

**Original article :**

**Role of heparin and N- acetylcystein in prevention of acute respiratory distress syndrome in suspected inhalation injury in burn**

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**Abstract:**

**Background:** This study was undertaken to identify the role of heparin and N- acetylcystein in prevention of acute respiratory distress syndrome in suspected inhalation injury in burn

**Material and Method:** One hundred patients were registered with inhalation lung injury in burn unit. Out of these hundred, fifty patients of inhalation injuries have been nebulised with heparin and n-acetylene cysteine (Group A) & fifty were control (Group B). An individual with inhalation injury has an injury consistent with inhalation of smoke or products of combustion between 30% - 75% total burnt surface area. All the patients were clinically evaluated for haematological, sputum culture, pus culture, chest X-ray, blood gases, including carboxyhaemoglobin and acid/base balance, blood Urea, serum creatinine & Bronchoscopy.

**Results:** There was no significant difference in age, sex and TBSA in between two groups. There was no significant difference was observed for the occurrence of lung injury in two groups however mortality rate was significantly lower in patients nebulized with heparin and n-acetylene cysteine as compared to control group.(P=0.002).

**Conclusion:** These results support the previously reported benefits of NH-AC in patients with ALI/ARDS & Highlights the need to start NH-AC therapy as early as possible.

**Keywords:** Inhalation Lung Injury, Acute Lung Injury, Acute Respiratory Distress Syndrome, Heparin, N-Acetylene Cystiene, Heparin

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**Introduction**

Inhalation burns can be caused by smoke, hydrofluoric acid, ammonia, chlorine, or other chemical agents after an individual inhales these toxic substances. Cyanide (CN) toxicity can come from exposure to the toxic debris of burning polyurethane, wool, or silk items. Upper airway edema, respiratory distress, and carbon monoxide (CO) toxicity are the hallmarks of injury from inhalation. These symptoms appear within 12 to 24 hours following the occurrence of the burn. Also, a rare condition may occur in which chemical toxicity or the heat from fire oxidizes lung haemoglobin, resulting in impaired oxygen transport and respiratory distress. Inhalation injury

is more likely to occur in fires in enclosed areas [1].

There are usually three phases for significant inhalation injuries. The first phase is marked by upper airway swelling and blockage, lower airway spasm, and effects of carbon monoxide poisoning. The second stage occurs after 3 to 4 days and consists of decreased oxygen levels and congestion within the lung tissue. The last phase starts about 3 to 10 days after the injury and consists of bronchitis and pneumonia. The focus of treatment differs from phase to phase [2]. Men are more likely than women to die from fire by a ratio of 3:2; both children and the elderly are also at increased risk for fire-related injury [3]. Exposure rates for

chemical burns are similar in adults and children, but burns from certain chemicals such as hydrofluoric acid are more common in men due to occupational exposure [4].

Among individuals in the US with burns over 5% of their total body surface area (TBSA), less than 10% have inhalation injuries; among those with burns over 85% of their TBSA, over 80% have inhalation injuries [5]. In 2003, over 145,000 chemical burns were reported to The American association of Poison Control Centres, of which 370 cases resulted in major chemical toxicity and 9,368 resulted in moderate chemical toxicity [6].

Treatment consists of intubation of victims for standard indications, positive pressure ventilation, pulmonary toilet, and antibiotics for established infection. There is no value to prophylactic intubation, steroids, or antibiotics. In practical terms, one can only support such patients while they go through a predictable 7- to 21-day period of endobronchial slough, secondary failure of gas exchange and compliance, infection, and healing[7].

Clinical problems that may need to be addressed in patients with inhalation injury. Intense bronchospasm from aerosolized irritants occurs during the first 24 to 48 hours, especially in young children. This is managed with nebulized beta2 agonists, although some will require intravenous bronchodilators such as terbutaline, aminophylline, or racemic epinephrine infusions. Steroids are only indicated in the initial 24 hours after inhalation injury[6].

Approximately half of those with ALI can be expected to develop pulmonary infection, either pneumonia or purulent tracheobronchitis. Infection typically occurs toward the end of the first week following injury[8].

White blood cell count, sputum culture, and chest x-ray must be closely monitored in susceptible individuals to combat infection[9].

Carbon monoxide poisoning commonly occurs in conjunction with inhalation injury. Its primary pathophysiology involves the reversible displacement of oxygen on the hemoglobin molecule. Some investigators recommend hyperbaric oxygen as a means of improving the prognosis of those suffering serious CO exposures and to prevent the development of neurologic sequelae. Small airway obstructions, caused by the formation of casts, may occur as necrotic endobronchial debris slough [10]. Studies have shown that the obstructing material is composed mainly of fibrin that has entrapped migrated neutrophils, shed bronchial epithelial cells, and thickened mucus[11].

In many cases, the cast is solid and hard to remove secondary to ALI induced damage to the ciliary transport function. Toilet bronchoscopy can greatly facilitate clearance of the airways. Vigilant pulmonary toilet is an essential component of the management of patients with inhalation injury. Nebulized heparin and N-acetylcysteine has been proposed as an adjunct to prevent small airway obstructions and improve pulmonary toilet in patients with inhalation injury[12].

Research in lung inhalation injury has focused on reducing airway obstruction and progressive ventilation/perfusion mismatch by preventing the formation of casts. Administration of nebulized or systemic heparin has been shown to decrease tracheobronchial cast formation and pulmonary edema in smoke inhalation injury[13].

Activation of the tissue factor-induced coagulation pathway in the alveolar compartment, accompanied by inhibition of the regional fibrinolytic system promotes the deposition of fibrin in alveoli and contributes to the formation of casts and the functional impairment of the lung. Microscopic

evaluation of airway obstruction in sheep with Acute Lung Injury, showed that aerosolized heparin significantly prevented cast formation, edema, cellular infiltrates, and congestion[14].

A retrospective comparison of 47 consecutive paediatric patients with smoke inhalation injury treated with mechanical ventilation plus nebulized heparin (NH) (5, 000IU) and the mucolytic agent N-acetylcysteine (NA) (3ml of 20% aerosolized solution), every 4 hours for the first 7 days after injury, revealed a significant decrease in reintubation rates incidence of atelectasis, and mortality in patientstreated with nebulized heparin and N-acetylcysteine comparedto controls.The beneficial effect of Nebulization with Acetyl cystein is related to its mucolytic effect[15].

On the other hand, Nebulization with Heparine benefits are related to its ability to prevent fibrin formation and its deposition in the alveolar space. This effect can be crucial in halting the development of ALI/ARDS or damage to the surfactant. The concentration of NH used in this study did not change platelet count or the partial thromboplastin time (PTT) in the pediatric patients. Considering the anatomical and histological differences between the pediatric and adults airways, nebulized heparin and N-acetylcysteine has been tested in adult patients with ALI. In a retrospective review, daily lung injury scores generated from the average scores of chest roentgenograms, PaO<sub>2</sub> to FiO<sub>2</sub> ratios, positive end expiratory pressure requirements (PEEP), and respiratory compliance showed that nebulized heparin and N-acetylcysteine significantly reduced lung injury scores and significantly reduced mortality within the first week of treatment compared to the control group.Systemically administered heparin has also been shown to ameliorate ALI[16].

Cox et al., compared adult sheep with smoke inhalation injury treated with mechanical ventilation plus continuous heparin infusion to sheep treated with mechanical ventilation alone. The heparin group received a 400 unit per kilogram bolus of heparin followed by a continuous infusion to maintain the activated clotting time between 250 to 300 seconds. The control group received a saline solution vehicle. Heparin treated sheep showed improved PaO<sub>2</sub> to FiO<sub>2</sub> ratios, lower PEEP requirements, fewer casts, and less pulmonary edema[17].

Drug treatment for lung injury after smoke inhalation is being addressed in clinical trials and animal models. Presently, In patient study, we would like to know the mechanism of action for heparin in smoke inhalation injury. The inhibition of clot formation in the blood vessels by heparin is common knowledge, but the inhibition of cast formation in the airway by heparin is a novel idea. Experiments have shown that heparin decreases tracheobronchial cast formation, improves oxygenation, minimizes barotrauma and reduces pulmonary edema in ovine models of severe smoke inhalation injury and in adult and pediatric patients with inhalation injury. In light of the high mortality associated with inhalation injury, the risk/benefit of using in conjuncture heparin and N –acetylene cysteine appears very favourable. So there was a Need of the Study because Inhalation injury in burn increases the ARDS. Heparin and N – acetylcystein has been shown to decrease the morbidity and mortality in both pediatric and adult patients.

**Material and Methods:** In this prospe-ctive100 patients with an injury consistent with inhalation of smoke or products of combustion between 35% - 75% TBSA were recruited. Out of hundred, fifty patients of inhalation injury was nebulized with heparin and n-acetylene cysteine & whereas in another fifty no nebulization was done.

Patients with polytrauma or blast injury, in cardiac arrest, History of coagulation disorder, Chronic obstructive pulmonary disease, Pneumonia diagnosed at admission, were excluded from the study.

The following Inhalation Injury treatment protocol was followed till 7 days of admission

- Titrate humidified oxygen to maintain SaO<sub>2</sub> > 90%
- Cough, deep breath exercises every 2 hourly
- Turn patient side to side every 2 hourly
- Chest physiotherapy every 4 hourly
- Aerosolize 3 cc's of 20% N-acetylcysteine with 2cc of normal saline every 4 hourly with a Bronchodilator
- Alternate aerosolizing 5000 units of Heparin with 3 cc's of normal saline every 4 hourly

- Nasotracheal suctioning as needed
- Early ambulation on post-operative day 5
- Sputum cultures for intubated patients every Monday, Wednesday and Friday.
- Pulmonary function studies prior to discharge and at out-patient visits on follow up.
- Patient/family education regarding inhalation injury

Written consent was taken from all patients. The study has been approved by institutional ethical committee.

### Results

The mean age of the patients was 31.46±10.90 years. There was female preponderance in both the groups. Table 1 show that there was no significant difference in age, sex and total burnt surface area (TBSA) in two groups. There was also no significant difference in biochemical and haematological profile in two groups.

**Table 1: Demographic and biochemical profile of two groups**

	Group A	Group B	Total	P value
Age	29.6±10.84	33.30±10.90	31.46±10.9	0.094
Sex(Female)	35(70.0%)	28(56.0%)	63(63%)	0.147
TBSA	0.53±0.13	0.57±0.14	0.557±0.138	0.182
Hb	11.21±2.06	10.94±2.49	11.07±2.28	0.563
TLC	5637±4499	4274±2634	4955±4126	0.099
Plt count	2.29±2.96	1.75±0.75	2.02±2.13	0.204
Na <sup>+</sup>	141.4±13.4	142.5±14.7	142.0±14.02	0.708
K <sup>+</sup>	4.44±1.38	4.25±1.71	4.34±1.55	0.540
Cl <sup>-</sup>	103.6±12.1	102.4±15.2	103.05±13.72	0.648
S Protein	4.74±1.06	4.00±0.72	4.37±0.98	0.000
S Creatinine	2.71±1.07	3.06±1.03	2.89±1.06	0.095
S Urea	80.3±43.14	128.4±46.4	104.4±50.74	0.000

Among the respiratory problem, Acute respiratory distress syndrome was most common(43%) followed by pneumonitis(14%). There was no

significant difference in occurrence of respiratory syndrome in two groups (Table 2).

**Table 2: Frequency of lung injury among two groups**

Type	Group A	Group B	Total	P value
ARDS	24(48)	19(38)	43(43)	0.419
Pleural Effusion	5(10)	7(14)	12(12)	0.759
Pneumonitis	4(8)	10(20)	14(14)	0.147

In Group B, only 12 patients with inhalation injury were get well and get discharged at least after 7 days of injury whereas 38 patients were died within 7 days of admission. However in Group A where nebulization was done, 28 individuals with

inhalation injury expired. The mortality rate was significantly lower in Group A as compared to Group B. Patients without nebulization had a 1.727 times more risk of death due to lung injury than patient's receiving nebulization.

**Table 3: Showing the association between the two study groups with the mortality outcome**

Outcome	Group A	Group B	P value, RR(95% CI)
Discharged	22	12	0.0020, 1.727(1.218-2.450)
Died	28	38	

**Discussion:**

This study supports present study done in regarding daily lung injury scores generated from the average scores of chest roentgenograms, PaO<sub>2</sub> to FiO<sub>2</sub> ratios, positive end expiratory pressure requirements (PEEP), and respiratory compliance showed that nebulized heparin and N-acetylcysteine significantly reduced lung injury scores and significantly reduced mortality within the first week of treatment compared to the control group. The beneficial effect of NA is related to its mucolytic effect. On the other hand, NH benefits are related to its ability to prevent fibrin formation and its deposition in the alveolar space. This effect can be crucial in halting the development of ALI/ARDS or damage to the surfactant [19].

Drug treatment for lung injury after inhalation injury is being addressed in clinical trials and animal models .The inhibition of clot formation in the blood vessels by heparin is common knowledge, but the inhibition of cast formation in the airway by heparin is a novel idea. Experiments have shown that Heparin & N-acetylcystein decreases tracheobronchial cast formation, improves oxygenation, minimizes barotrauma and reduces pulmonary edema in ovine models of severe smoke inhalation injury and in adult and pediatric patients with inhalation injury[20]. In light of the high mortality associated with inhalation injury, the risk/benefit of heparin appears very favourable[21]. In present study we observed a decreased mortality rate in patients nebulized with heparin and N-acetylcysteine..

Similar to our study Miller et al [22] reported significant improvement in LIS scores, pulmonary compliance, and hypoxia scores in patients treated with heparin, NAC, and albuterolsulfate nebulized every 4 hours. Holt et al [23] failed to demonstrate significant improvement in primary outcome measures in their study group that received heparin 5,000 IU. Elsharnouby et al[24] also reported that nebulization had no effect on length of ICU stay and mortality.

In conclusion present study have shown that heparin decreases tracheobronchial cast formation, improves oxygenation, minimizes barotrauma and reduces pulmonary edema of severe smoke inhalation injury and in adult and paediatric patients with inhalation injury. In light of the high mortality associated with inhalation injury, the risk/benefit of heparin and N –acetylene cysteine appears very favourable

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