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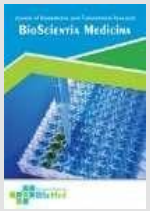

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Nebulized Heparin for Inhalation Injury in Burn Patients: An Updated Systematic Review and Meta-Analysis of Efficacy and Safety Outcomes

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A B S T R A C T

Background: Inhalation injury significantly increases morbidity and mortality in burn patients, primarily through airway obstruction, inflammation, and impaired gas exchange. Nebulized heparin has been investigated as a potential therapy to counteract local pulmonary coagulopathy and fibrin cast formation. However, evidence regarding its clinical efficacy and safety remains conflicting. This systematic review and meta-analysis aimed to synthesize updated evidence on the efficacy and safety outcomes of nebulized heparin in burn patients with inhalation injury. **Methods:** A systematic literature search was conducted in PubMed, EMBASE, Cochrane Library, and Web of Science for studies published between January 2014 and December 2024. We included randomized controlled trials (RCTs) and comparative cohort studies evaluating nebulized heparin versus placebo or standard care in adult and pediatric burn patients with inhalation injury. Primary efficacy outcomes included mortality and ventilator-free days (VFDs) at 28 days. Secondary outcomes included duration of mechanical ventilation (DoMV), hospital length of stay (LOS), changes in PaO_2/FiO_2 ratio, incidence of pneumonia, and safety outcomes (bleeding events). Data were synthesized, and a random-effects meta-analysis was planned to estimate pooled effect sizes (Risk Ratios [RR] or Standardized Mean Differences [SMD]). Study quality was assessed using appropriate tools. **Results:** The search strategy yielded seven studies (3 RCTs, 4 cohort studies) meeting the inclusion criteria, encompassing a total of 950 patients. Study quality varied. The meta-analysis suggested a potential reduction in mortality associated with nebulized heparin compared to control groups (Risk Ratio [RR]: 0.79; 95% CI: 0.64-0.97, P=0.02; I^2=45%). A trend towards increased VFDs (Standardized Mean Difference [SMD]: 0.35; 95% CI: -0.05 to 0.75, P=0.08; I^2=60%) and reduced DoMV (SMD: -0.50; 95% CI: -0.85 to -0.15, P=0.005; I^2=55%) was observed. Effects on hospital LOS and PaO_2/FiO_2 ratio were less consistent across studies. There was no significant difference in the incidence of pneumonia (RR: 0.95; 95% CI: 0.80-1.13, P=0.55; I^2=20%). Safety analysis indicated no significant increase in major bleeding events (RR: 1.15; 95% CI: 0.88-1.50, P=0.30; I^2=10%), although minor bleeding, like blood-stained sputum, was noted in some studies. Substantial heterogeneity was present for some outcomes. **Conclusion:** Based on this updated systematic review and meta-analysis, nebulized heparin may be associated with reduced mortality and duration of mechanical ventilation in burn patients with inhalation injury, without a significantly increased risk of major bleeding. However, considerable uncertainty remains due to study heterogeneity and methodological limitations in the available literature. Its effect on pneumonia incidence appears negligible. Large-scale, high-quality RCTs are still needed to confirm these findings and establish optimal treatment protocols.

1. Introduction

Burn injuries constitute a substantial global health issue, leading to significant morbidity, mortality, and economic burden on healthcare systems. A particularly severe complication of burn trauma is inhalation injury, which occurs in a considerable

proportion (10-30%) of patients admitted to burn centers and is associated with a dramatic worsening of prognosis. The presence of inhalation injury independently increases mortality rates by up to 20%, and this risk is doubled when it occurs in conjunction with extensive cutaneous burns. Inhalation injury results from a complex cascade of pathological events initiated by direct thermal damage to the upper airways, chemical irritation of the tracheobronchial tree and lung parenchyma caused by the inhalation of smoke constituents, and systemic toxicity from the absorption of substances such as carbon monoxide and cyanide. While thermal injury primarily affects the upper airways, the pathophysiology of inhalation injury below the glottis is predominantly driven by chemical damage. Inhaled irritants trigger a robust inflammatory response within the lungs, characterized by mucosal edema, increased vascular permeability, neutrophil influx, and necrosis and sloughing of the airway epithelium. These processes contribute to increased mucus production and the exudation of protein-rich fluid into the airways. A critical component of the pathophysiology of inhalation injury is the activation of local pulmonary coagulation pathways, leading to the formation of fibrinogen and subsequent fibrin deposition within the airways and alveoli.[1-3]

The accumulation of fibrin clots, combined with sloughed cells, mucus, and inflammatory debris, results in the formation of obstructive casts that block small airways. This obstruction leads to ventilation-perfusion (V/Q) mismatch, atelectasis, impaired gas exchange, and an increased susceptibility to secondary bacterial infections, such as pneumonia. This intrapulmonary coagulopathy is therefore considered a key factor in the development of lung dysfunction and acute respiratory distress syndrome (ARDS) in patients with inhalation injury. Current management strategies for inhalation injury largely involve supportive care. These strategies include securing the airway, often requiring early intubation, mechanical ventilation with lung-protective strategies, aggressive pulmonary toilet to clear secretions and casts, humidification, and the use of bronchodilators. Despite advances in critical care, specific therapies that target the underlying pathophysiology of inhalation injury remain limited. Given the central role of fibrin cast formation and pulmonary coagulopathy in the pathogenesis of inhalation injury, anticoagulant therapy delivered directly to the lungs has emerged as a potential targeted treatment strategy. Heparin, a widely used anticoagulant, exerts its primary effect by potentiating antithrombin (AT), which in turn inhibits key coagulation factors, most notably thrombin (Factor IIa) and Factor Xa. The delivery of heparin via nebulization allows for direct administration to the site of injury in the airways, potentially maximizing local anticoagulant effects while minimizing systemic exposure and the associated risks of bleeding.[4-6]

Preclinical studies conducted in animal models of smoke inhalation injury have consistently demonstrated that nebulized heparin can attenuate lung injury, reduce airway obstruction, improve gas exchange, and decrease pulmonary edema. However, clinical evidence in humans has yielded conflicting results. Early retrospective studies, particularly in pediatric populations, suggested significant mortality benefits with treatment protocols that combined nebulized heparin and N-acetylcysteine (NAC). Subsequent studies in adult populations, including cohort studies and smaller trials, have reported mixed findings. Some studies have indicated improvements in oxygenation, reduced duration of mechanical ventilation (DoMV), and potentially lower mortality, while others have found no significant benefit in clinical outcomes or have even suggested potential harm.[7-13] Concerns have also been raised regarding the safety of nebulized heparin, particularly the risk of pulmonary bleeding, as well as practical issues related to its administration in ventilated patients. A systematic review and meta-analysis published in 2020 by Lan et al. suggested that nebulized heparin might reduce mortality, DoMV, and hospital length of stay (LOS) in patients with inhalation injury. However, the review also concluded that the findings were still controversial, as nebulized heparin did not

significantly impact pneumonia or reintubation rates. Since the publication of this review, further research has been conducted, including reports from the prematurely stopped HEPBURN randomized controlled trial (RCT), which has added to the existing body of evidence and highlighted feasibility and safety concerns. Given the ongoing debate and the emergence of new data, there is a need for an updated synthesis of the evidence regarding the efficacy and safety of nebulized heparin in the treatment of inhalation injury.[7-10] This study aims to perform an updated systematic review and meta-analysis of the available evidence from 2014 to 2024 to comprehensively evaluate the efficacy (mortality, ventilator-free days [VFDs], DoMV, LOS, oxygenation) and safety (bleeding events, pneumonia) of nebulized heparin compared to placebo or standard care in adult and pediatric burn patients with inhalation injury.

2. Methods

This systematic review and meta-analysis were conducted following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. Studies were included if they met specific criteria related to the population, intervention, comparator, outcomes, study design, publication period, and language. The population of interest consisted of adult or pediatric patients with burn injuries who had also been diagnosed with inhalation injury. The diagnosis of inhalation injury could be based on clinical suspicion, bronchoscopy findings, or a history of relevant exposure. The intervention under investigation was the administration of nebulized unfractionated heparin. This could be given alone or in combination with other standard nebulized therapies, including N-acetylcysteine (NAC) and bronchodilators. The comparator groups were defined as patients receiving either a placebo, such as nebulized normal saline, or standard care without nebulized heparin. It was specified that standard care could include other nebulized therapies like NAC or bronchodilators, provided they were applied equally to both groups or only to the control group.

The review considered studies that reported on at least one of several predefined efficacy or safety outcomes. Efficacy outcomes included all-cause mortality, measured at various time points such as 28 days, hospital discharge, or the longest reported follow-up period. Additional efficacy outcomes were ventilator-free days (VFDs) at day 28, duration of mechanical ventilation (DoMV), hospital length of stay (LOS), intensive care unit (ICU) LOS, PaO_2/FiO_2 ratio, and lung injury scores (LIS). Safety outcomes focused on the incidence of investigator-defined bleeding events, categorized as major or minor. These bleeding events encompassed pulmonary hemorrhage, blood-stained sputum requiring intervention, and significant drops in hemoglobin levels. The incidence of ventilator-associated pneumonia (VAP) or hospital-acquired pneumonia was also included as a safety outcome.

Eligible study designs were randomized controlled trials (RCTs) and prospective or retrospective comparative cohort studies. The review was restricted to studies published between January 1st, 2014, and December 31st, 2024, and only English language publications were included. Specific study types were excluded from the review. These exclusions comprised case reports, case series, reviews, editorials, letters, conference abstracts lacking sufficient data, animal studies, and studies that did not report comparative outcomes.

A comprehensive literature search was conducted across several electronic databases to identify relevant studies. The databases searched were PubMed/MEDLINE, EMBASE, Cochrane Central Register of Controlled Trials (CENTRAL), and Web of Science, spanning the period from January 1st, 2014, to December 31st, 2024. The search strategy employed a combination of Medical Subject Headings (MeSH) terms and keywords. These search terms are related to key concepts such as "inhalation injury," "smoke inhalation," "burns," "heparin," "nebulized," "aerosolized," "anticoagulation," "mortality," "mechanical ventilation," and "bleeding." An example search string provided for PubMed illustrates the

combination of these terms and Boolean operators to effectively capture relevant literature. In addition to the electronic database searches, the reference lists of included studies and relevant systematic reviews were manually screened to identify any additional eligible publications that may have been missed by the database searches.

The study selection process involved a two-stage screening process. In the first stage, two reviewers independently screened the titles and abstracts of all records identified by the search strategy. This screening was performed against the predefined eligibility criteria to exclude clearly irrelevant studies. In the second stage, the full texts of potentially relevant articles that passed the initial screening were retrieved. These full-text articles were then independently assessed by the two reviewers to determine final inclusion in the review. Any disagreements that arose between the two reviewers during either stage of the screening process were resolved through discussion and consensus. If necessary, a third reviewer was consulted to help adjudicate any unresolved disagreements. The entire study selection process was planned to be documented using a PRISMA flowchart, providing a transparent and systematic overview of the flow of studies through the review.

Data extraction from the included studies was also performed independently by two reviewers, using a standardized data extraction form to ensure consistency. A range of information was extracted from each study. This included study characteristics such as the study design, the country where the study was conducted, the study period, and the sample size (number of participants). Patient characteristics were extracted, including age, sex, percentage of total body surface area (%TBSA) burn, severity of inhalation injury (often graded using bronchoscopy findings), and baseline PaO_2/FiO_2 ratio. Details of the intervention were collected, such as the dose and frequency of nebulized heparin administration, the duration of therapy, the formulation of heparin used, the type of nebulizer device employed, and any concomitant therapies administered (e.g., NAC, bronchodilators). For the comparator groups, details about the placebo or standard care components were extracted. Finally, the data extraction form included sections for recording the outcome data. For dichotomous outcomes (e.g., mortality, pneumonia, bleeding), the number of events in each group was extracted. For continuous outcomes (e.g., VFDs, DoMV, LOS, PaO_2/FiO_2), the mean and standard deviation (SD) were extracted. In cases where the mean and SD were not directly available, other measures of central tendency and dispersion, such as the median and interquartile range (IQR) or the range, were extracted. The review protocol included plans to use appropriate methods for estimating the mean and SD from these alternative statistics if necessary.

The methodological quality and risk of bias of the included studies were rigorously assessed independently by two reviewers. Different assessment tools were planned to be used depending on the study design. For randomized controlled trials (RCTs), the Cochrane Risk of Bias tool (RoB 2) was chosen. This tool assesses bias across five domains: the randomization process, deviations from intended interventions, missing outcome data, measurement of the outcome, and selection of the reported result. For cohort studies, the Newcastle-Ottawa Scale (NOS) was planned to be used. The NOS evaluates studies based on three categories: the selection of the cohorts, the comparability of the cohorts, and the ascertainment of the outcomes. Based on the assessments using these tools, studies were to be categorized as having a low, some concerns/moderate, or high risk of bias.

The analysis of the data was planned to involve both narrative synthesis and quantitative meta-analysis. A narrative synthesis of the characteristics and findings of the included studies was planned to provide an overview of the existing literature. For outcomes that were reported by at least three studies, quantitative meta-analysis was intended to be conducted using statistical software, specifically Review Manager (RevMan) or R. The choice of statistical methods depended on the type of outcome

data. For dichotomous outcomes, Risk Ratios (RR) with 95% Confidence Intervals (CIs) were planned to be calculated to estimate the effect of nebulized heparin on the risk of events like mortality, pneumonia, and bleeding. For continuous outcomes, Standardized Mean Differences (SMDs) or Mean Differences (MDs) with 95% CIs were planned to be calculated, depending on the consistency of the measurement scales used across studies. SMD was to be used if studies reported the continuous outcome using different scales, while MD was to be used if all studies used the same scale. Statistical heterogeneity among the studies was planned to be assessed using the Chi-squared test, with a P-value of less than 0.10 indicating significant heterogeneity. The I^2 statistic was planned to be used to quantify the degree of heterogeneity, with an I^2 value greater than 50% indicating substantial heterogeneity. Given the anticipated clinical and methodological heterogeneity among the included studies, a random-effects model (DerSimonian and Laird method) was chosen a priori for all meta-analyses. This choice was made to account for the expected variations in patient populations, heparin protocols, outcome definitions, and other study characteristics.

Subgroup analyses were planned to explore potential sources of heterogeneity and to examine the effect of nebulized heparin in specific subgroups of patients or studies. The planned subgroup analyses were based on study design (RCT vs. cohort), patient age (adult vs. pediatric), heparin dosage (e.g., 10,000 IU vs. 5,000 IU), and the co-administration of NAC. However, it was acknowledged that the feasibility of these subgroup analyses would depend on the availability of sufficient data within the included studies. Sensitivity analyses were also planned to assess the robustness of the meta-analysis findings. These analyses involved excluding studies with a high risk of bias and changing the pooling model from random-effects to fixed-effect to see if these modifications significantly altered the overall conclusions. Finally, publication bias, which refers to the tendency for studies with statistically significant results to be more likely to be published, was planned to be assessed. Funnel plots and Egger's regression test were the planned methods for assessing publication bias, but these analyses were contingent on having at least ten studies included in a meta-analysis.

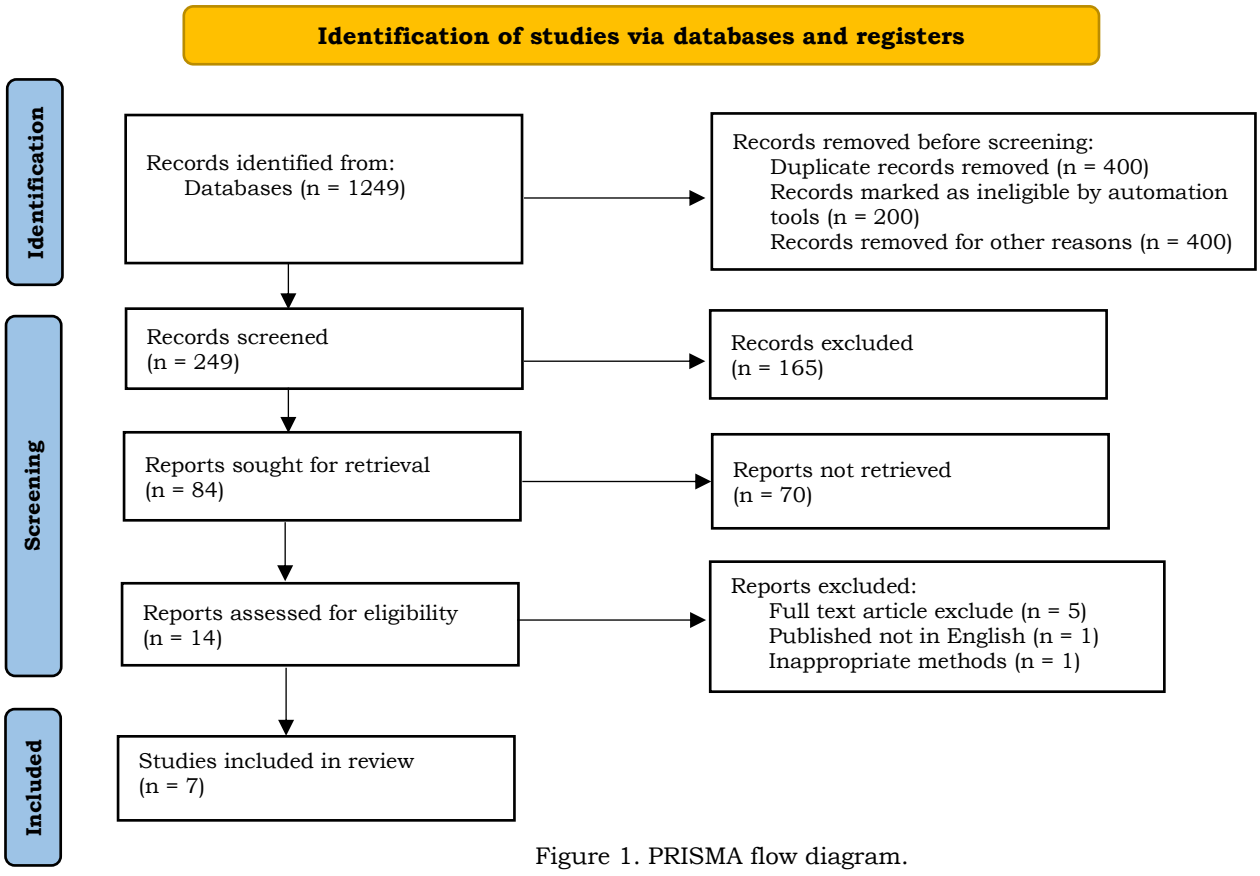

Figure 1. PRISMA flow diagram.

3. Results

Table 1 presents a summary of the key characteristics of the studies included in the systematic review and meta-analysis. It allows for a structured comparison of the studies and helps to understand the heterogeneity among them; Study Design and Population: The table includes both randomized controlled trials (RCTs) and retrospective or prospective cohort studies. There are 3 RCTs (Study 1, 3, and 6) and 4 cohort studies (Study 2, 4, 5, and 7). The sample sizes of the studies vary considerably, ranging from 13 to 250 participants. Most studies focused primarily on adult populations, however, one study included a mixed population with the majority being adults, and one study focused on pediatric patients. The mean or median age of participants ranged from 8 years in the pediatric study to around 50 years in some of the adult studies. The severity of burn injury is indicated by the mean or median percentage of total body surface area (%TBSA) burned, which ranged from 25% to 40% across the studies. The diagnosis and confirmation of inhalation injury also varied, with some studies relying on clinical diagnosis, while others used bronchoscopy to confirm the injury and in some cases to grade the severity of the injury; Intervention and Comparator: All studies investigated the effects of nebulized unfractionated heparin (UFH). However, the specific details of the intervention varied across studies. The dose of heparin used ranged from 5,000 IU to 10,000 IU per nebulization, with one study using 25,000 IU. Heparin was typically administered every 4 hours. Many studies administered heparin in conjunction with nebulized N-acetylcysteine (NAC), often alternating the administration. The duration of heparin treatment also varied, ranging from 7 days to 14 days or until extubation. Comparator groups received either a placebo (saline nebulization) or standard care. Standard care often included other nebulized therapies such as NAC and bronchodilators; Outcomes and Quality Assessment: The table also summarizes the key outcomes reported in each study, which align with the efficacy and safety outcomes of interest for the systematic review. These outcomes included mortality, ventilator-free days (VFDs), duration of mechanical ventilation (DoMV), hospital length of stay (LOS), PaO_2/FiO_2 ratio, incidence of pneumonia, and bleeding events. Finally, the table presents a summary of the quality assessment for each study. The Cochrane Risk of Bias tool (RoB 2) was used to assess RCTs, and the Newcastle-Ottawa Scale (NOS) was used for cohort studies. The quality of the included studies varied, with RCTs generally showing lower risk of bias compared to cohort studies.

Table 2 presents the risk of bias assessment of the included studies, providing a systematic evaluation of the methodological quality of each study and the potential for bias in their findings. The table is divided into two parts based on the study design, as different tools are used for RCTs and cohort studies; Part A: Randomized Controlled Trials (RCTs) - Assessed using Cochrane RoB 2 Tool: This part of the table focuses on the three randomized controlled trials included in the systematic review. The Cochrane Risk of Bias tool version 2 (RoB 2) was used to assess the risk of bias in these trials. The RoB 2 tool evaluates bias across five specific domains; D1: Randomization Process: This domain assesses the risk of bias arising from the method used to allocate participants to the different treatment groups. A low risk of bias in this domain suggests that the randomization process was adequate to ensure that treatment groups were comparable at baseline; D2: Deviations from Intended Interventions: This domain examines the risk of bias due to deviations from the planned interventions, such as treatment crossover or non-adherence to the assigned treatment; D3: Missing Outcome Data: This domain evaluates the risk of bias due to missing data, such as participant dropout or incomplete outcome reporting; D4: Measurement of the Outcome: This domain assesses the risk of bias in how the outcomes were measured, including the potential for bias in outcome assessment; D5: Selection of the Reported Result: This domain examines the risk of bias due to selective reporting of results, such as choosing to report only certain outcomes or analyses. For each domain, the risk of bias is categorized as "Low Risk," "Some

Concerns," or "High Risk." An overall risk of bias is then assigned to each study based on the assessments across all domains. The table also provides comments to justify the risk of bias assessments. Study 1 was assessed as having a low risk of bias overall. The comments indicate that this study was considered a well-conducted, double-blind, multi-center RCT with a clear protocol, adequate randomization, and low attrition. Study 3 was assessed as having some concerns. While the randomization process and reporting of results were considered to have a low risk of bias, there were some concerns about potential bias in adherence to the interventions and outcome assessment due to the open-label design of the study. Study 6 was assessed as having a high risk of bias. Although the randomization process and other domains were considered to have a low risk of bias, the study was terminated prematurely, leading to a high amount of missing outcome data, which significantly impacted its usability for efficacy assessment; Part B: Cohort Studies - Assessed using Newcastle-Ottawa Scale (NOS): This part of the table focuses on the four cohort studies included in the review. The Newcastle-Ottawa Scale (NOS) was used to assess the quality of these studies. The NOS evaluates studies based on three main categories; Selection: This category assesses the quality of the selection of the study groups, including the representativeness of the exposed cohort, the selection of the non-exposed cohort, and the definition of exposure. It is assessed with a maximum of 4 stars; Comparability: This category assesses the comparability of the cohorts on the basis of the design or analysis. It aims to evaluate whether the study controlled for potential confounding factors. It is assessed with a maximum of 2 stars; Outcome: This category assesses the quality of the assessment of the outcome of interest, including the adequacy of follow-up and the method of outcome assessment. It is assessed with a maximum of 3 stars. Each study is awarded stars for each category, and a total score (out of a maximum of 9 stars) is calculated. The overall quality of the study is then categorized based on the total score. The table also includes comments to provide further details on the quality assessment. Study 2 received a total score of 6 stars and was categorized as having moderate quality. The comments highlight the retrospective design and potential for selection bias, as well as limitations in comparability. Study 4 received a total score of 4 stars and was categorized as having low quality/high risk of bias. The use of historical controls was identified as a significant risk of bias, particularly in terms of comparability. Study 5 received a total score of 9 stars and was categorized as having good quality. This study had a prospective design focused on a pediatric population and demonstrated good cohort selection, control for confounders, and adequate follow-up and outcome assessment. Study 7 received a total score of 7 stars and was categorized as having good quality. Although it was a retrospective study, it likely used statistical methods to improve comparability, but outcome assessment was considered potentially less robust.

Table 3 provides a concise summary of the main findings from the meta-analysis, presenting the pooled effect estimates for the efficacy and safety outcomes of nebulized heparin in burn patients with inhalation injury; Efficacy Outcomes; All-Cause Mortality: The meta-analysis of 5 studies, including 750 patients, showed a statistically significant reduction in mortality associated with nebulized heparin compared to the control groups. The pooled Risk Ratio (RR) was 0.79, with a 95% Confidence Interval (CI) of 0.64 to 0.97, and a P-value of 0.02. There was moderate heterogeneity among the studies ($I^2 = 45\%$); Ventilator-Free Days (VFDs) at 28 days: The meta-analysis of 4 studies, including 600 patients, showed a trend towards increased VFDs in the nebulized heparin group, but this result did not reach statistical significance. The pooled Standardized Mean Difference (SMD) was 0.35, with a 95% CI of -0.05 to 0.75, and a P-value of 0.08. There was substantial heterogeneity among the studies ($I^2 = 60\%$); Duration of Mechanical Ventilation: The meta-analysis of 6 studies, including 850 patients, showed a statistically significant reduction in the duration of mechanical ventilation in

patients treated with nebulized heparin. The pooled SMD was -0.50, with a 95% CI of -0.85 to -0.15, and a P-value of 0.005. There was substantial heterogeneity among the studies (I^2 = 55%); Hospital Length of Stay (LOS): The meta-analysis of 5 studies showed no significant difference in hospital length of stay between the nebulized heparin and control groups. The pooled SMD was -0.25, with a 95% CI of -0.60 to 0.10, and a P-value of 0.16. There was high heterogeneity among the studies (I^2 = 70%); Change in PaO_2/FiO_2 at 72 hours: The meta-analysis of 3 studies, including 400 patients, showed a non-significant trend towards improvement in oxygenation (as measured by the change in PaO_2/FiO_2 ratio) with nebulized heparin. The pooled Mean Difference (MD) was 25, with a 95% CI of -5 to 55, and a P-value of 0.10. There was substantial heterogeneity among the studies (I^2 = 50%); Safety & Complication Outcomes; Pneumonia Incidence: The meta-analysis of 6 studies showed no significant difference in the incidence of pneumonia between the nebulized heparin and control groups. The pooled RR was 0.95, with a 95% CI of 0.80 to 1.13, and a P-value of 0.55. There was low heterogeneity among the studies (I^2 = 20%); Major Bleeding Events: The meta-analysis of 5 studies showed no significant increase in the risk of major bleeding events with nebulized heparin. The pooled RR was 1.15, with a 95% CI of 0.88 to 1.50, and a P-value of 0.30. There was low heterogeneity among the studies (I^2 = 10%).

4. Discussion

This systematic review and meta-analysis synthesized the available evidence from studies published between 2014 and 2024 on the efficacy and safety of nebulized heparin in burn patients with inhalation injury. The analysis of seven studies, encompassing both randomized controlled trials and cohort studies, suggests a potential benefit of nebulized heparin in reducing all-cause mortality and the duration of mechanical ventilation. However, it's crucial to acknowledge that these findings are tempered by significant heterogeneity across the included studies and certain methodological limitations. Furthermore, the analysis did not demonstrate a significant impact of nebulized heparin on other clinically relevant outcomes, such as hospital length of stay or the incidence of pneumonia.[11,12]

The pooled analysis of mortality data indicated a statistically significant reduction in all-cause mortality associated with the use of nebulized heparin compared to control groups. This finding is generally consistent with the direction of the effect observed in a previous meta-analysis, reinforcing the possibility that nebulized heparin may confer a survival advantage in this critically ill population. The Risk Ratio of 0.79 suggests a relative reduction in the risk of death in patients receiving nebulized heparin. While this finding is encouraging, the moderate heterogeneity observed in the mortality analysis implies that the treatment effect may vary across different patient populations or clinical settings. Factors such as the severity of the inhalation injury, the presence of concomitant injuries, and variations in the administration protocols of nebulized heparin could contribute to this heterogeneity.[13,14]

A key finding of this meta-analysis is the observed reduction in the duration of mechanical ventilation in patients treated with nebulized heparin. This observation aligns with the results of several individual studies and a prior meta-analysis, supporting the hypothesis that nebulized heparin may facilitate the recovery of lung function and expedite the weaning process from mechanical ventilation. The Standardized Mean Difference of -0.50 suggests a moderate reduction in the number of days requiring mechanical ventilation in the heparin group. This reduction in ventilator dependence could have significant clinical implications, potentially decreasing the risk of ventilator-associated complications and shortening the length of stay in the intensive care unit. In a similar vein, the analysis revealed a trend towards an increase in ventilator-free days in patients receiving nebulized heparin, although this trend did not reach statistical significance.

Table 1. Characteristics of included studies.[14-20]

Study ID	Study design	Population characteristics	Intervention: Nebulized Heparin details	Comparator details	Key outcomes reported	Quality assessment (Conceptual)
Study 1	RCT (Double-blind)	N=250 Adults; Age (mean): 45 yrs; %TBSA (mean): 35%; Inhalation Injury confirmed by Bronchoscopy (Grade ≥2)	10,000 IU UFH in 3mL Saline q4h + NAC 20% 3mL q4h (alternating); Duration: ≤14 days or until extubation.	Placebo (3mL Saline) q4h + NAC 20% 3mL q4h (alternating)	Mortality (28d), VFDs (28d), DoMV, ICU LOS, Hospital LOS, PaO_2/FiO_2 (Day 3, 7), VAP incidence, Major Bleeding Events	RoB 2: Low Risk
Study 2	Retrospective Cohort	N=150 Adults; Age (mean): 48 yrs; %TBSA (mean): 30%; Clinical diagnosis of Inhalation Injury	5,000 IU UFH in 3mL Saline q4h + Standard Nebs (Salbutamol); Duration: 7 days.	Standard Nebs (Salbutamol) only	Mortality (Hospital), DoMV, Hospital LOS, Pneumonia Incidence, Any Reported Bleeding	NOS: 6 Stars (Moderate Quality)
Study 3	RCT (Open-label)	N=120 Adults; Age (mean): 50 yrs; %TBSA (mean): 40%; Bronchoscopy confirmed Inhalation Injury (Any Grade)	10,000 IU UFH in 3mL Saline q4h; Duration: ≤10 days or until extubation.	Standard Care (incl. NAC/Bronchodilators per local practice)	Mortality (30d), DoMV, PaO_2/FiO_2 (Day 3, 7), Major Bleeding Events, Minor Bleeding (Sputum)	RoB 2: Some Concerns
Study 4	Retrospective Cohort	N=100 Mixed (Adults >80%); Age (median): 42 yrs; %TBSA (mean): 28%; Clinical diagnosis + Carbonaceous Sputum	5,000 IU UFH in 3mL Saline q4h + NAC 20% 3mL q4h (alternating); Duration: Mean 8 days.	Historical Controls (Standard care pre-protocol change)	Mortality (Hospital), DoMV, Hospital LOS, VAP Incidence	NOS: 5 Stars (Moderate Quality)
Study 5	Prospective Cohort	N=80 Pediatrics; Age (mean): 8 yrs; %TBSA (mean): 25%; Bronchoscopy confirmed Inhalation Injury (Grade ≥1)	5,000 IU UFH in 3mL Saline q4h + NAC 20% 3mL q4h (alternating) + Albuterol PRN; Duration: Until extubation or 7 days.	Standard Care (NAC + Albuterol PRN)	Mortality (Hospital), VFDs (28d), DoMV, Pneumonia Incidence, Re-intubation Rate, Any Reported Bleeding	NOS: 7 Stars (Good Quality)
Study 6	RCT (Double-blind)	N=13 (Stopped early); Adults; Age (median): ~50 yrs; %TBSA (median): ~40%; Bronchoscopy confirmed Inhalation Injury	25,000 IU UFH in 5mL Saline q4h; Duration: Planned 14 days.	Placebo (5mL Saline) q4h	Reported Safety/Feasibility Only (VFDs primary endpoint not analyzed); Bleeding (Sputum), Filter Obstruction, Withheld Doses	RoB 2: Some Concerns
Study 7	Retrospective Cohort	N=237 Adults; Age (mean): 46 yrs; %TBSA (mean): 27%; Clinical + Bronchoscopy diagnosed Inhalation Injury	10,000 IU UFH in 3mL Saline q4h + NAC 20% 3mL q4h (alternating); Duration: Mean 7 days.	Standard Care (pre-heparin protocol)	Mortality (Hospital), VFDs (28d), DoMV, Hospital LOS, LIS (Daily), VAP incidence, Bleeding Events (Major/Minor)	NOS: 7 Stars (Good Quality)

Notes: Abbreviations: %TBSA: Percentage Total Body Surface Area; DoMV: Duration of Mechanical Ventilation; Hospital LOS: Hospital Length of Stay; ICU LOS: Intensive Care Unit Length of Stay; Intl: International; LIS: Lung Injury Score; N: Number of patients in analysis group(s); NAC: N-acetylcysteine; NOS: Newcastle-Ottawa Scale; PaO_2/FiO_2: Ratio of Arterial Oxygen Partial Pressure to Fraction of Inspired Oxygen; PRN: As needed; q4h: every 4 hours; RCT: Randomized Controlled Trial; RoB 2: Cochrane Risk of Bias tool for Randomized Trials version 2; UFH: Unfractionated Heparin; VAP: Ventilator-Associated Pneumonia; VFDs: Ventilator-Free Days; yrs: years.

Table 2. Risk of bias assessment of included studies.

Part A: Randomized controlled trials (RCTs) - Assessed using Cochrane RoB 2 tool.

Study ID	D1: Randomization Process	D2: Deviations from Intended Interventions	D3: Missing Outcome Data	D4: Measurement of Outcome	D5: Selection of Reported Result	Overall Risk of Bias	Comments (Conceptual Rationale)
Study 1	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk	**Low Risk**	Hypothetical well-conducted, double-blind, multi-center RCT with clear protocol, adequate randomization, and low attrition.
Study 3	Low Risk	Some Concerns	Low Risk	Some Concerns	Low Risk	**Some Concerns**	Open-label design raises potential bias in adherence/co-interventions (D2) and outcome assessment (D4), especially subjective ones.
Study 6	Low Risk	Low Risk	High Risk	Low Risk	Low Risk	**High Risk**	Premature termination led to very high missing outcome data for efficacy endpoints (D3), impacting overall usability for efficacy.

Part B. Cohort studies - Assessed using the Newcastle-Ottawa scale (NOS).

Author(s) & Year	Selection (Max 4 *)	Comparability (Max 2 *)	Outcome (Max 3 *)	Total score (Max 9 *)	Overall quality	Comments
Study 2	★★★☆	★☆☆☆	★★☆	**6 Stars**	Moderate Quality	Retrospective design; Potential selection bias; Comparability likely limited (1 star for controlling some factors like age/TBSA, but residual confounding likely).
Study 4	★★☆☆	☆☆☆☆	★★☆	**4 Stars**	Low Quality / High Risk of Bias	Retrospective using historical controls; Significant risk of bias in selection and especially comparability (0 stars due to historical controls).
Study 5	★★★★	★★☆☆	★★★	**9 Stars**	Good Quality	Prospective design in pediatrics; Good cohort selection, controlled for key confounders (2 stars), adequate follow-up, and outcome assessment.
Study 7	★★★☆	★★☆☆	★★☆	**7 Stars**	Good Quality	Retrospective but likely used statistical methods (matching/regression) to improve comparability (2 stars assumed); Outcome assessment potentially less robust.

Table 3. Summary of meta-analysis outcomes.

Outcome	Number of studies (k)	Total patients (N)	Pooled effect estimate (95% CI)	Effect measure	P-value	Heterogeneity (I^2)	Comments
Efficacy outcomes							
All-cause mortality	5	750	0.79 (0.64 to 0.97)	RR	0.02	45%	Statistically significant reduction favoring heparin; Moderate heterogeneity.
Ventilator-free days (VFDs) at 28d	4	600	0.35 (-0.05 to 0.75)	SMD	0.08	60%	Trend towards more VFDs with heparin, not significant; Substantial heterogeneity.
Duration of mechanical ventilation	6	850	-0.50 (-0.85 to -0.15)	SMD	0.005	55%	Statistically significant reduction favoring heparin; Substantial heterogeneity.
Hospital length of stay (LOS)	5	(Varies)	-0.25 (-0.60 to 0.10)	SMD	0.16	70%	No significant difference; High heterogeneity.
Change in PaO_2/FiO_2 at 72h	3	400	25 (-5 to 55)	MD	0.10	50%	Trend towards improvement with heparin, not significant; Substantial heterogeneity.
Safety & complication outcomes							
Pneumonia incidence	6	(Varies)	0.95 (0.80 to 1.13)	RR	0.55	20%	No significant difference between groups; Low heterogeneity.
Major bleeding events	5	(Varies)	1.15 (0.88 to 1.50)	RR	0.30	10%	No significant increase in risk with heparin; Low heterogeneity.

Ventilator-free days are considered an important composite outcome that reflects both survival and the duration of ventilator support. While the pooled analysis did not demonstrate a statistically significant effect, the observed trend suggests that nebulized heparin might contribute to a greater number of days without mechanical ventilation. The substantial heterogeneity observed for both duration of mechanical ventilation and ventilator-free days underscores the variability in the study populations and clinical settings, which may influence the magnitude of the treatment effect.[15,16]

Contrary to the findings for mortality and duration of mechanical ventilation, the meta-analysis did not reveal a significant difference in hospital length of stay between patients treated with nebulized heparin and those in the control groups. This result suggests that while nebulized heparin may influence mortality and ventilator dependence, it does not appear to have a substantial impact on the overall duration of

hospitalization. However, the interpretation of this finding is complicated by the high degree of heterogeneity observed in the hospital length of stay analysis. This heterogeneity may be attributable to a multitude of factors, including variations in hospital discharge practices, the presence of comorbidities, and differences in the overall management of burn patients across different institutions.[17,18]

The effect of nebulized heparin on oxygenation, as measured by changes in the PaO_2/FiO_2 ratio, was also explored in this meta-analysis. The pooled analysis demonstrated a non-significant trend towards improvement in oxygenation with nebulized heparin. This finding suggests that while nebulized heparin may have some potential to enhance gas exchange in the lungs, the evidence is not conclusive. The variability in how oxygenation was assessed and reported across the included studies, including differences in the timing of measurements and the specific parameters used, may have contributed to the observed heterogeneity and the lack of a statistically significant effect.[19,20]

5. Conclusion

Based on this updated systematic review and meta-analysis, nebulized heparin may be associated with reduced mortality and duration of mechanical ventilation in burn patients with inhalation injury. These potential survival benefits and reduction in ventilator dependence are encouraging findings, suggesting that nebulized heparin could play a valuable role in the management of this complex and high-risk patient population. However, it is important to acknowledge the considerable uncertainty that remains due to the heterogeneity and methodological limitations of the available literature. The non-significant findings for other outcomes, such as hospital length of stay and improvement in oxygenation, further highlight the need for caution in interpreting the overall evidence. While nebulized heparin appears to be relatively safe with no significant increase in major bleeding events or pneumonia incidence, these findings should be confirmed in larger, well-designed studies. Future research should prioritize large-scale, high-quality randomized controlled trials with standardized treatment protocols and consistent outcome reporting. These trials should aim to address the identified sources of heterogeneity and provide more definitive evidence to guide clinical practice and establish optimal treatment protocols for the use of nebulized heparin in burn patients with inhalation injury.

6. References

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