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Effect of inhaled iloprost on gas exchange in inhalation injury

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ABSTRACT

Objective: Inhalation injury is an independent risk factor for mortality in burn patients. The purpose of this study was to observe the effect of inhaled iloprost on gas exchange in patients with inhalation injury and acute respiratory failure as measured by an improved PaO_2/FiO_2 ratio.
Methods: Patients admitted to the burn intensive care unit from 2013 to 2014 meeting Berlin criteria for acute respiratory distress syndrome (ARDS) with a diagnosis of inhalation injury and who received inhaled iloprost were included. Medical records were reviewed to collect patient demographics, characterize iloprost prescribing practices, and observe changes in oxygenation and hemodynamic status after iloprost administration. Differences were evaluated using a *t*-test with cluster corrected standard errors.
Results: A total of eight patients were included with 157 different PaO_2/FiO_2 ratios calculated. All patients had moderate or severe ARDS with a baseline PaO_2/FiO_2 ratio of 131.9 mmHg (IQR 119.3–197.3). Median duration of iloprost therapy was 5 days (IQR ± 7). A statistically significant increase in PaO_2/FiO_2 ratio was observed after iloprost administration with a mean increase of 9.7 mmHg (95% CI 1.8–17.7, $p = 0.023$). Inhaled iloprost had no effect on hemodynamic parameters.
Conclusions: Inhaled iloprost for inhalation injury and ARDS after burn injury was associated with a small but statistically significant improvement in oxygenation.

1. Introduction

Inhalation injury occurs in approximately 20% of all burns and is an independent risk factor for mortality in burn patients [1]. In a recent meta-analysis, the presence of inhalation injury in patients with severe burns approximately doubled the mortality rate (13.9% vs. 27.6%) [2]. Injury results from the inhalation of smoke or chemical products with damage mediated through thermal injury, direct contact of particulate matter on lung tissue, and subsequent inflammatory response. Though thermal injury primarily occurs above the carina, this injury can result in profound swelling of upper airway structures including the tongue, epiglottis, and aryepiglottic folds. Chemical injury from substances produced from burning material accounts for the majority of inhalation injury and occurs throughout the respiratory tract leading to altered mucociliary clearance, increased airway exudation, alveolar collapse from surfactant loss, and macrophage activation [3–5]. In addition to inhalation injury, burn patients experience multiple mechanisms of lung injury leading to acute respiratory distress syndrome (ARDS) including systemic inflammation secondary to burn wounds and increased risk for both pneumonia and ventilator-induced lung injury [6]. Further, patients with inhalation injury have increased fluid requirements, often requiring aggressive resuscitation leading to pulmonary edema and further progression of respiratory failure [7–9].

Given the lack of evidence for efficacy of pharmacologic strategies in reducing morbidity or mortality of patients with ARDS, management traditionally focuses on treatment of the underlying condition and supportive care (i.e. fluid management and low tidal

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volume ventilation) [10,11]. However, pharmacologic modalities continue to be explored, including inhalation options with limited systemic side-effect profiles. Prostacyclins are agents that induce smooth muscle relaxation via upregulation of cyclic adenosine monophosphate (cAMP), thereby causing pulmonary vasodilation and decreasing pulmonary hypertension and ventilation-perfusion mismatch. Due to this vasodilation, hypotension is a common side effect of prostacyclins when administered systemically. When nebulized, systemic side-effects are largely avoided [12]. Additionally, inhaled agents are only distributed to undamaged lung parenchyma capable of receiving ventilation. Because increased blood flow occurs only in aerated lung tissue, gas exchange is maximized leading to improvement in capillary oxygenation and increases in PaO_2 [13]. Additionally, upregulation of cAMP may produce beneficial anti-inflammatory effects, which may mediate the deleterious inflammatory processes that occur in burn and inhalation injury [14].

To date, data on the use of inhaled prostacyclins to improve gas exchange and oxygenation in inhalation injury are limited though evidence suggests that pulmonary hypertension is present in inhalation injury [15]. Most studies exploring inhaled prostacyclins in adults with ARDS have focused on aerosolized epoprostenol (also known as prostacyclin or PGI_2) and have shown statistically significant improvements in the PaO_2/FiO_2 ratio, though none of the patients studied had inhalation injury [16–18]. The largest study evaluating inhaled iloprost (a synthetic analog of prostacyclin) in patients with ARDS demonstrated a significant increase in the PaO_2/FiO_2 ratio, though only three patients had inhalation injury [19]. In the present study, we hypothesized that inhaled iloprost would be associated with improved oxygenation as measured by an improved PaO_2/FiO_2 ratio without significant change in hemodynamic status.

2. Materials and methods

2.1. Study population, design, and data collection

Patients admitted to the burn intensive care unit (ICU) of North Carolina Jaycee Burn Center between August 1, 2013 and March 1, 2015 were screened for inclusion by evaluating for the presence of inhalation injury and ARDS in order to be included in our retrospective cohort analysis. The North Carolina Jaycee Burn Center is a 36-bed unit with over 1,500 acute care admissions annually. Patients were subsequently screened for use of inhaled iloprost during admission to the burn ICU. Inhalation injury was physician diagnosed upon initial bronchoscopy by the presence of any of the following: soot, mucosa inflammation, mucosal sloughing, or secretions [20]. ARDS was diagnosed according to consensus conference criteria as the acute onset of diffuse pulmonary infiltrates, a PaO_2/FiO_2 ratio <300 mmHg while on mechanical ventilation, the presence of a recognized cause of ARDS, and the absence of clinical evidence of a cardiac source [21]. Exclusion criteria included patients $\leq$18 years old and pregnancy. All patients were managed using standard burn ICU protocols based upon current best practices. Patients were initiated on iloprost therapy, including dose, frequency, and duration, based on individual physician discretion. This study was approved by the University of North Carolina (UNC) institutional review board.

Medical records were reviewed to collect patient demographics, characterize iloprost prescribing practices, and identify changes in oxygenation and hemodynamic status after iloprost administration. Demographic characteristics included age, sex, percent total body surface area (%TBSA) burn, hospital mortality, and length of stay. Prescribing practices were characterized by iloprost dose strength, dose frequency, and length of use. To assess changes in oxygenation, laboratory measures including venous and arterial blood gas values were collected in addition to mechanical ventilation settings to assess PaO_2 and PaO_2/FiO_2 ratio. A secondary objective was to characterize the effect of inhaled iloprost on hemodynamic status as measured by changes in mean arterial pressure (MAP) and systolic blood pressure (SBP). Changes in vasoactive medications were also recorded. All collected hemodynamic values were recorded hourly for the duration of inhaled prostacyclin administration.

2.2. Statistical analysis

Descriptive statistics were performed to characterize patient demographics and iloprost prescribing practices. To identify differences in PaO_2/FiO_2 ratio after inhaled prostacyclin administration, difference scores were computed by subtracting the PaO_2/FiO_2 ratio before and after the administration of each iloprost dose. Difference scores were similarly computed for MAP and SBP. A *t*-test with cluster corrected standard errors was used to assess improvement. A two-tailed *p*-value less than 0.05 was considered statistically significant. SAS software was used to perform statistical tests (Cary, NC) [22]. Data are presented as mean ± standard deviation (SD) for continuous variables and percentages for categorical variables, unless otherwise noted.

3. Results

A total of eight patients met inclusion criteria. Demographic characteristics are summarized in Table 1. Five patients were ventilated with a volumetric diffusive respirator (VDR) and three patients were ventilated with airway pressure release ventilation (APRV). At the time of iloprost initiation, median PaO_2 was 86.5 mmHg (IQR 70.8–124.3), and median baseline FiO_2 was 60% (IQR 50–77.5). The median baseline PaO_2/FiO_2 ratio was 131.9 mmHg (IQR 119.3–197.3). All patients were prescribed neuromuscular blockade at the time of iloprost initiation. Most

Table 1
Demographic characteristics.

Characteristic	All participants (n = 8)
Male, *n* (%)	6 (75)
Age (years)	48.5 (28.2–68.6)
Weight (kg)	94.0 (60.5–127.5)
TBSA burn (%)	32.5 (8.5–56.5)
Duration of iloprost Therapy	5 (0–12)
Hospital mortality, *n* (%)	3 (37.5)
Length of stay (days)	5 (83.3)
ICU length of stay (days)	6 (75.0)
Characteristics at time of iloprost initiation and discontinuation	
Characteristic	**Initiation**	**Discontinuation**
Neuromuscular blocker, *n* (%)	8 (100)	3 (37.5)
Arterial pH	7.4 (7.3–7.5)	7.4 (7.3–7.4)
PaO_2 (mmHg)	86.5 (70.8–124.3)	125.5 (99–150)
FiO_2 (%)	60 (50–77.5)	50 (45–55)
PaO_2/FiO_2 (mmHg)	131 (119–197)	225 (166–331)
Ventilator mode, *n* (%)		
VDR	5 (62.5)	3 (37.5)
Frequency (cycles/minute)	600	600
I:E ratio	1.6:1 (1.6–2.1)	1.6:1 (1.1–1.6)
APRV	3 (37.5)	5 (62.5)
P_{high} (mmHg)	38 (36–38)	30 (25–36)
P_{low} (mmHg)	0 (0)	0 (0)
T_{high} (sec)	4 (3–4)	3.5 (3–3.9)
T_{low} (sec)	0.6 (0.6)	0.8 (0.6–0.8)

Results reported as median (IQR) unless otherwise noted.
VDR: volumetric diffusive respirator; APRV: airway pressure release ventilation.

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