Safety of Nebulized Epinephrine in Smoke Inhalation Injury

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This pilot study was conducted to profile safety of nebulized racemic epinephrine when used as a therapy for smoke inhalation injury in severely burned children. We enrolled 16 patients who were 7 to 19 years of age ([mean ± SD], 12 ± 4 years) with burns covering more than 30% of the TBSA (55 ± 17%) and smoke inhalation injury, as diagnosed by bronchoscopy at burn center admission. Patients were randomized to receive either standard of care (n = 8), which consisted of nebulized acetylcysteine, nebulized heparin, and nebulized albuterol, or to receive standard of care plus nebulized epinephrine (n = 8). Primary endpoints were death, chest pain, and adverse changes in cardiopulmonary hemodynamics (arrhythmia, arterial blood pressure, electrocardiographic [ST segment] changes, and peak inspiratory pressure). Additional endpoints included total days on ventilator, pulmonary function, and physiological cardiopulmonary measurements at intensive care unit discharge. No adverse events were observed during or after the nebulization of epinephrine, and no deaths were reported that were attributable to the administration of nebulized epinephrine. The groups did not significantly differ with regard to age, sex, burn size, days on ventilator, pulmonary function, or cardiopulmonary fitness. Results of this pilot trial indicate epinephrine to be safe when administered to pediatric burn patients with smoke inhalation injury. Current data warrant future efficacy studies with a greater number of patients. (J Burn Care Res 2017;38:396–402)

Burns are often the result of childhood accidents. The American Burn Association estimates that 95% of burn injuries are accidents,[1] leading to 265,000 deaths around the world annually, mainly in low- and middle-income countries.[2] According to the most recent National Burn Repository (NBR), the percentage of patients with only smoke inhalation injury is 1.1% and with smoke inhalation injury plus burns is almost 10%.[1] Others have reported the frequency of smoke inhalation injury plus burns is as high as 19.6%[3,4] among patients admitted to burn centers.

Additionally, in the age groups of > 60 years of age, case fatality greatly increases at the level of 20% TBSA with inhalation injury and above as compared with < 60 years of age.[1]

Despite recent advances in critical care and the management of burn patients, smoke inhalation injury continues to substantially increase the morbidity and mortality after burns.[5]

In a classic study published in 1987 that described a large clinical experience at the U.S. Army Institute of Surgical Research, the predicted mortality among patients with burns was 20% higher when inhalation injury was present that when it was not; if secondary pneumonia developed, mortality was 60% higher.[6]

Dr. Sheridan published in 2016 in the New England Journal of Medicine that the complex physiological processes underlying inhalation injury remain poorly understood and specific therapeutic interventions remain ineffective.[7]

Smoke inhalation injury leads to airway lumen narrowing or occlusions through bronchospasm, increased

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This study was supported by the National Institutes of Health (P50 GM060338, UL1 TR000071, R01 GM056687, and R01 HD049471) and Shriners Hospitals for Children (84080 and 84050). It was also supported by the US Army Medical Research and Materiel Command, through the Military Burn Research Program under Award No. W81XWH-12-2-0086. Opinions, interpretations, conclusions and recommendations are those of the author and are not necessarily endorsed by the U.S. Army. In conducting research using animals, the investigator(s) adheres to the laws of the United States and regulations of the Department of Agriculture.

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1559-047X/2017

DOI: 10.1097/BCR.0000000000000575

mucus secretion, formation of airway casts, and increased airway blood flow. Augmented airway blood flow, in particular, plays a critical role in the pathogenesis of acute lung injury after smoke inhalation.[8,9] A 20-fold increase in bronchial blood flow occurs immediately after inhalation injury, resulting in lung edema and pulmonary transvascular fluid flux.[10–12] Moreover, increased plasma exudates in the airway play a role in the formation of obstructive casts,[13] which diminish pulmonary function, and may cause atelectasis, pneumonia, and barotrauma respiratory distress.[14,15]

The successful results obtained with the ligation of the bronchial artery in sheep are not feasible in humans. Therefore, we decided to pursue a pharmacological approach that would mimic the effects of ligation of the bronchial artery.

The major pathophysiology seen after inhalation injury arises from microvascular changes.[16] Combined thermal and inhalation injury leads to upregulation of cytokines such as interleukin-1 in lung tissue. Both interleukin-1 and endotoxin activate NF-kB, which induces the synthesis of iNOS and iNOS catalyses. This leads to the production of large amounts of the vasodilator nitric oxide[17] to produce bronchial vasodilation.

Reactive oxygen species combine with nitric oxide (a potent vasodilator), constitutively formed in the endothelium, to form reactive nitrogen species.[18]

The latter produce edema in the burned area by increasing the microvascular pressure and permeability to protein.[19]

Successful treatment of patients with burns and smoke inhalation injury largely depends on the prevention of airway occlusion and ventilator-induced lung injury while providing necessary mechanical ventilator support until needed. Thus, a single pharmacological agent that can decrease bronchospasm, reduce airway wall edema, and prevent the airway transudation would be highly valuable for this purpose. The agent should also target the airway obstruction that results from augmented airway blood flow. Epinephrine is a nonspecific adrenergic receptor agonist that induces vasoconstriction via alpha-one receptor stimulation and bronchodilation via beta-two agonist effects.[20] Vasoconstriction can reduce the blood flow to glands and decrease mucus secretion. Thus, administering nebulized epinephrine into the airway may be an effective way to moderate most of the detrimental airway changes after smoke inhalation injury. Additional advantages of epinephrine are its low cost and availability in powder and liquid forms, which can be easily aerosolized.

We have previously investigated the efficacy and safety of nebulized epinephrine in a well-characterized smoke inhalation injury ovine model. We found that epinephrine significantly reduced pulmonary transvascular fluid flux to water and protein when compared with the control treatment.[21] It also reduced airway blood flow and attenuated pulmonary dysfunction.[22] Given the beneficial effects of nebulized epinephrine in this experimental model, we conducted this pilot study to test the safety of nebulized epinephrine when used as a therapy for inhalation injury in burn patients.

METHODS

Patients and Study Design

This prospective randomized study was conducted in children admitted to our burn center from September 2014 to September 2016. The study protocol was approved by the institutional review board (University of Texas Medical Branch, Galveston, TX). Parents or legal guardians provided informed consent before enrollment. To be included in the study, all children must have been between 7 and 19 years of age. This age range was selected based on our previous experience in administering the Six-Minute Walk Test (6MWT) and use guidelines suggested by the American Thoracic Society (ATS) for pulmonary function tests; children who are 7 years or older can properly follow the instructions to do these tests, and reliable results can be obtained. Other inclusion criteria were thermal burns (flame alone or combination of flame and electrical) covering more than 30% of the TBSA, confirmed inhalation injury, and admission to the burn unit within 96 hours of injury. Exclusion criteria were pregnancy and preexisting use of alpha- or beta-receptor blocking agents. Inhalation injury was confirmed by bronchoscopy in all patients. Bronchoscopic findings had to have included soot deposits, erythema, edema, mucosal blisters and erosion, and hemorrhage. At admission, height and weight were measured.

Primary endpoints were adverse events (arrhythmia, increase in blood pressure, shock, dyspnea, ST segment changes, chest pain, and death). Secondary endpoints were length of time on ventilator (LOV), length of stay (LOS) in the intensive care unit (ICU), pulmonary function which includes forced expiratory volume in the first second (FEV1), percent predicted FEV1, forced vital capacity (FVC), percent predicted FVC, pneumonia, pulmonary mechanics (tidal volume, peak inspiratory pressure, positive end expiratory pressure), albuterol doses required, and distance covered in the 6MWT.

Treatment Groups and Standard of Care

Patients were randomly allocated to either of the following groups:

1) Standard of care (SOC) group

- Albuterol 2.5 mg in 3 ml of saline, nebulized as needed for wheezing over 7 days;
- Acetylcysteine (20% solution), 3 ml nebulized every 4 hours over 7 days;
- Heparin (5,000 units/3 ml), 3 ml solution nebulized every 4 hours over 7 days;
- Percussion and postural drainage (chest physical therapy), routine every 4 hours, mechanical.

2)Intervention group (SOC plus epinephrine [SOC + EPI])

- Racemic epinephrine (2.25% solution, 0.5 mL in 3 mL of saline) administered every 4 hours for 7 consecutive days.

For the nebulization, a respiratory therapist adjusted the settings and characteristics of the ventilator and set the nebulizer according to previously published recommendations.[23] This included the following:

- Suctioning of endotracheal and airway secretions;
- Placing drug in nebulizer to correct fill volume;
- Placing nebulizer in the inspiratory line 18 inches from the patient y-piece;
- Turning off flow-by or continuous flow during nebulization;
- Adjusting the inspiratory time for a longer cycle time;
- Setting gas flow to nebulizer at 8 L/min;
- Using continuous flow from an external gas source;
- Adjusting ventilator volume or pressure limit to compensate for additional flow;
- Tapping nebulizer periodically until nebulizer begins to sputter;
- Monitoring patient for adverse outcomes (see primary outcomes);
- Assessing outcome and documenting findings.

Since the ventilators used in the study did not have a built-in nebulizer for nebulization strictly during inspiration, we continuously nebulized the medication at the prescribed dose and in the manner delineated above. To reduce the amount of drug that may have been deposited in the ventilator tubes rather than in the airway of the patients, we followed all the recommendations given by Dolovich[24] per the bullets above.

LOV, LOS, Presence of Pneumonia, and Albuterol Doses

The total days of mechanical ventilation, LOS, LOS/TBSA, LOS/TBSA third degree burn, and the presence of pneumonia were recorded as reported on the medical records. The total number of albuterol doses needed during the first 7 days of hospitalization were also recorded.

Functional Capacity Testing

On ICU discharge, patients' physical functional capacity was assessed via the 6MWT. The 6MWT was performed indoors along a long, flat, straight, and enclosed corridor that is seldom traveled and has a hard surface. The walking course was 30 m in length and had turnaround points that were marked with cones (such as orange traffic cones) according to the ATS guidelines.[25] Briefly, patients were instructed to walk at their fastest pace and to cover the longest possible distance over a 6-minute period while under the supervision of trained clinical research assistants.

Pulmonary Function Testing and Ventilator Variables

Lung volumes were assessed during scheduled outpatient visits within the first week of discharge from the ICU. The pulmonary function testing (PFT) study variables included FVC, FEV1, and diffusing capacity of the lungs for carbon monoxide (DLCO). All spirometry measurements were performed using a PFT system (Medical Graphics PF/DX, St. Paul, MN) with the subject in an upright position. Lung volumes were corrected for body temperature and atmospheric pressure. Subjects correctly performed at least 2 practice forced maximal inhalations and exhalations before any spirograms were recorded. All expected values were obtained using validated general population equations, and normal predicted values were obtained from Knudson et al.[26] The procedures were performed in accordance with the guidelines from the ATS.[27] The criteria that were used to determine whether the subjects performed the maximal spirometry maneuvers included 1) appropriate flow-volume curve shape, 2) lack of artifacts in results such as coughing, premature termination of the test, expiratory effort, or delayed onset of measurement, 3) sustained expiration for a minimum of 3 seconds, and 4) performance deemed satisfactory by the tester.[28] Ventilator parameters such as tidal volume, peak inspiratory pressure, and positive end expiratory pressure were obtained from the electronic medical record.

Adverse Events

The patients were closely observed during the administration of the drug by the respiratory therapist as well as by the ICU nurse. Heart rate, electrocardiogram

trace (ST segment change), arrhythmia, blood pressure, and oxygen saturation were constantly monitored to detect any possible adverse events directly related to the nebulization of epinephrine.

Statistical Analysis

Measurements were transferred to an encrypted spreadsheet, and statistical analyses were performed using Excel (Microsoft, Richmond, VA). Normally distributed measurements are presented as mean ± SD. Continuous measurements such as age, TBSA burn, TBSA full-thickness burn, height, weight, LOS, ventilator days, FEV1, FEV1%, FVC, FVC%, and DLCO were compared between groups using a Student's *t*-test for matched pair samples. Sex was compared using a chi-square test. Significance was accepted at $P < 0.05$.

RESULTS

Patient Characteristics

Sixteen patients were enrolled, 8 in the SOC group (5 males and 3 females) and 8 in the SOC + EPI group (6 males and 2 females; Table 1). Mean age was 13 ± 4 years in the SOC group and 11 ± 2 years in the SOC + EPI ($P = 0.481$). The groups did not statistically significantly differ with respect to percent TBSA burned (58 ± 14% for SOC vs 49 ± 18% for SOC + EPI; $P = 0.277$), percent TBSA full-thickness burn (51 ± 20% for SOC vs 43 ± 24% for SOC + EPI; $P = 0.502$), height (148.6 ± 19.5 cm for SOC vs 144.8 ± 19.2 cm for SOC + EPI; $P = 0.713$), or weight (52.3 ± 21.7 kg for SOC vs 42.1 ± 14.9 kg for SOC + EPI; $P = 0.306$).

Adverse Events and Mortality

The main goal of the study was to determine the safety of the nebulized epinephrine for children with smoke inhalation injury. Neither group had any adverse event such as arrhythmia, shock, dyspnea, ST segment changes, or chest pain that was related to the administration of nebulized epinephrine. In addition, there were no deaths during acute hospitalization.

Table 1. Patient characteristics*

Characteristics	Standard of Care, n = 8	Standard of Care Plus Epinephrine, n = 8	*P*
Sex, male:female	5:3	6:2	NA
Age (yr)	13 ± 4	11 ± 2	0.481
Height (cm)	148.6 ± 19.5	144.8 ± 19.2	0.713
Weight (kg)	52.3 ± 21.7	42.1 ± 14.9	0.306
TBSA burn (%)	58 ± 14	49 ± 18	0.277
TBSA full-thickness burn (%)	51 ± 20	43 ± 24	0.502

*Values are presented as mean ± SD unless otherwise noted.
NA, not applicable.

LOV, LOS, Presence of Pneumonia, and Albuterol Doses

LOV was 7.5 ± 5.5 days in the SOC + EPI group and 10.1 ± 7.6 days in the SOC group ($P = 0.470$; Table 2). LOS was 47.4 ± 44.4 days in the SOC + EPI group and 55.2 ± 25.6 days in the SOC + EPI group ($P = 0.687$). LOS normalized to TBSA burned was similar between groups (LOS/TBSA burned = 0.9), as was LOS normalized to TBSA full-thickness burn (LOS/TBSA full-thickness burn = 1). Pneumonia occurred in 4 of the 8 SOC patients (50%) and only 3 of the 8 SOC + EPI patients (37.5%). The number of doses of albuterol required was 6.7 ± 9 and 5.1 ± 8 for SOC and SOC + EPI patients, respectively ($P = 0.748$).

Functional Capacity Testing, PFT, and Ventilator Variables

The distance walked in the 6MWT was 253 ± 268 ft for the SOC group and 588 ± 384 ft for the SOC + EPI group ($P = 0.079$; Table 2). PFT variables were comparable in the 2 groups: FEV1 (2.1 ± 0.9 L for SOC vs 2.4 ± 1.79 L for SOC + EPI; $P = 0.787$), percent predicted FEV1 (86.3 ± 85% for SOC vs 90.6 ± 31.5% for SOC + EPI; $P = 0.837$), FVC (2.5 ± 1.2 L for SOC vs 3.1 ± 1.9 L SOC ± EPI; $P = 0.735$), and percent predicted FVC (87.3 ± 9.4% for SOC vs 97.1 ± 23% for SOC + EPI; $P = 0.554$). DLCO was also similar in both groups (12.6 ± 4 mL/min/mm Hg for SOC vs 12.7 ± 10 mL/min/mm Hg for SOC + EPI; $P = 0.991$). The percent predicted DLCO was comparable in both groups as well (74.5 ± 23% for SOC vs 147 ± 114% for SOC + EPI; $P = 0.692$; Table 3). Tidal volume (432 ± 209 mL for SOC vs 338 ± 138 mL for SOC + EPI; $P = 0.371$), peak inspiratory pressure (29 ± 2 mm Hg for SOC vs 23 ± 9 mm Hg for SOC + EPI; $P = 0.119$), and positive end expiratory pressures were also similar between groups (8.0 ± 0.4 mm Hg for SOC vs 7.0 ± 2.1 for SOC + EPI; $P = 0.262$; Table 2).

DISCUSSION

The major finding of the study was that the nebulization of racemic epinephrine in children 7 to 19 years old with smoke inhalation injury was safe, as no adverse effects such as an increase in heart rate or

Table 2. Length of ventilation, length of ICU stay, and six-minute walk test*

Characteristics	Standard of Care, n = 8	Standard of Care Plus Epinephrine, n = 8	*P*
Length of ventilation (d)	10.1 ± 7.6	7.5 ± 5.5	0.470
Length of stay (d)	55.2 ± 25.6	47.4 ± 44.4	0.687
Length of ICU stay/TBSA burn	0.9	0.9	NA
Length of ICU stay/TBSA full-thickness burn	1	1	NA
Six-minute walk test (ft)	253.5 ± 268.8	588.1 ± 384.4	0.079
Presence of pneumonia, n (%)	50.0	37.5	NA
Tidal volume (mL)	432 ± 209	338 ± 138	0.371
Peak inspiratory pressure (mm Hg)	29 ± 2	23 ± 9	0.119
Positive end expiratory pressure (mm Hg)	8.0 ± 0.4	7.0 ± 2.1	0.262
Albuterol doses required in intensive care unit, n	6.7 ± 9.0	5.1 ± 8.0	0.748

*Values are presented as mean ± SD unless otherwise noted.
NA, not applicable.

mean arterial blood pressure, arrhythmia, elevation of ST segment, or death were observed during or after the nebulization period.

Although determining the efficacy of nebulized epinephrine was not a primary goal of this study because of the limited numbers of patients in each arm, we were able to investigate some key variables, for example, LOV, as secondary endpoints. It is premature to draw any conclusion regarding the efficacy of nebulized epinephrine, given the lack of any significant differences in the variables measured and the limited number of enrolled patients. Nevertheless, our data suggest that patients treated with epinephrine may have experienced improved physical endurance, but there are differences between the groups regarding age, weight, and burn size that are clinically significant and this may explain the results in the distance walked during the 6MWT. The difference of the distance walked could also be related to the decrease in LOV and LOS. It has previously been reported that muscle loss increases with sustained LOS in the ICU, a condition known as ICU-acquired weakness that is related to inactivity in the ICU plus the hypermetabolic state of critically ill patients.[29,30] It is possible that the decrease in ICU days resulted in better daily activities (i.e., eating, bathing, dressing, toileting, and walking).[31] The 6MWT is a valid outcome in ICU survivors; it has been used in a prior ICU randomized controlled trial[32] and predicts patient-centered outcomes including mortality and quality of life.[33]

Table 3. Pulmonary function tests*

Characteristics	Standard of Care, n = 8	Standard of Care Plus Epinephrine, n = 8	*P*
FEV1 (L)	2.1 ± 0.9	2.4 ± 1.79	0.787
FEV1, % predicted	86.3 ± 85	90.6 ± 31.5	0.837
FVC (L)	2.5 ± 1.2	3.1 ± 1.9	0.735
FVC, % predicted	87.3 ± 9.4	97.1 ± 23	0.554
DLCO (mL/min/mm Hg)	12.6 ± 4	12.7 ± 10	0.991
DLCO, % predicted	74.5 ± 23	147.1 ± 114	0.692

FEV1, forced expiratory volume in the first second; FVC, forced vital capacity; DLCO, diffusing capacity of the lungs for carbon monoxide.
*Values are presented as mean ± SD.

Factors reducing the 6MWD: shorter height, older age, higher body weight, female sex, impaired cognition, a shorter corridor (more turns), pulmonary disease (chronic obstructive pulmonary disease, asthma, cystic fibrosis, interstitial lung disease), cardiovascular disease (angina, myocardial infarction, congestive heart failure, stroke, transient ischemic attack, peripheral vascular disease), musculoskeletal disorders (arthritis, ankle, knee, or hip injuries, muscle wasting, etc.)

Factors increasing the 6MWD: taller height (longer legs), male sex, high motivation, a patient who has previously performed the test, medication for a disabling disease taken just before the test, and oxygen supplementation in patients with exercise-induced hypoxemia.[25]

The results of this pilot study showing that nebulized epinephrine is well tolerated without any adverse effects and may have beneficial effects in burn patients with smoke inhalation injury mandate larger prospective randomized clinical studies on efficacy. The use of nebulized epinephrine for the treatment of smoke inhalation injury is innovative, as no studies have investigated the local use of epinephrine in the airway to treat smoke inhalation injury in the pediatric population. The dual action of epinephrine (alpha-one and beta-two adrenergic receptor agonist) enables it to counter multiple pathophysiologic changes that develop in the airway after an inhalation injury. For example, it produces

bronchial vasoconstriction, and it diminishes the formation of mucus casts by reducing the blood flow to the mucus glands. It also reduces transvascular fluid flux and protein leakage into the airway, preventing the formation of obstructive casts in the airway that prevent adequate oxygenation. Finally, it has bronchodilating effects that reduce inherent bronchospasm arising after an inhalation injury.

There are a few limitations of this study. One is that the severity of inhalation injury was not graded in the study patients. Fiber-optic bronchoscopy is necessary for diagnosis of smoke inhalation injury. However, whether the severity of mucosal injury, as assessed through bronchoscopy, is capable of predicting clinically meaningful outcomes remains a matter of debate.[34] The severity can also be assessed through tomography if patients show airflow narrowing.[35] As there is no clear consensus on the diagnosis and grading of inhalation injury, our patients were diagnosed by bronchoscopy, which allowed us to determine whether there was any evidence of smoke inhalation injury. However, as mentioned, severity of inhalation injury was not graded. Differing injury severity likely leads to variations in the hospital course and progress of the patient. Thus, failure to classify the patients into groups with mild, moderate, or severe injuries must be taken into account when interpreting the study data because the number of ventilator days and other outcomes will be worse in patients with severe smoke inhalation injury than in those with a mild injury, regardless of the administration of nebulized epinephrine.

Other limitations of this study are the relatively small number of patients and the relatively late arrival of the patients to the burn center for care. It is well established that, in children with severe burns, early burn center transfer shortens hospital stay and decreases complications.[36] All patients in this study arrived within the first 96 hours post burn. This late arrival is typical because patients are referred to our hospital from all over the world and time is needed to complete necessary paperwork and arrange transport. Edema reaches its maximum in the first 48 hours post burn, so epinephrine is being started after the edema peak and this may explain why our results are not statistically significant. Given that epinephrine would be expected to be more effective when initiated right after the injury, decreasing this time from burn to epinephrine treatment may provide significant results as to its effectiveness, even if the sample size must be sacrificed.

Another limitation of the study is the nonstandardized treatment that patients receive prior to their arrival. Overresuscitation (fluid overload) can lead to pulmonary edema even in a patient with no inhalation injury. Moreover, the aggressive use of high tidal volume when ventilating a patient significantly increases the incidence of pneumothorax and the high comorbidity and risk of death that this complication imply.[37] A final limitation could be that the treatment was administered for only the first 7 days of hospitalization. It is possible that epinephrine has benefits when used beyond 7 days or that nebulized racemic epinephrine is most effective when administered for the entire time that the patient is on the ventilator.

Findings from this pilot study will be used to design a large-scale randomized clinical trial with the goal of translating these findings into clinical practice. Increasing the inclusion age range will extend the potential benefits to more subjects, especially infants, who have a smaller airway diameter and are at greater risk of airway occlusion. Future studies should also examine extended treatment times and be multicenter investigations.

ACKNOWLEDGMENTS

The authors thank Dr. Kasie Cole for editing and proofreading the article, Clark R. Andersen, MS, for support in performing the statistical analyses, Julianna M. Bores for scientific support, Dr. Karel Capek for his unconditional guidance to Sagrario Gonzalez, MD, to Katrina Caszatt, and to the team of respiratory therapists for the collaboration to perform this research.

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