






Nebulized Heparin for Adult Patients With Smoke Inhalation Injury: A Review of the Literature

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Abstract

Objective: To review the clinical effects of nebulized heparin and N-acetylcysteine (NAC) in patients with smoke inhalation injury (IHI) and provide recommendations for use. **Data Sources:** A search of PubMed, MEDLINE, and Scopus databases was completed from database inception through April 15, 2020, using terms: heparin, acetylcysteine, smoke inhalation injury, and burn injury. **Study Selection and Data Extraction:** All studies pertaining to efficacy and safety of nebulized heparin and/or NAC for IHI in adult patients were evaluated. Reference lists were reviewed for additional publications. Nonhuman studies, non-English, and case report publications were excluded. **Data Synthesis:** Eight studies were included. Four demonstrated positive outcomes, 3 demonstrated no benefit or possible harm, and 1 assessed safety. Supporting trials treated patients within 48 hours of injury with 10 000 units of nebulized heparin with NAC for 7 days or until extubation. Two trials with negative findings treated patients within 72 hours, or unspecified, with 5000 units of nebulized heparin with NAC for 7 days, while the third used 25 000 units within 36 hours but was grossly underpowered for analysis. Clinical findings include reduced duration of mechanical ventilation and improved lung function with possible increase risk of pneumonia and no evidence of increased bleeding risk. **Conclusions:** Nebulized heparin may improve oxygenation and reduce duration of mechanical ventilation in IHI. If nebulized heparin is used, 10 000 units every 4 hours alternating with NAC and albuterol at 4-hour intervals is recommended. Sterile technique should be emphasized. Monitoring for bronchospasm or new-onset pneumonia should be considered.

Keywords

heparin, acetylcysteine, smoke inhalation injury, burn injury

Introduction

Burn and fire-related inhalation injury (IHI) carry a significant burden of morbidity and mortality. Over one million burns occur annually in the United States and up to 20% present with IHI.¹ Smoke IHI independently increases mortality by 25% to 65% and has been shown to substantially increase complications such as pneumonia, prolonged mechanical ventilation, hyperinflation, and acute respiratory distress syndrome (ARDS).^{2–5} Although thermal injury can occur through steam inhalation or prolonged heat exposure, the majority of IHI is attributed to chemical injury through inhalation of carbonaceous compounds and combustion by-products including nitrogen and sulfur aldehydes and oxides.^{4,6–8} Inhalation of carbon monoxide and cyanide can also worsen outcomes, but this occurs by a systemic mechanism rather than localized injury to the lungs.⁷

Smoke IHI may be suspected in patients with facial burns, singed nasal hairs, carbonaceous sputum, or a presenting clinical scenario describing smoke exposure in a closed space.^{6,8,9} Rales, rhonchi, wheezes, and hypoxia are infrequently observed on physical examination.⁶ Exclusion of an IHI diagnosis by chest radiographs is discouraged as changes on imaging are seldom present until secondary complications occur (ie, pneumonia or ARDS).^{5,6,9} Airway

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mucosa can be assessed with chest computed topography, but some prefer fiber-optic bronchoscopy for diagnosis. If, however, fiber-optic bronchoscopy is performed within the first 48 hours, it may result in a false negative or underestimation of disease severity as damage to the parenchymal tissue has not fully developed.^{4,7,10} Xenon scanning has been used to evaluate parenchymal damage in research, though is cost prohibitive and not common in practice.^{4,6}

IHI can be classified based on anatomical location and severity. Classification based on anatomy include upper airway (supraglottic), lower airway (subglottic), or lung parenchyma.⁴ Upper airway injury is usually due to direct thermal injury, whereas lower airway and parenchymal injuries are associated with chemical irritation or steam injury.^{4,6} Severity of IHI is influenced by the smoke composition and duration of smoke and heat exposure.¹¹ The Abbreviated Injury Score (AIS) for IHI is a severity grading scale classified by bronchoscopic examination scores ranging from grade 0 (absence of injury) to grade 4 (massive injury with evidence of mucosal sloughing, necrosis, or endoluminal obliteration).^{8,9,11} Higher grades of severity (grades 2, 3, and 4) have been correlated with increased mortality risk.^{8,9,11} Although frequently used in the literature for severity classification, this severity scale is not standard of care in clinical practice.

Smoke IHI occurs in 4 physiologic phases: exudation, degeneration, proliferation, and reparation.^{1,12} The first 3 phases involve obstructive cast formation, airway edema, and airway narrowing.^{1,12} The exudative phase is characterized by an increase in microvascular permeability caused by neuropeptide release, which leads to inflammation, plasma extravasation, and pulmonary edema.^{4,12} The degenerative phase is defined by neutrophil-mediated epithelial damage, migration of exudate into the airways, and formation of airway casts and fibrin clots.^{1,13} Accumulation of these casts may increase the risk of pneumonia and induce atelectasis or barotrauma.^{4,6} The proliferative phase is marked by further parenchymal damage as impaired mucociliary function and surfactant inactivation produces an aggregation of mucus, which contributes to airway narrowing and further ventilation perfusion mismatching.^{3,6-8} Narrowing of the airways leads to air trapping and alveolar hyperinflation, causing direct alveolar damage.³ Finally, the reparative phase describes patient recovery. Tissue that has sustained mild injury can return to baseline, but severe tissue injury can be complicated by prolonged or permanent intra-alveolar fibrosis.¹⁴

Nonpharmacologic Treatment

The cornerstones of nonpharmacologic treatment for IHI are pulmonary clearance techniques and mechanical ventilation optimization. Therapeutic coughing, either reflexive or voluntary, promotes airway clearance of mucus and

fibrin casts and should be encouraged every 1 to 2 hours.⁶ This technique can be limited by pain and medications that suppress the cough reflex such as opioids, H1 antagonists, and GABA_a agonists.¹⁵ Chest physiotherapy, including percussive therapy and vibrations on exhalation, increases bronchial drainage.⁶ Care should be taken to avoid disturbance of skin graft sites with either method. Nasotracheal airway suctioning is largely effective at removing secretions but can induce bradycardia and hypoxia.⁶ Therapeutic bronchoscopy is also effective at removing secretions and foreign particles, thereby reducing atelectasis, and has been shown to reduce duration of mechanical ventilation in patients with IHI who subsequently developed pneumonia.^{8,9,16} Ventilator strategies such as high-frequency percussive ventilation, high-frequency oscillatory ventilation, and prone positioning have been shown to improve pulmonary clearance and oxygenation, though the optimal approach is currently unknown.^{4,8,9,17}

Pharmacologic Treatment

The negative sequelae attributed to IHI originate from a multitude of pathophysiologic pathways, which present several possible targets for pharmacologic intervention. However, numerous interventions including corticosteroids, prophylactic antibiotics, exogenous surfactant replacement, nebulized nitric oxide, parenteral heparin, and allopurinol have not shown definitive improvement in clinical outcomes after IHI.¹⁸⁻²² Two promising treatment options are nebulized heparin and N-acetylcysteine (NAC), which may improve ventilation-perfusion matching and prevent atelectasis and barotrauma through the inhibition of obstructive cast formation.⁴

Nebulized NAC and β -Agonist Mechanism of Action

NAC acts as a mucolytic and free radical scavenger.^{12,23,24} Free sulfhydryl groups hydrolyze disulfide bonds between mucin monomers causing depolymerization of larger glycoprotein oligomers.²³ The resulting mucus breakdown can slow or prevent the propagation of obstructive casts as they are primarily composed of mucus and extravascular plasma during the initial phase of formation.¹² NAC has additionally been shown to decrease nitric oxide production in animal models.²⁴ This diminishes the inflammatory response thereby preventing endothelial damage and vascular permeability.³ The reduction in nitric oxide also improves the mismatch in ventilation and perfusion by minimizing inappropriate perfusion of poorly ventilated lung tissue.³ One concern with NAC administration is airway irritation resulting in bronchospasm, especially in patients with asthma.^{4,25} This is of special consideration in patients with IHI as they are prone to bronchospasm secondary to airway

debris and cytokines.^{5,18} Bronchodilators are, therefore, commonly coadministered.^{1,12,26-28} In addition to alleviation of bronchospasm, nebulized β_2 adrenergic agonists such as epinephrine, albuterol, and levalbuterol may improve mucociliary clearance, pulmonary compliance, and ventilation-perfusion matching.^{4,29}

Nebulized Heparin Mechanism of Action

Heparin potentiates antithrombin III activity, preventing activated factor X from converting prothrombin to thrombin and inhibiting the conversion of fibrinogen to fibrin.^{10,30} These mechanisms inhibit the cross-linking of fibrin, which is critical in the formation of obstructive casts. An additional benefit of reduced fibrin formation is the preservation of surfactant activities that are critical for preventing reduced lung compliance, atelectasis, and ultimately decreased functional residual capacity.^{1,31} Increased risk of bleeding is a primary concern with the administration of nebulized heparin, though limited safety data have been published. A study in healthy subjects sought to assess the systemic coagulopathy effects of inhaled heparin, escalating doses up to 32 000 units.³² Authors identified a dose-dependent effect on anti-factor Xa and activated partial thromboplastin time (aPTT), but changes were relatively small and deemed clinically insignificant.

These theoretical alterations in IHI pathophysiology have sparked numerous investigations to determine the utility of nebulized heparin and NAC in this vulnerable population. Therefore, the aim of this review is to evaluate existing literature regarding the efficacy and safety of nebulized heparin and NAC therapy in patients with IHI and provide recommendations for their use in clinical practice.

Methods

A search of the PubMed, MEDLINE, and Scopus databases from inception through April 15, 2020, was completed utilizing the following terms: heparin, acetylcysteine, smoke inhalation injury, and burn injury. All abstracts and titles were screened to identify studies pertaining to the efficacy, safety, or pharmacology of nebulized heparin and/or NAC in patients with IHI. Case reports and studies including an exclusively pediatric population were excluded. Nonhuman studies and non-English language publications were excluded. Reference lists were reviewed to identify additional relevant publications. All identified articles in which nebulized heparin and/or NAC was used for IHI were reviewed by the authors (MJT, CVM, MKP) for possible inclusion. Data abstracted included patient population included, intervention(s) provided (including dose, frequency, timing, and duration), mortality, hospital and intensive care unit (ICU) length of stay (or ICU-free days), duration of mechanical ventilation (or ventilator-free days),

pulmonary function markers, and any safety endpoints reported (eg, bleeding, coagulation laboratory values, pneumonia).

Results

After application of exclusion criteria, 13 articles were reviewed by the authors for inclusion. Three articles were excluded as they were case reports, 1 was excluded based on a pediatric population, and 1 was excluded as the publication was limited to study protocol description, and no results were reported (Figure 1). One study included both pediatric and adult patients in their retrospective evaluation; however, the decision was made to include the article as pediatric patients comprised only 16% of the study population.¹² A total of 8 studies remained for inclusion in the qualitative review (Figure 1). The majority of these studies were retrospective and observational (6 studies),^{1,12,26-28,33} with only 2 prospective, randomized controlled trials.^{34,35} One of the retrospective, observational studies reported only safety data.³³ No additional studies were identified through the review of reference lists. Study design and interventions are summarized in Table 1. Efficacy and safety outcomes reported are summarized in Table 2.

Efficacy of Nebulized Heparin/NAC

The first of 5 retrospective studies evaluating the efficacy of nebulized heparin, NAC, and albuterol in humans was performed by Holt and colleagues in 2008.¹² This was a large retrospective study of both pediatric and adult patients with IHI between 1999 and 2005 using the American Burn Association and Trauma Registry for the American College of Surgeons database.¹² The diagnosis of IHI was made by bronchoscopy, elevated carboxyhemoglobin, or clinical suspicion based on mechanism of injury; grade of injury was not reported. Initiation of an institutional protocol was based on physician discretion. The protocol utilized nebulized heparin 5000 units/mL, 3 mL of 20% NAC solution, and 3 mL of 0.083% albuterol every 4 hours for the first 7 days post-admission or until extubation. Patients who received the protocol ($n = 62$) were compared with a control group who did not receive NAC or nebulized heparin ($n = 88$). Mean percent total body surface area (TBSA) burned was similar between protocol and control groups (27% vs 31.6%, $P = .29$), although no other severity of illness scores were reported. No significant differences were detected for length of stay, mortality, ventilator days, unplanned reintubation, or $\text{PaO}_2\text{-FiO}_2$ ratios. Twenty-five pediatric patients were included in this study, and although the authors did not specify the group these patients were assigned to, they mentioned there was no difference in the pediatric subgroup analysis.

In contrast, Miller and colleagues found positive outcomes associated with a higher dose of nebulized heparin

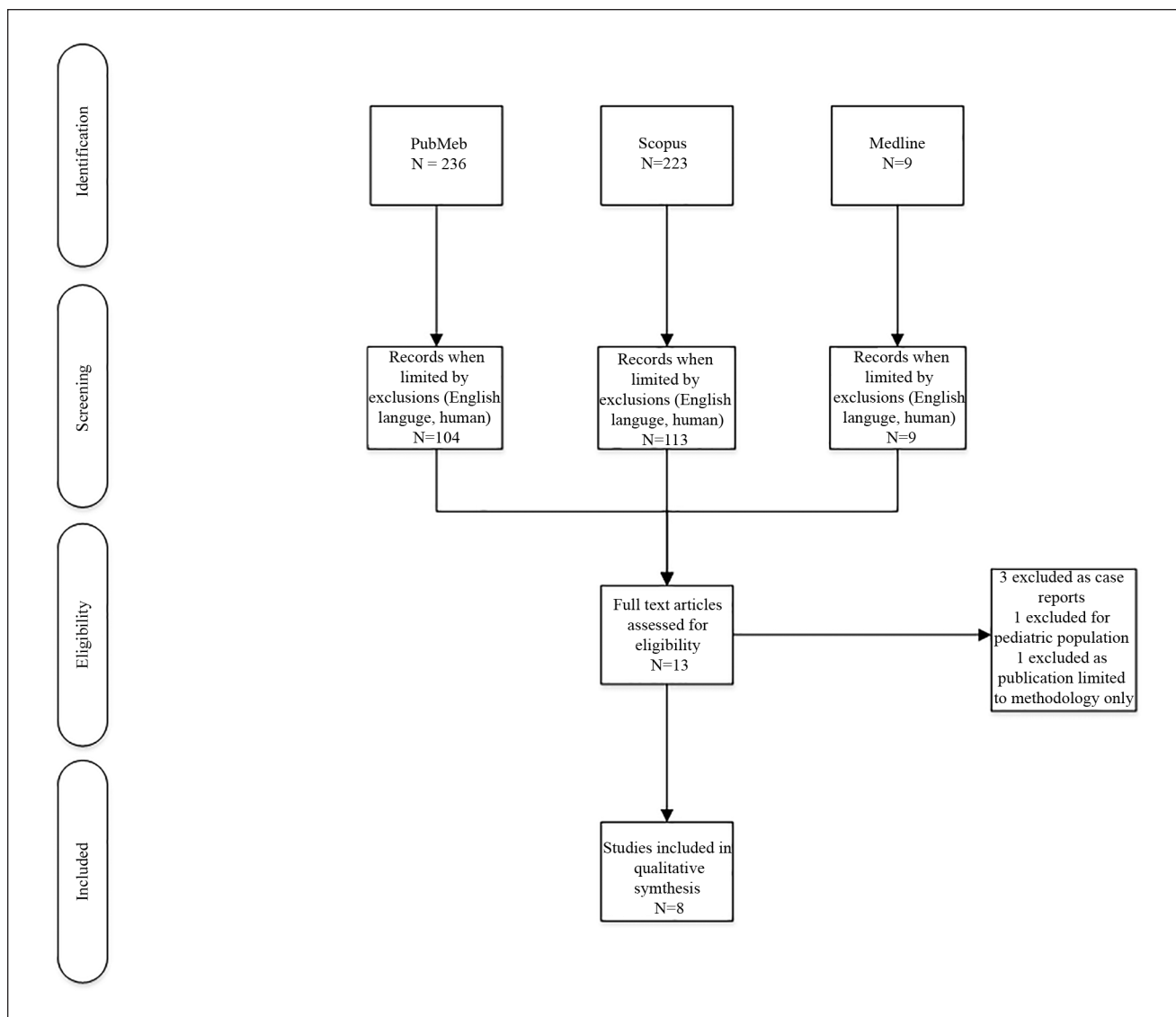


Figure 1. Flow diagram for study inclusion.

(10 000 units) in a retrospective study.¹ The primary objective of this study was to determine if the combination therapy (nebulized heparin, NAC, and albuterol) reduced 28-day mortality or lung injury scores (LIS). The authors did not indicate a primary outcome for the analysis. Patients with bronchoscopy-confirmed IHI admitted within 48 hours of injury were treated with a nebulized heparin protocol (n = 16) and compared with historical controls (n = 14) over a 5-year period. The protocol arm received 10 000 units of nebulized heparin sulfate in 3 mL of normal saline every 4 hours alternating with 3 mL of 20% nebulized NAC and 0.5 mL of albuterol every 4 hours for 7 days, beginning the day of admission. The historical control was allowed to receive 0.5 mL nebulized albuterol every 4 hours as needed. Groups were matched based on Acute

Physiology, Age, Chronic Health Evaluation (APACHE)-III score, and similar mechanical ventilation strategies (tidal volume 5-8 mL/kg, plateau pressure ≤ 20 cm H₂O) were utilized in both arms. Baseline severity of illness and LIS were similar between groups; however, the control group had a greater percent TBSA burned compared with the protocol group (44% vs 23%).³⁶ The protocol group experienced significantly lower mean LIS scores on days 2 to 7, with improved lung compliance and reduced hypoxemia as prominent contributors to this finding. The protocol arm was associated with an absolute risk reduction of 0.366 for 28 day mortality and a number needed to treat of 2.73. This study was limited, however, by a lack of statistical analysis regarding the possible impact of differing TBSA between groups on clinical outcomes.

Table 1. Study Design and Treatment Interventions of Nebulized Heparin Studies.

	Holt et al ¹²	Miller et al ¹	Yip et al ³³	Eisharmouby et al ³⁴	Kasheff et al ²⁸	McIntire et al ²⁶	McGinn et al ²⁷	Glas et al ³⁵
Design	Single-center, retrospective cohort	Single-center, retrospective, matched cohort based on APACHE-III, LIS	Single-center, retrospective cohort	Single-center, randomized, double-blind	Single-center, retrospective, matched cohort based on gender, burn severity, age	Single-center, retrospective cohort based on %TBSA burned, age	Single-center, retrospective cohort	Multicenter, randomized, double-blind, placebo-controlled
Population	<ul style="list-style-type: none"> Adult and pediatric patients IHI based on ABA/TRACS Admitted 1999-2005 	<ul style="list-style-type: none"> Adults Bronchoscopy-confirmed IHI Mechanically ventilated Admitted over a 5-year period 	<ul style="list-style-type: none"> Adults Bronchoscopy-confirmed IHI Mechanically ventilated Admitted 2006-2009 (treatment) or 2001-2005 (control) 	<ul style="list-style-type: none"> Adults Bronchoscopy-confirmed IHI Mechanically ventilated 	<ul style="list-style-type: none"> Adults Suspected or bronchoscopy confirmed IHI Admitted January 2011 to July 2012 (treatment) or 2006-2010 (control) 	<ul style="list-style-type: none"> Adults Bronchoscopy-confirmed IHI Mechanically ventilated >24 hours Admitted June 2014 to February 2016 (treatment) or January 2000 to February 2016 (control) 	<ul style="list-style-type: none"> Adults Suspected IHI Mechanically ventilated Admitted between August 2014 and March 2016 	<ul style="list-style-type: none"> Adults Bronchoscopy-confirmed IHI Mechanically ventilated for <24 hours
Treatment group	N = 62	N = 16	N = 52	N = 15	N = 20	N = 36	N = 22	N = 7
Treatment timing and duration	Within 72 hours of injury; 7 days	Within 48 hours of injury; 7 days	No time limit; 7 days or at discretion of physician	Within 24 hours of injury; duration not reported	No time limit; 7 days	Within 48 of injury; 7 days or until extubation	On admission; 5 days or until extubation	Within 36 of injury; 14 days or until extubation
Heparin dosing	5000 units every 4 hours	10 000 units every 4 hours	5000 units every 4 hours	10 000 units every 4 hours	5000 units every 4 hours	10 000 units every 4 hours	5000 units every 4 hours	25 000 units every 4 hours
Mucolytic and β-agonist therapy	NAC 20% 3 mL + albuterol every 4 hours	NAC 20% 3 mL + albuterol every 4 hours	NAC 20% 3 mL + salbutamol every 4 hours	NAC 20% 3 mL + salbutamol every 4 hours	NAC 20% 3 mL + albuterol every 4 hours	NAC 20% 3 mL or 4% sodium bicarbonate 3 mL + albuterol every 4 hours	NAC (dose not reported) + albuterol; frequency not reported	No routine use of mucolytics; allowed only if problematic viscous mucus
Comparator group	N = 88	N = 14	N = 11	N = 14	N = 20	N = 36	N = 26	N = 6
Comparator interventions	No intervention β-agonists allowed	No intervention Albuterol every 4 hours as needed	No intervention Supportive care	Heparin 5000 units every 4 hours + NAC 20% 3 mL + salbutamol every 4 hours	No intervention Albuterol or NAC as needed at the discretion of physician	No intervention	No intervention Albuterol ± ipratropium at the discretion of the physician	Placebo (0.9% sodium chloride) every 4 hours

Abbreviations: ABA/TRACS, American Burn Association/Trauma Registry for the American College of Surgeons; APACHE, Acute Physiology, Age, Chronic Health Evaluation; IHI, smoke inhalation injury; LIS, lung injury score; NAC, N-acetylcysteine, TBSA, total body surface area.

Table 2. Efficacy and Safety Outcomes of Nebulized Heparin for Smoke Inhalation Injury.

	Holt et al ¹²	Miller et al ¹	Yip et al ³³	Esharnouby et al ³⁴	Kashefi et al ²⁸	McIntire et al ²⁶	McGinn et al ²⁷	Glas et al ³⁵
Efficacy outcomes								
Mortality	No difference, 24% vs 20% P = .20	Lower mortality in treatment group, 6% vs 43%, RR = 0.0055 (95% CI = 0.0314-0.02004)	No difference, 36.5% vs 54.5%, P = .32	No difference, 3% vs 6% P = .6	No difference, 25% vs 30% vs 72% P = .72	No difference in 28-day mortality, 2.8% vs 2.8%, P = 1	No difference, 22.7% vs 23.1%, P = .99	—
Hospital LOS (days)	No difference, 31 vs 31.9	—	—	—	No difference, 15.3 vs 16.3, P = .8	No difference, 17 vs 22, P = .195	No difference, 9.0 vs 18.5, P = .093	—
ICU LOS (days)	—	—	No difference, 6 vs 7, P = .86	No difference, 19 vs 25, P = .17	—	—	Shorter in treatment group, 5.5 vs 13, P = .033	No difference in ICU-free days and alive at day 90, 71 vs 49, P = .73
Duration of mechanical ventilation (days)	No difference, 18.2 vs 17.2, P = .76	—	No difference, 5 vs 5, P = .63	Shorter for treatment group, 11 vs 19, P = .037	No difference, 8.5 vs 8.8, P = .9	No difference, 7.0 vs 14.5, P = .60	Shorter for treatment group, 3.0 vs 6.5, P = .022	No difference in ventilator-free days and alive at day 28, 16 vs 20, P = .62
Pulmonary function	No difference in markers of oxygenation	Lower LIS, days 2-7 Lower lung resistance, days 2 and 4 Lower average hypoxemia score in first 7 days	—	Lower LIS on days 5-7	—	—	Heparin associated with duration of mechanical ventilation in multivariable linear regression model (P = .039)	—
Safety outcomes								
Pneumonia	No difference, 63% vs 50%, P = .12	—	No difference, 17.3% vs 18.2% P = .86	No difference, 27% vs 43%, P = .4	Increased in treatment group, 45% vs 11%, P = .03	No difference in VAP, 63.9% vs 72.2% P = .0376	Increased in treatment group 18% vs 0%, P = .0376	28.5% vs 16.7%, No statistical analysis performed
Bleeding	—	—	No difference in PT or aPTT No difference in platelet trends	No significant effect on coagulation parameters or platelet count No significant blood staining of bronchial secretions	—	No difference in major bleeding: 5.6% vs 11.1%, P = .394 No difference in minor bleeding: 58.3% vs 52.8%, P = .635	—	No bleeds in either group One patient per group required blood transfusion for severe hemorrhage 7 and 13 days after last nebulization One patient in heparin group with aPTT > 150 seconds aPTTs similar between groups; during nebulization: 36 vs 31 seconds After nebulization period: 33 vs 40 seconds No HIT in either group One patient in the placebo group with ARDS
Other	No difference in unplanned reintubation, 14% vs 8%, P = .20	—	No difference in incidence of sepsis, 38.5% vs 63.6%, P = .18 No difference in incidence of ARDS, 23.1% vs 36.4%, P = .45	—	No difference in incidence of sepsis, 40% vs 33%, P = .7 No difference in incidence of ARDS, 15% vs 10%, P = 1 No documented complications directly attributed to administration of the protocol	—	—	No HIT in either group One patient in the placebo group with ARDS Two patients in heparin group with ventilatory problems (high airway pressures) Feasibility: 127 of 429 heparin nebulizations withheld

Abbreviations: aPTT, activated partial thromboplastin time; ARDS, acute respiratory distress syndrome; CI, confidence interval; HIT, heparin-induced thrombocytopenia; ICU, intensive care unit; LIS, lung injury score; LOS, length of stay; PT, prothrombin time; RR, relative risk; VAP, ventilator-associated pneumonia.

A study by Kashefi and colleagues also failed to detect a significant clinical benefit from the administration of nebulized heparin and NAC in a pre-/post-protocol implementation study.²⁸ Patients treated with IHI with an institutional protocol ($n = 20$) were matched 1:1 to historical controls based on sex, percent TBSA burned, and age ($n = 20$). Mechanical ventilation was not required for inclusion, and the number of individuals requiring mechanical ventilation at any given time was not reported. The protocol group received nebulized heparin 5000 units/3 mL every 4 hours alternating with 3 mL of 20% NAC and 2.5 mg of albuterol every 4 hours for the first 7 days after admission. Time from injury to initiation of the protocol was not reported. The historical control group received as needed NAC and albuterol at the discretion of the physician. The primary outcome was duration of mechanical ventilation; however, the authors did not describe how they accounted for patients who never required mechanical ventilation. The groups were well matched for age, sex, and burn size, and the majority of patients had an LIS of 0 to 1. However, more patients in the protocol group presented with grade 1 IHI (79% vs 47%, $P = .01$). No difference in mean duration of mechanical ventilation was detected between protocol and historical controls (8.5 vs 8.9 days, $P = .9$). No significant differences in mortality, length of stay, or incidence of ARDS were found.

A retrospective, case-control study (HIHI study) evaluated a similar treatment strategy utilizing a higher dose of nebulized heparin (10 000 units every 4 hours) in a pre-/post-protocol implementation study. Protocol patients ($n = 36$) were matched to historical controls ($n = 36$) based on percent TBSA burned and age.²⁶ The protocol consisted of nebulized heparin 10 000 units every 4 hours alternating with a mucolytic (NAC or 4% sodium bicarbonate) and albuterol therapy every 4 hours for 7 days or until extubation. Use of the protocol was at the discretion of the physician. Patients were similar at baseline, with the exception of higher smoking incidence in the protocol group (63.9% vs 38.9%, $P = .034$). The primary outcome of duration of mechanical ventilation was not statistically different between the protocol and control groups (median 7 vs 14.5 days, $P = .06$). However, after excluding 5 patients who died or were discharged on the ventilator, 2 in the protocol group (1 death, 1 discharged on ventilator) and 3 in the control group (1 death, 2 discharged on ventilator), the protocol group had a shorter duration of mechanical ventilation (median 7 vs 14.5 days, $P = .044$). In addition, the protocol group had more ventilator-free days than the control group (median 21 vs 13.5 days, $P = .031$). The authors did not report how ventilator-free days were determined for patients who died before day 28 or for patients who were discharged on the ventilator. The small sample size may have contributed to the lack of a statistically significant difference in the primary outcome, as they lacked power to detect a

difference. In addition, the exclusion of patients who either died or were discharged on mechanical ventilation appears to be a post hoc analysis, which was not indicated by the authors. These findings were potentially confounded further by an increased incidence of repeat bronchoscopy in the protocol group, which may have included therapeutic bronchoscopy (72.2% vs 50%, $P = .053$). As the use of nebulized heparin protocol was at the discretion of the treating physician, 42 patients did not receive treatment after protocol implementation, indicating a risk for treatment bias in the protocol group.

McGinn and colleagues performed a retrospective, observational, cohort study comparing a nebulized heparin, NAC, and albuterol protocol ($n = 22$) to albuterol \pm ipratropium only ($n = 26$).²⁷ The protocol was initiated on admission at the discretion of the provider and was continued for 5 days or until extubation and consisted of nebulized heparin 5000 units every 4 hours with NAC and albuterol, though administration details were not provided for these agents. Protocol patients had a significantly shorter median duration of mechanical ventilation (3 vs 6.5 days, $P = .022$) and ICU length of stay (5.5 vs 13 days, $P = .033$), though individuals treated with the protocol had smaller burns (median percent TBSA burned 5.25% vs 29%, $P = .009$). Multivariable linear regression analysis controlling for age, percent TBSA burned, and AIS inhalation grade suggested that the protocol was independently associated with reduced duration of mechanical ventilation. No significant differences in hospital length of stay or mortality were observed.

Two prospective studies examining the efficacy of nebulized heparin have been published. Elsharnouby and colleagues performed a prospective, double-blind, randomized controlled trial comparing 2 nebulized heparin dosing strategies: 5000 ($n = 14$) and 10 000 units/mL ($n = 15$) administered every 4 hours in patients requiring mechanical ventilation for bronchoscopy-confirmed IHI.³⁴ Patients with percent TBSA burn greater than 50% were excluded. Patients in both groups received 3 mL of 20% NAC and salbutamol every 4 hours, alternating with nebulized heparin. All patients received fiber-optic bronchoscopy on day 1 and were resuscitated using the Parkland formula. Patient demographics, percent TBSA burned, APACHE II score, and bronchoscopy scores were similar at baseline. The LIS was not different between groups on days 1 to 4 but was significantly improved in the high-dose heparin group on days 5 to 7. The mean duration of mechanical ventilation was reduced in the high-dose heparin group (11 vs 19 days, $P = .037$). No differences in ICU length of stay or mortality were observed between groups.

The final prospective evaluation of nebulized heparin was published by Glas and colleagues in 2020.³⁵ However, this multicenter, randomized, double-blind, placebo-controlled trial was stopped early due to slow recruitment and high cost

of blinded placebo medication. Patients were randomized to receive either 25 000 units nebulized heparin every 4 hours or placebo within 36 hours of IHI, and therapy was continued for 14 days or until extubation or death. Routine use of mucolytics use discouraged, and use was only allowed at the discretion of the attending provider when viscous mucus was problematic. A total of 13 patients ($n = 7$ heparin vs $n = 6$ placebo) were enrolled prior to termination. No differences in ICU-free days and alive at day 28 or ventilator-free days and alive at day 28 were observed, although this study was grossly underpowered.

Safety of Nebulized Heparin/NAC

Yip and colleagues retrospectively compared patients who received nebulized heparin 5000 units, 3 mL of 20% NAC, and salbutamol 5 mg every 4 hours ($n = 52$) with historical controls ($n = 11$).³³ Patients in the control group had higher percent TBSA burned compared with the protocol group (51% vs 20%, $P = .09$), although this difference was not statistically significant. Prothrombin time, aPTT, and platelet values were similar between both the groups over 7 days. No differences in bloody secretions from the endotracheal tube, wound bleeding, hemoserous exudates, or bleeding from other sites were observed. Combined rates of bleeding from all sites were high in both the groups; however, the protocol arm had a lower numerical rate (71% vs 81%, $P = .87$). Limitations include the lack of a standardized definition for bleeding, reliance on documentation of bleeding within the medical record, and that blood transfusion requirements and changes in hemoglobin were not reported.

The HIHI study discussed above also evaluated bleeding as a secondary endpoint and categorized bleeding events as major and minor.²⁶ Major bleeds either prompted discontinuation of heparin or were documented as clinically significant, while minor bleeds required both documented hemoptysis and a positive gastroccult or hemoccult. No difference was detected between protocol ($n = 36$) and control groups ($n = 36$) in the incidence of major (5.6% vs 11.1%, $P = .394$) or minor bleeding (58.3% vs 52.8%, $P = .635$). One patient receiving nebulized heparin had documented alveolar hemorrhage, which prompted discontinuation. Of note, the HIHI study is the first to report the incidence of bleeding in patients receiving 10 000 units of nebulized heparin per dose.²⁶ Kashefi and colleagues attributed no episodes of bleeding to heparin, though bleeding was not defined.²⁸ In the study by Glas and colleagues, no severe bleeding was reported, and there was no difference in rates of transfusions between the groups. There was 1 patient in the treatment arm of this study who had an aPTT greater than 150 seconds; however, this normalized after discontinuation of the heparin nebulization.³⁵ Most studies evaluating coagulopathy associated with nebulized heparin excluded patients with

hypersensitivity to heparin and those with bleeding disorders or platelet counts less than 50 000/ μL .^{1,26,33} Nebulized heparin has not been shown to increase the rates of clinically significant bleeding at doses of up to 25 000 units in patients not meeting the aforementioned exclusion criteria. Furthermore, no studies in patients with IHI have documented any cases of heparin-induced thrombocytopenia.

Increased risk of pneumonia has also been reported with nebulized heparin for IHI. Six of the 7 included studies comparing nebulized heparin with a control group reported rates of pneumonia, with 2 reporting statistically higher rates of pneumonia with nebulized heparin.^{12,26-28,33,35} Holt and colleagues were the first to report a higher incidence of pneumonia in patients receiving heparin, although this finding was not statistically significant (63% vs 50%, $P = .12$).¹² Yip and colleagues reported no difference in the incidence of pneumonia (17.3% vs 18.2%).³³ Kashefi and colleagues were the first to find a significantly higher incidence of pneumonia among patients treated with nebulized heparin (45% vs 11%, $P = .03$) when compared with historical controls.²⁸ In contrast, the HIHI study did not observe any differences in rates of ventilator-associated pneumonia between protocol and control groups (63.9% vs 72.2%, $P = .448$).²⁶ McGinn and colleagues also found a higher incidence of pneumonia among those who received the heparin protocol (18% vs 0%, $P = .04$).²⁷ Glas and colleagues found the incidence of pneumonia to be similar between heparin and placebo groups (2 vs 1 patient); however, these findings are limited by the premature cessation of the trial due to low enrollment and were not statistically analyzed.³⁵

Discussion

The use of nebulized heparin and NAC for IHI remains controversial. To date, of the 7 trials reporting efficacy endpoints, there are 4 trials favoring and 3 trials opposing routine use. Trials supporting the use of nebulized heparin and NAC for IHI started therapy early within 24 to 48 hours of injury with 10 000 units of nebulized heparin every 4 hours for 5 to 7 days or until extubation. In contrast, 2 of the 3 trials opposing routine use initiated therapy later, within 72 hours of injury (or did not specify timeframe), with 5000 units of nebulized heparin every 4 hours for 7 days. Early initiation (within 48 hours) with higher dosing (10 000 units) may therefore be most effective.^{12,28,34} One study utilizing a higher dose of heparin (25 000 units), within 36 hours of IHI, was terminated early and was, therefore, not powered to detect a difference in the primary efficacy endpoint.³⁵ Clinical outcomes vary, and only reduction in mechanical ventilation duration and improvements in LIS have been replicated in 2 retrospective studies.^{1,27} Elsharnouby and colleagues saw improvement in LIS over days 5 through 7, while Miller and colleagues reported an improvement over days 2 through 7.^{1,34} No study reported

changes in LIS beyond 7 days, making it difficult to determine clinical benefit beyond this time; however, nebulized heparin and NAC were continued until extubation in the studies that reported benefit in other clinical outcomes. These promising outcomes are tempered, however, by the potential for an increased risk of pneumonia associated with nebulized heparin and NAC therapy. It had been historically hypothesized that reduced rates of pneumonia could be anticipated in those treated with nebulized heparin due to the reduction of cast formation and improved lung surfactant activity; however, this correlation has not been demonstrated, and in fact, a higher risk of pneumonia has been seen.³² It is possible that these findings are due to frequent disruptions in the ventilator circuit for the administration of medications, which may compromise sterility. In addition, inconsistency may exist in the preparation of nebulized medications under sterile conditions.²⁸

Many limitations such as small sample size, retrospective design, provider bias, and uneven distribution of confounding variables exist in the majority of the discussed studies making definitive conclusions elusive. There is also limited information reported on ventilator management strategies, which could affect clinical outcomes such as ventilator days and markers of pulmonary function (eg, oxygenation, LIS). In addition, it is difficult to distinguish the benefit of NAC versus nebulized heparin due to the comparator group lacking both interventions in multiple of the studies discussed.^{1,12,27}

Consideration should be given to the acquisition or creation of these inhaled products and potential barriers to their administration. Heparin for nebulization does not currently exist as a manufactured product, but it is available as 5000 unit/mL and 10 000 unit/mL products intended for intravenous injection.³⁷ Most studies that provided information on the concentration of heparin utilized, compounded either 5000 units/3 mL or 10 000 units/3 mL products diluted in normal saline, with one study using a 25 000 unit/5 mL dose.^{1,28,34,35} The authors suggest that nebulized heparin be compounded in polypropylene containers, stored for up to 10 days if kept refrigerated (2-8°C) or for 4 days at room (20-25°C) temperature.^{38,39} NAC for nebulization exists as a manufactured product in a 20% solution, and all studies that give a detailed description of their inhaled NAC product utilize 3 mL of this solution (600 mg) per dose.^{1,12,28,33,34,40}

Barriers specific to nebulized heparin therapy include training of respiratory personnel, the creation of a protocol for administration, and development of an order within the electronic medical record system. In one study, 24% of scheduled doses were omitted for all patients enrolled, which highlights the difficulty in feasibility of every 4-hour nebulization in patients with IHI.³⁵ Safety concerns exist regarding this preparation as it could be incorrectly administered (intravenous or subcutaneous rather than inhaled) or compounded. Strict adherence to administration protocols

and aseptic technique should be employed to mitigate these risks. Safety concerns have also been raised regarding the risk of localized and systemic bleeding. Only one study, to date, has reported bleed incidence as a primary outcome; however, a standard definition of major and minor bleeding was not employed to assess these outcomes.³³ This makes it difficult to compare with other studies where bleeding is reported without the use of nebulized heparin.

Barriers specific to inhaled NAC include bronchospasm and medication interactions. Inhaled NAC should be administered with β -agonists, and patients should be closely monitored for wheezing with lung auscultation after administration to detect bronchospasm.²⁵ The 2 β -agonists described in previous studies, albuterol and salbutamol, are commercially available and typically administered with NAC at doses of 2.5 mg and 5 mg, respectively.^{12,28,33} NAC 20% solution has undergone *in vitro* compatibility testing with a myriad of other potentially nebulized medications and is notably compatible with nitrous oxide and colistimethate sodium (must be used immediately after mixing), but not amphotericin.⁴⁰ A summary of other known interacting medications can be found in the NAC package insert.⁴⁰

Avoidance of concomitant administration is considered best practice for scenarios when compatibility data are unavailable. With continuously nebulized medications such as epoprostenol, this practice may not be feasible. Although no *in vitro* compatibility data exist for inhaled heparin, NAC, and epoprostenol, a single case utilizing these therapies reported no apparent drug incompatibilities with concomitant administration.⁴¹

Though the combination of nebulized heparin and NAC has been almost exclusively evaluated in patients requiring invasive mechanical ventilation, it may be reasonable to administer these medications to patients only requiring non-invasive mechanical ventilation support. This can be accomplished by connecting a nebulizer to a single-limb circuit close to the patient and, when possible, utilizing low inspiratory pressures and prolonged inspiratory time to aid in aerosol deposition.⁴² Such an administration method could also be employed for most situations when interruption of the ventilator circuit is not feasible.

Conclusion

Current evidence suggests that nebulized heparin with NAC may have benefits for patients with IHI requiring intubation. Based on the available literature, if nebulized heparin is used for IHI, we recommend nebulized heparin 10 000 units every 4 hours alternating with nebulized NAC and albuterol at opposite 4-hour intervals (patient would receive treatment with either regimen every 2 hours). Initiation should occur within 48 hours of injury to maximize benefit. It is reasonable to continue treatment for 7 days or until liberation from mechanical ventilation. Administration to

patients not requiring mechanical ventilation may also be feasible to prevent escalation of respiratory support. Standardized compounding and sterile preparation and administration processes should be developed to safeguard against contamination and inappropriate administration. Routine monitoring of coagulation tests is unlikely to be valuable, but clinicians should be observant to signs of bronchospasm or new-onset pneumonia.

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