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Nebulized heparin for burned patients with inhalation injury: a review

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ABSTRACT

The presence of inhalation injury has a negative impact on the evolution of burned patients, being associated with increased mortality. It occurs as a direct consequence of thermal action, or secondary to the presence of respiratory irritants or absorption of toxins, and actual therapeutic management is mainly supportive. Several clinical findings are relevant to raising suspicion and guiding further examinations, fiberoptic bronchoscopy being the gold standard of diagnosis and staging. In burned patients with inhalation injuries, various reports showed that nebulized heparin (5,000 or 10,000 units) with a 4-hour administration regimen leads to improved outcome, reduces the days of mechanical ventilation and consequently the length of hospital stay, reduces pulmonary complications and improves lung function, having a safe profile, with fewer side effects.

Keywords: inhalational injury, burned patients, nebulized heparin, bleeding

BACKGROUND, EPIDEMIOLOGY, PATHOPHYSIOLOGY

Burns continue to be a major health problem, especially in low- and middle-income countries, with inhalation injury (called smoke inhalation injury) being the leading cause of death and associated with increased morbidity. It has an incidence of 10-20% and may occur even in the absence of skin damage. The airway burns risk increases directly proportional with the increase in the percentage of total body surface burned area (% TBSA) [1-4].

After a severe burn, specific organ failure can complicate the management in the early phase, having a clinical sequence represented by resuscitation and hemodynamic failure, inhalation injury, acute respiratory distress syndrome, renal, hepatic, and gastrointestinal failure, and infections [5]. Despite important breakthroughs in the management of critical burn patients, treatment of inhalation injuries continues to be largely symptomatic, therefore it remains an area of continuous research.

During a fire, some components are responsible for inhalation injury development, like the heat, various systemic toxins, especially carbon monoxide and cyanide (can impair oxygen transport), some particles (can reach the alveoli and reduce pulmonary compliance), or respiratory irritants (can trigger severe inflammatory reactions) [6]. Regarding the pathophysiology of inhalation injury, it appears as a direct consequence of thermal energy, secondary to chemical irritation of the subglottic airways due to smoke inhalation, or after systemic absorption of various chemicals or metabolites [7].

In this environment, the fibrin cast formation is favored, with the reduction of surfactant production, atelectasis development, increased airway resistance, and decreased compliance [8]. All the above-mentioned lead not only to the loss of hypox-

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ic pulmonary vasoconstriction and to the appearance of ventilation-perfusion mismatch, but also to pulmonary edema development [9].

INHALATION INJURY – CLINICAL FINDINGS, SYMPTOMS, DIAGNOSIS

The main clinical findings and manifestations in patients with inhalation injury are presented in Table 1 [10, 11]. Chest X-ray is not relevant in the initial phase, chest computed tomography (CT) and fiberoptic bronchoscopy being the main tools for diagnosis confirmation, with an underestimation the extent of lesions in this stage [12-14]. Bronchoscopy can reveal airway mucosal edema, erythema or mucosal friability, necrosis, the presence or absence of soot or carbonaceous deposits, and airway obstruction [15,16].

TABLE 1. Relevant signs and symptoms in patients with inhalation injuries

head (face), neck or chest burns
burned eyelashes, eyebrows, nasal hairs
burned lips and nostrils
carbonaceous sputum
stridor, hoarseness
cough, dyspnea
wheezing
shortness of breath
increased respiratory distress
use of accessory respiratory muscles
increased work of breathing
cyanosis
dizziness, nausea, vomiting
impaired cognition

THE MECHANISM OF ACTION AND RECOMMENDED TREATMENT

Nebulized anticoagulants, mainly heparin, are used to prevent fibrin cast formation, deposition, and subsequent airway obstruction responsible for the development of acute respiratory distress syndrome (ARDS) in burned patients [17]. Besides, by limiting the fibrin and cast formation, the surfactant function can be restored, reducing the risk of atelectasis [18]. Heparin manifests a rapid anticoagulant effect by binding to antithrombin III [17]. It is known the anti-inflammatory effect of heparin and its role in limiting fibrin and casts formation, and pulmonary edema, by inactivating thrombin and activating factor X [4,17,19].

There are various reports about the nebulized heparin in limiting the pulmonary damage to inhalation injuries, with dosing of 5,000-10,000 units (U) in 3 mL of 0.9% saline solution, alternating with N-acetylcysteine (NAC), 3 mL of 20% solution, every 4 hours, leads to oxygenation improvement and increased pulmonary compliance [4,20]. In this context, NAC is used as mucolytic, having anti-inflammatory and antioxidant effects [21]. For maximum effects, this treatment should be initiated in the first 48 hours after injury and continued for 7-10 days [20,22].

Miller et al. showed that the use of heparin, 10,000 U, along with 600 mg of NAC, nebulized at 4 hours each, in association with nebulized albuterol (a bronchodilator) every 4 hours, leads to reduced mortality, and decreases the lung injury scores [23]. Nebulized epoprostenol, a prostaglandin that acts as a selective pulmonary vasodilator, showed good results in severe ARDS cases, can be added, due to promising effects on oxygenation and mortality [24]. This regimen has also shown good results in some reported cases, reducing the time spent on mechanical ventilation and improving the outcome [20, 25].

McIntire et al. reported a decrease in mechanical ventilation use (days) in case of nebulized heparin use, with no impact on mortality or bleeding events [26]. A study published by Holt et al. found out that nebulized heparin and NAC lead to improved arterial oxygenation, but with no benefit in terms of clinical outcome [27]. In addition, this aerosol therapy does not reduce the risk of pneumonia or reintubation rate [28]. The use of nebulized heparin plus NAC in children with inhalation injuries appears to decrease the reintubation, the risk of pulmonary atelectasis, and improves survival [22].

SAFETY AND EFFICIENCY OF NEBULIZED HEPARIN

The vast majority of reports and clinical trials showed that nebulized heparin could be safely used in burned patients [29]. Special attention should be given to cases that present or develop coagulopathy because of the risk of bleeding [30]. In these patients, coagulation tests should be evaluated regularly [26,29,30]. Reported studies emphasized that nebulized heparin is not associated with systemic coagulopathies [29].

CONCLUSIONS

Inhalation injury remains a cornerstone in burned patients' management, being associated with high mortality and morbidity. Despite the paucity of research in this field, the therapeutic management in these cases is mainly symptomatic. Various reports show that nebulized heparin, along with NAC, and in some cases albuterol, improves burned patients' outcome, decrease mortality, mechanical ventilation, and hospitalization stay, improves oxygenation, reduces the risk of pulmonary atelectasis and pulmonary complications, having a safe profile.

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REFERENCES

1. Peck M, Pressman MA. The correlation between burn mortality rates from fire and flame and economic status of countries. *Burns.* 2013 Sep;39(6):1054-9.
2. Guo F, Zhu YS, Huang J et al. National experts consensus on clinical diagnosis and treatment of inhalation injury (2018 version). *Chinese journal of burns.* 2018 Nov 1;34(11):770-5.
3. Peck MD, Kruger GE, van der Merwe AE et al. Burns and fires from non-electric domestic appliances in low and middle income countries Part I. The scope of the problem. *Burns.* 2008 May;34(3):303-11.
4. Miller AC, Elamin EM, Suffredini AF. Inhaled anticoagulation regimens for the treatment of smoke inhalation-associated acute lung injury: a systematic review. *Critical care medicine.* 2014 Feb;42(2):413.
5. Gauglitz G, Williams F. Overview of complication of severe burn injury. UpToDate 2021; https://www.uptodate.com/contents/overview-of-complications-of-severe-burn-injury, accessed 27 February 2022.
6. Prien T, Traber DL. Toxic smoke compounds and inhalation injury—a review. *Burns.* 1988 Dec 1;14(6):451-60.
7. Merrel P, Mayo D. Inhalation injury in the burn patient. *Crit Care Nurs Clin North Am.* 2004 Mar;16(1):27-38.
8. Sousse LE, Herndon DN, Andersen CR et al. High tidal volume decreases adult respiratory distress syndrome, atelectasis, and ventilator days compared with low tidal volume in pediatric burned patients with inhalation injury. *Journal of the American College of Surgeons.* 2015 Apr; 220(4):570-578.
9. Murakami K, Traber DL. Pathophysiological basis of smoke inhalation injury. *Physiology.* 2003 Jun;18(3):125-9.
10. Jones SW, Williams FN, Cairns BA, Cartotto R. Inhalation injury: pathophysiology, diagnosis, and treatment. *Clinics in plastic surgery.* 2017 Jul 1;44(3):505-11.
11. Micak RP. Inhalation injury from heat, smoke, or chemical irritants. UpToDate; https://www.uptodate.com/contents/inhalation-injury-from-heat-smoke-or-chemical-irritants, accessed 2 March 2022.
12. Lee MJ, O'Connell DJ. The plain chest radiograph after acute smoke inhalation. *Clinical radiology.* 1988 Jan 1;39(1):33-7.
13. Toon MH, Maybauer MO, Greenwood JE et al. Management of acute smoke inhalation injury. *Critical care and resuscitation.* 2010 Mar;12(1):53-61.
14. Walker PF, Buehner MF, Wood LA et al. Diagnosis and management of inhalation injury: an updated review. *Critical Care.* 2015 Dec;19(1):1-2.
15. Sheridan RL. Fire-related inhalation injury. *New England journal of medicine*. 2016 Aug 4;375(5):464-9.
16. Dries DJ, Endorf FW. Inhalation injury: epidemiology, pathology, treatment strategies. *Scandinavian journal of trauma, resuscitation and emergency medicine*. 2013 Dec;21(1):1-5.
17. Mlcak RP, Suman OE, Herndon DN. Respiratory management of inhalation injury. *burns.* 2007 Feb 1;33(1):2-13.
18. Holley AD, Reade MC, Lipman J, Cohen J. There is no fire without smoke! Pathophysiology and treatment of inhalation injury in burns: a narrative review. *Anaesthesia and intensive care.* 2020 Mar; 48(2):114-22.
19. Toon MH, Maybauer MO, Greenwood JE et al. Management of acute smoke inhalation injury. *Critical care and resuscitation.* 2010 Mar;12(1):53-61.
20. Ashraf U, Bajantri B, Roa-Gomez G et al. Nebulized heparin and N-acetylcysteine for smoke inhalation injury: a case report. *Medicine.* 2018 May;97(19).
21. Juschten J, Tuinman PR, Juffermans NP et al. Nebulized anticoagulants in lung injury in critically ill patients—an updated systematic review of preclinical and clinical studies. *Annals of translational medicine.* 2017 Nov;5(22):444.
22. Desai MH, Mlcak R, Richardson J et al. Reduction in mortality in pediatric patients with inhalation injury with aerosolized heparin/ acetylcystine therapy. *The Journal of burn care & rehabilitation.* 1998 May 1;19(3):210-2.
23. Miller AC, Rivero A, Ziad S et al. Influence of nebulized unfractionated heparin and N-acetylcysteine in acute lung injury after smoke inhalation injury. *Journal of burn care & research.* 2009 Mar 1;30(2):249-56.
24. Dube KM, Ditch KL, Hills L. Use of nebulized heparin, nebulized N-acetylcysteine, and nebulized epoprostenol in a patient with smoke inhalation injury and acute respiratory distress syndrome. *Journal of Pharmacy Practice.* 2017 Dec;30(6):663-7.
25. McGinn KA, Weigartz K, Lintner A et al. Nebulized heparin with N-acetylcysteine and albuterol reduces duration of mechanical ventilation in patients with inhalation injury. *Journal of pharmacy practice.* 2019 Apr;32(2):163-6.
26. McIntire AM, Harris SA, Whitten JA et al. Outcomes following the use of nebulized heparin for inhalation injury (HIHI Study). *Journal of burn care & research.* 2017 Jan 1;38(1):45-52.
27. Holt J, Saffle JR, Morris SE, Cochran A. Use of inhaled heparin/N-acetylcystine in inhalation injury: does it help?. *Journal of burn care & research.* 2008 Jan 1;29(1):192-5.
28. Yip LY, Lim YF, Chan HN. Safety and potential anticoagulant effects of nebulised heparin in burns patients with inhalation injury at Singapore General Hospital Burns Centre. *Burns.* 2011 Nov 1;37(7):1154-60.
29. Lan X, Huang Z, Tan Z et al. Nebulized heparin for inhalation injury in burn patients: a systematic review and meta-analysis. *Burns & trauma.* 2020 Jan 1;8.
30. Chopra A, Burkey B, Calaman S. A case report of clinically significant coagulopathy associated with aerosolized heparin and acetylcysteine therapy for inhalation injury. *Burns: journal of the International Society for Burn Injuries.* 2011 Nov;37(7):e73-5.