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# Is inhaled prophylactic heparin useful for prevention and management of pneumonia in ventilated ICU patients?☆

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ABSTRACT

*Purpose:* The purpose was to determine the efficacy of prophylactic inhaled heparin for the prevention and treatment of pneumonia in patients receiving mechanical ventilation (MV).
*Methods:* A phase 2, double-blind, randomized controlled trial stratified for study center and patient type (non-operative, postoperative) was conducted in 3 university-affiliated intensive care units. Patients aged at least 18 years and requiring invasive MV for more than 48 hours were randomized to usual care, nebulization of unfractionated sodium heparin (5000 U in 2 mL), or nebulization with 0.9% sodium chloride (2 mL) 4 times daily with the main outcome measures, the development of ventilator-associated pneumonia (VAP), ventilator-associated complication, and Sequential Organ Failure Assessment scores in patients with admission pneumonia or developing VAP. Trial registration: ACTRN12612000038897.
*Results:* A total of 214 patients were enrolled (72 usual care, 71 inhaled sodium heparin, 71 inhaled sodium chloride). There were no differences between treatment groups in terms of the development of VAP using either Klompas criteria (6%-7%, $P = 1.00$) or clinical diagnosis (24%-26%, $P = .85$).
*Conclusion:* Low-dose nebulized heparin cannot be recommended for prophylaxis against VAP or to hasten recovery from pneumonia in patients receiving MV.



## 1. Introduction

Unfractionated heparin (UFH) is an inexpensive naturally occurring sulfated glycosaminoglycan [1] which promotes mucociliary clearance [2], decreases sputum viscidity [2], displays antibacterial effects on

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common respiratory pathogens [3], and has anti-inflammatory properties [4]. Clinical applications have been reported in airway burns [5] and respiratory conditions where there is a significant sputum production or airway inflammation [6]. With these therapeutic effects, the potential role of UFH in preventing and treating lung infections including ventilator-associated pneumonia (VAP) remains insufficiently investigated.

Nebulized administration to maximize drug concentrations in the epithelium of the airway may also enhance effectiveness. Indeed, UFH is simple and safe to administer by ventilator nebulizer with less than 1% of a 90 000-U dose found in blood [7]. Doses of 30 000 U twice daily are not associated with significant changes in the coagulation profile [8]. Furthermore, recent work exploring the clinical role of nebulized UFH has demonstrated an 18% increase in ventilator-free days in critically ill patients at risk of developing acute respiratory distress syndrome (ARDS) [9].

With this strong theoretical background supporting the potential beneficial effects of nebulized UFH, we performed a feasibility Phase-2b, double-blind, multicenter, randomized controlled trial in patients receiving mechanical ventilation (MV) to investigate the effectiveness of Inhaled Prophylactic Heparin In the preVention and treAtment of Pneumonia (IPHIVAP). Primary study end points were the incidence, severity, and time to develop VAP. The incidence of ventilator-associated complications (VACs), rate of resolution of pneumonia, and incidence and time to bacterial airway colonization were secondary end points.

## 2. Materials and methods

### 2.1. Study population

Patients aged at least 18 years who had received less than 24 hours of invasive MV at the time of enrolment and commencement of study drug but were likely to require invasive MV for more than 48 hours were eligible for study inclusion. Patient exclusions included pregnancy, patients with treatment limitations or who were moribund, contraindications to subcutaneously administered heparin, systemic anticoagulation at enrolment, and previous enrolment in the study. Routine subcutaneous thromboembolism prophylaxis (≤15 000 U of UFH per day or equivalent) and low-dose heparin to prevent clotting of continuous renal replacement therapies were permitted.

### 2.2. Randomization

The study was coordinated from the Burns, Trauma, and Critical Care Research Centre of the University of Queensland. Secure randomization and data management were maintained by the Chinese University of Hong Kong. Subjects were randomized to the 3 groups by concealed allocation. A permuted block method stratified by study center and patient type (nonoperative compared with postoperative) was used. The 3 groups included the following: (*a*) intervention group—nebulized unfractionated sodium heparin (2 mL, 5000 U) every 6 hours, (*b*) placebo group 1—nebulized 0.9% sodium chloride 2 mL every 6 hours, (*c*) placebo group 2—no prophylactic nebulized treatment (usual care). Apart from the "usual care" group, clinicians and data collectors remained blinded. Treatment groups remained blinded during analysis.

### 2.3. Study drug preparation and administration

Study drugs were prepared as sodium heparin 5000 U (1 mL David Bull Laboratories, Lidcombe, New South Wales, Australia) made up to 2 mL with sterile 0.9% sodium chloride (Pfizer Pharmaceuticals). The placebo was 0.9% sodium chloride (2 mL). Both were made using an aseptic technique by trained research staff not involved in clinical care of the patients to ensure maintenance of blinding for all study and clinical staff.

Participants received study drug until they ceased MV for more than 48 hours or were discharged from the ICU. If the patient required ventilation again for the same ICU admission, the study drug continued in the same treatment arm.

### 2.4. Ventilation strategies and nebulizer use

As part of a pragmatic trial, unit nebulizers were used as per manufacturer's instructions for the ventilators available. This allowed the intervention to be consistent with daily routine prophylaxis management. Nebulizers were placed at the distal end of the inspiratory limb proximal to the patient Y-connector for both hot water humidified and heat and moisture exchange circuits in line with best practice guidelines [10-12]. Where a heat and moisture exchanger was used, this was removed before nebulization. The Aeroneb Pro and Pro X, which are vibrating sieving mesh nebulizers, were used integrated into the Puritan Bennett 840 (Covidien) ventilators. Micro Mist jet nebulizers (Hudson RCI Teleflex Medical) were used as an integrated system on the AVEA (Carefusion) ventilators. All ventilators maintained minute and tidal volume during nebulization. Humidification technique and all additional nebulized therapies as deemed necessary by the treating clinician were recorded; however, nebulized saline to treat thick secretions was not permitted. Although the ventilation mode was not specified for the study, all participating units had written ventilation protocols specifying a volume strategy, typically SIMV with tidal volumes of 7 to 8 mL/kg in the absence of lung disease, or either a pressure or volume strategy with tidal volumes of 6 mL/kg or less in the presence of pulmonary restriction. Although plateau pressures were not routinely used in the participating units, peak pressures were kept below 30 cm $H_2O$ in the absence of airway obstruction. Where there was perceived airway obstruction, plateau pressures were kept as low as possible, and intrinsic positive end-expiratory pressure or expiratory flow waveforms analysis was used to determine the adequacy of lung emptying. Where there was no airway obstruction, a minimal positive end-expiratory pressure of 5 cm $H_2O$ was standard. Pressure support of 8 to 10 cm $H_2O$ was standard in the absence of a specific weaning regimen.

### 2.5. Data collection

The study sample was defined by criteria including age, sex, Acute Physiologic And Chronic Health Evaluation (APACHE) II score [13], McCabe comorbidities [14], admission Sequential Organ Failure Assessment score (SOFA) [15], admission type, intensive care and hospital mortality, lengths of stay, and primary diagnoses in accordance with the Adult Patient Database of the Australian and New Zealand Intensive Care Society Centre for Outcome and Resource Evaluation. Chronic obstructive pulmonary disease diagnosis used the criteria of the American Thoracic Society [16]. Antibiotic use and clinical indications were recorded. Community-acquired pneumonia (CAP) [17], health care–associated pneumonia (HCAP) [18], and aspiration pneumonia (AP) were determined by the treating clinicians at ICU discharge. In addition, a Clinical Pulmonary Infection Score [19] was calculated at the time of diagnosis. Patients were screened daily for the development of ARDS using the Berlin criteria [20], and improvement was monitored by the rate of change in daily $Pao_2/Fio_2$ ratios and chest radiograph scores [21]. Radiographs were reviewed by the principal investigator at each site who was a board-registered intensive care specialist. Smoking history was collected. The SOFA scores were calculated at diagnosis and daily for all patients with pneumonia. Endotracheal secretions were recorded for each 24-hour period as the total number of suctions; and the volume of secretions, as the daily sum of each suction: 0 = nil, scant/small = 1, moderate = 2, large = 3, copious = 4. The number of suctions each hour with blood was tallied for each day.