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REVIEW

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Is inhaled heparin a viable therapeutic option in inhalation injury?

Abstract

Inhalation injury is a major cause of morbidity and mortality in patients with burns. Presence of airways injury adds to the need of fluid supplementation, increases risk of pulmonary complications. Due to many mechanisms involved in pathophysiology the treatment is complex. Among them the formation of fibrin casts inside airways constitutes a prominent element. The material residing in tracheobronchial tree causes ventilation-perfusion mismatch, complicates mechanical ventilation, provides a medium for bacterial growth. Many studies of animal models and single centre human studies investigated inhaled anticoagulation regimens employing heparin in management of inhalation injury. Simultaneously safety, especially in connection with possible bleeding risk, was the subject of research. The results suggest positive impact on treatment results, with low risk of side effects. This paper revise the available clinical data on inhaled heparin use in patients with burns.

Key words: inhalation injury, inhaled heparin, burn

Adv Respir Med. 2019; 87: 184–188

Introduction

Inhalation injury is an independent risk factor contributing to high mortality in patients with burns [1–3]. A risk of airways injury increases with total body surface affected by the burn. According to the data from the United States, a burn of 20% of total body surface area corresponds to a 2.2% chance of inhalation injury. On the other hand, when 80–99% of body surface is affected, the airways are also damaged in 14% of patients [4]. Nonetheless, a clinically significant inhalation injury can be present despite a lack of cutaneous burns [5]. Acute lung injury in adult, hospitalised patients with burns is estimated at 3–30% of all cases. Differences are caused by lack of generally accepted diagnostic criteria for such an injury [6–9]. In comparison with paediatric population, the occurrence of acute lung injury is estimated at 3–15% [10, 11]. Furthermore, if a subgroup with the most severe injury, in which burn severity resulted in patients death, the percentage of individuals with inhalation injury reaches 50% [7]. Available Polish data on inhalation injury in burns patients is of poor quality. Similarly to global data, Polish data are almost exclusively based on a single centre experience. Analysis of hospital admissions to regional burn centre during a two-year period showed that isolated airways injury was present only among 0.5% of patients. Hospitalisations of subjects with burn of unspecified body region (which can include inhalation injury) accounted for 50.6% of the analysed admissions [12]. Available data on paediatric population does not report cases of inhalation injury [13].

Pathophysiology

Despite constant progress in the field of burns pathophysiology, many issues are still unresolved, therefore, treatment is mainly based on symptomatic therapy [14]. A few mechanisms are responsible for damage to the respiratory tract and lung tissue (called inhalation injury or smoke inhalation injury) caused by inhalation of various irritants. Thermal injury, excluding damage caused by steam, is limited to the upper airways. Deeper structures, like the tracheobronchial tree, are damaged by chemical irritants with hydrophobic

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DOI: 10.5603/ARM.2019.0029
Received: 17.03.2019

ISSN 2451–4934

properties and particulate matter [15]. Chemical irritation of the airways' mucosa stimulates nerve fibres present in the airways and causes production of various proinflammatory cytokines [16, 17]. It results in a considerable increase of blood flow and capillary permeability to proteins in the pulmonary vascular bed [18]. Simultaneously, reaction to released chemoattractants causes accumulation of immunocompetent cells, mainly neutrophils, in the respiratory system. Thermal and chemical injury damages epithelial lining of the respiratory tract mucosa, which sheds into the airways' lumen [19]. All the aforementioned mechanisms add to accumulation of material in the alveoli and bronchial tree. The material consists of mucus, inflammatory cells, exfoliated epithelial cells and fibrin. On the other side, vascular changes contribute to the congestion of surrounding tissues. [20, 21]. Finally, the affected airways became partially or fully obstructed, which in succession causes collapse of associated alveoli. At the same time fibrinogen present in the exudate transforms into fibrin. Over time the initially liquid material inside the airways forms casts which are hard to mobilise and evacuate [22]. Furthermore, the presence of fibrin disrupts the function of surfactant changing the surface tension. It adds to the atelectasis caused by lack of airways patency preventing effective alveolar ventilation. Simultaneously, in open parts of the lung, local areas of compensatory emphysema develop. Increasing ventilation-perfusion mismatch results in acute respiratory insufficiency. In cases when mechanical ventilation becomes necessary, it may be needed to use higher inspiratory pressures, which subsequently, may cause pressure injury (barotrauma) [22, 23]. In the first 24–48 hours after inhalation injury, it presents itself as obstructive ventilatory defect, as a manifestation of airways occlusion by secretions. Therefore, therapy at this stage consists of airways toilet through techniques which include airway suction and therapeutic bronchoscopy. Simultaneously, intravenous fluid regulation allows control over the local oedema in the airways. However, it is worth noting that inhalation injury in burn patients is connected with higher need for intravenous infusion in comparison to patients without airways damage [24, 25]. A reduction in airways clearance caused by mucosa damage and the presence of fibrin promotes bacterial growth in the residual secretions. It increases the risk of secondary bacterial pneumonia, which usually develops between 3–6 day after inhalation injury. Pathogens causing this inflammation commonly arise from patients' own bacterial flora, present during hospital admission [26]. Consequently, at this point infection control becomes the main concern in management. It is especially important given the 25% mortality of pneumonia in this group of patients [26, 27].

Animal models

The aforementioned mechanisms justify the use of inhalation anticoagulants to limit formation and facilitate the evacuation of fibrin casts causing airways obstruction. Among anticoagulants inhaled, heparin is often used to this end. It is based on results of many studies on animal models. It has been proved that heparin used alone or in combination with other anticoagulants has a positive impact on the ventilation-perfusion mismatch, alveolar-arterial gradient, post-burn elevation of pulmonary blood flow, mean airway pressure [28–31]. Nonetheless, some of the previously mentioned influences were proven only for heparin used in connection with other medication [28, 29].

Clinical trials

Systematic search of literature allows to find 7 retrospective clinical trials pertaining therapy of inhalation injury in humans using nebulised heparin in combination with N-acetylcysteine. The addition of this mucolytic is motivated by impairment of airway clearance during inhalation injury and antioxidant properties of N-acetylcysteine. Six trials investigated potential benefits of inhaled anticoagulation in patients with inhalation injury, the seventh was concerned with safety of nebulised heparin. The oldest retrospective study by Desai *et al.* was performed on a group of paediatric patients. Therapeutic protocol used 5000 I.U. of heparin and 3 millilitres of 20% solution of N-acetylceysteine. Both medications were administered by nebulisation every 4 hours. Therapy was continued for 7 days. Significant reduction in mortality was noted for the treatment group [32]. A study by Holt from 2008 used similar treatment protocol, but also included salbutamol. The results stand in opposition to the outcomes obtained by Desai. Initial analysis covering both paediatric and adult group failed to prove significant differences between treatment and control groups. Further analysis of 25 paediatric patients also failed to demonstrate statistically significant differences. It is worth noting that the use of inhaled antico-

Table 1. Studies concerning use of inhaled heparin in patients with inhalation injury

Study	Number of patients	Inhalation treatment protocol	Results
Desai 1998	90	5000 I.U. heparin + 3 ml 20% N-acetylcysteine every 4 h for 7 days	Lower mortality, less cases of reintubation and atelectasis
Holt 2008	150	5000 I.U. heparin + 3 ml 20% N-acetylcysteine every 4 h for 7 days + salbutamol 2,5 mg (at physicians discrecy)	No significant differences between groups
Rivero 2007	16	10000 I.U. heparin + 3 ml 20% N-acetylcysteine	Lower lung injury score during first week of treatment
Miller 2009	30	10000 I.U. heparin + 3 ml 20% N-acetylcysteine + salbutamol 2,5 mg every 4 h for 7 days	Lower lung injury score, lower mortality
Elsharnouby 2013	29	5000 or 10000 I.U. heparin alternating with 3 ml 20% N-acetylcysteine every 2 h	Lower lung injury score, no impact on mortality
Kashefi 2014	40	5000 I.U. heparin + 3 ml 0.9% NaCl alternating with 3 ml 20% N-acetylcysteine + salbutamol 2,5 mg every 4h for 7 days	No impact on mortality, duration of mechanical ventilation, higher incidence of pneumonia
McIntire 2016	72	10000 I.U. heparin + salbutamol 2,5 mg + 3 ml 20% N-acetylcysteine or 3 ml 4% $NaHCO_3$ every 4 h for 7 days	Lower duration of ventilation, no impact on mortality or incidence of pneumonia

agulation was left to the discretion of physician in charge. Moreover, not all cases of inhalation injury were confirmed by bronchoscopy examination. The mentioned elements could have resulted in selection bias [33]. On the other side, Desai's results were proven in small (16 patients) group studied by Rivero [34]. A protocol similar to the one employed by Holt was studied by Miller. Differences included an increase of heparin dose to 10 000 I.U. and the use of salbutamol in regular intervals. The study was designed to verify Desai's results in an adult group using objective quantification of lung state, employing LUNG Injury Score originally designed to appraise ARDS [35]. Although the results proved a positive effect of therapy on Lung Injury Score and mortality, the authors remarked that they should be confirmed in larger, multicentre prospective trial [36]. The prospective HEPBURN trial was registered in 2013. It was planned to fill the gap noticed by Miller. Exclusion criteria proposed in the HEPBURN trial can be treated as potential contraindication for inhaled heparin therapy: history of pulmonary haemorrhage in preceding 3 months, clinically significant coagulation disorder, allergy to heparin, history of thrombocytopenia after heparin use, pregnancy, lactation, aspiration, history of COPD needing chronic oxygen therapy or non-invasive mechanical ventilation. According to ClinicalTrials.gov website, the HEPBURN study was terminated in 2017 because of financial issues [37]. Elsharnouby *et al.* investigated the difference in clinical outcome of two different heparin doses on burn patients with inhalation injury. Although lower lung injury scores and shorter duration of mechanical ventilation were achieved, it had no impact on mortality. It is worth noting that the both studied doses had no influence on coagulation test results [38]. The 2014 study by Kashefi *et al.* tried a different approach — study and control groups were matched for sex, burn severity and age. The study results showed statistically significant higher incidence of pneumonia in the treated group (45% *vs* 11%). The study protocol assumed heparin administration twice less often than in previous researches, i.e. once every 8 h. The authors suggested that the patients could have been underdosed [39]. The approach based on matching cohorts for burn severity and age was repeated in a study from centre in Indianapolis. However, dosing was four times higher than the one used by Kashefi — 10000 I.U. of heparin was administered every 4 hours. In contrast to the previous study, no impact on pneumonia was noted, yet duration of ventilation was significantly lowered (7 days *vs* 14.5 days) [40]. Table 1 sums up results of available studies.

Side effects

The use of inhaled heparin in patients with burns can raise concerns about potential clinically significant bleeding events. There is a case report about a 2-year-old male in whom administration of heparin according to the protocol proposed by Desai, resulted in clinically significant coagulopathy. Coagulation disorder

resolved after heparin use cessation. The authors concluded that in a healthy patient, clinically significant absorption and systemic effects after inhaled administration of heparin are unlikely. Yet, in cases of profound airway damage such connection can be plausible. The authors stress the importance of regular monitoring of coagulation tests results during therapy [41]. A study of healthy volunteers examined potential side effects of inhaled heparin in doses delivered to the lower airways up to 32 000 I.U. (which relates to an administered dose of 400 000 I.U.). At that dosing heparin has no influence on spirometric values (FEV1, FVC), clinically noticeable bleeding or sense of dyspnoea. At the same time anti-Xa values and activated partial thromboplastin time change were statistically significant, but without any clinical consequences [42]. A retrospective study on safety of inhaled anticoagulants use in patients with inhalation injury was performed on 63 subjects. The typical time of inhalation therapy was 7 days, but due to a slower recovery in some patients, this time was elongated up to 16 days. Anomalies in coagulation tests and bleeding episode caused treatment discontinuation in 1 patient. Nonetheless, the authors failed to prove connection between coagulation disorder and the used therapy. Obtained data confirm a lack of significant influence of nebulised heparin on bleeding risk in patients with inhalation injury [43]. Dixon performed a series of studies concerning potential therapeutic use and safety of inhaled heparin in various clinical situations. Clinical situations studied included: acute lung injury, invasive mechanical ventilation, state after cardiac surgery with cardiopulmonary bypass. No study showed connection between heparin use and risk of adverse reactions, including bleeding episodes. In patients with acute lung injury, nebulised heparin doses up to 400 000 I.U. were related to a rise of APPT and PT to 64 and 50 s respectively, without any clinical symptoms [44–46]. Available data confirm safety of inhaled heparin in various clinical settings, even in doses exceeding the ones used in inhalation injury. Simultaneously, coagulation tests should by regularly monitored during therapy.

Conclusions

Animal models and single centre clinical trials proved clinical utility of inhaled heparin therapy in inhalation injury. This therapeutic approach is not connected with clinically significant side effects or risks, including bleeding. There are no studies confirming heparin utility in multicentre, prospective trials. Basing on available evidence, we suggest that heparin is a viable option in inhalation injury, and its inclusion should be considered in all burn patients with confirmed airways damage.

Conflict of interest

The authors declare no conflict of interest.

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