also, in a study of patients at risk for pulmonary toxicity from chemotherapy, inhaled fluticasone reduced the incidence of delayed pulmonary toxicity compared with historical controls. Although this population did not have ARDS, the study at least suggested that ICS may protect against a pulmonary injury [25]. In a retrospective cohort study of adult patients from Olmsted County, Minnesota, at risk for ALI, the use of ICS was associated with decreased risk of ALI in patients with pneumonia [26].

Given the experimental animal data and limited clinical trial experience, along with the established anti-inflammatory effects of corticosteroids and the potential to avoid negative systemic effects with inhaled delivery, we performed a propensity-matched analysis of a multicenter prospective cohort to assess if prehospital ICS use reduced inpatient incidence of the ALI among at-risk patients.

2. Materials and methods

2.1. Setting

The United States Critical Illness and Injury Trials Group investigated 5584 patients admitted to 22 hospitals to evaluate the Lung Injury Prediction Score (LIPS) [6]. This secondary analysis of the ICS effect on incidence of ALI was accepted by the LIPS ancillary studies committee at the time of the conception of original LIPS study. The development of the LIPS cohort was approved and overseen by the institutional review board at each participating center.

2.2. Study participants

Details of the study population have been described previously [6]. Briefly, adult patients (>18 years) admitted to academic and community acute care hospitals were eligible if they had at least 1 major risk factor for ALI, including sepsis, shock, pancreatitis, pneumonia, aspiration, high-risk trauma, or high-risk surgery (including major cardiac and thoracic surgery). Patients were excluded if they had ALI at the time of admission, were transferred from an outside hospital, died in the emergency department, were admitted for comfort or hospice care, or readmitted during the study period. [6]

2.3. Predictor variables

The exposure of interest was ICS therapy determined at the time of hospital admission, obtained from the patient or family, and documented in the medical record. Any ICS medication, including combinations with β-agonists, was taken into account. Baseline characteristics consisting of demographic information and clinical data (comorbidities, medications, vital signs, laboratory studies) were collected at the time of admission or preoperatively for surgical patients. These clinical variables were used to generate the LIPS score as a measure of the baseline risk of developing ALI at the time of admission. The Acute Physiology and Chronic Health Evaluation (APACHE) II score was also assessed on the day of admission as a measure of disease severity [6].

2.4. Outcome variables

The primary outcome was the development of ALI during the hospitalization, as determined by the standard American-European Consensus Conference criteria at the time of the study conception [27]. The term *ALI*, therefore, included all patients with hypoxemia in the range of Pao_2/Fio_2 less than 300. This is in contrast with the recent Berlin definition [28], which reclassified ALI into ARDS of varying severity. Secondary outcome measures included the ARDS (hypoxemia in the range of Pao_2/Fio_2 <200), need for invasive mechanical ventilation, and hospital mortality. These secondary outcomes should be regarded as exploratory only because we have not performed adjustments for multiple comparisons beyond the assessment for the primary outcome. Patients were followed up for the duration of their hospital stay up to 90 days.

2.5. Statistical analyses

Patients were categorized into 2 groups on the basis of whether they were receiving ICS therapy at admission. The entire cohort was used to summarize the unadjusted risk for ALI and other outcome variables by the prehospital use of ICS.

To test the hypothesis that ICSs are protective for the development of ALI, propensity scores were developed to facilitate matching of patients with preadmission ICS use to those not exposed to ICS. This approach was implemented to account for the inherent differences in baseline characteristics between the 2 observational cohorts defined by the use of ICS at the time of admission. To approximate randomization, we used 50 variables captured at baseline (Table 1) to generate a comprehensive logistic regression model for the probability of being on ICS (ie, the propensity score). The patient's baseline risk for developing ALI based on the LIPS score and the severity of illness from the APACHE II score were also incorporated into this model. Subsequently, each patient on ICS was matched based on the logit of their propensity score by a greedy algorithm (the shortest Euclidean distance within the caliper width of one quarter of SD) [29] with up to 4 participants not on ICS. Finally, by using each matched set as a stratum, a conditional logistic regression model was used to estimate the independent risk (odds ratio [OR]) of ALI and other secondary outcomes from the prehospital use of ICS. Given our previous experience where the use of ICS was associated with decreased risk of ALI in patients with pneumonia [26], preplanned identical analyses were also performed on a subgroup of patients with at least 1 risk factor for ALI by direct pulmonary mechanisms (pneumonia, documented aspiration on admission, chest contusion, smoke inhalation, and near drowning). We also performed a post hoc sensitivity analysis on the primary outcome of ALI in a whole cohort by logistic regression that included ICS use and all 31 variables found to be statistically significant in the primary univariate analysis.

Risk estimates were reported as OR with their 95% confidence intervals (CIs). A P value less than .05 was considered statistically significant. We used the Fisher exact test to compare contingency tables and, when appropriate, t test, to compare distributions of continuous variables. All statistical analyses were performed using JMP 9.0 statistical software and SAS 9.1.3 (SAS Institute Inc, Cary, NC).

3. Results

3.1. Baseline information and unadjusted analyses

A total of 5584 patients admitted to the hospital with risk factors for ALI were enrolled in the prospective LIPS cohort [6]. We excluded 458 patients who were receiving systemic corticosteroids (SCS) at the time of admission. The remaining 5126 patients, 401 (8%) of which were using ICS at the time of the hospitalization, served as the

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