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Is Inhaled Prophylactic Heparin Useful for Prevention and Management of Pneumonia in Ventilated ICU Patients?

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the IPHIVAP investigators of the Australian and New Zealand Intensive Care Society Clinical Trials Group

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Abstract

Purpose: To determine whether prophylactic inhaled heparin is effective for the prevention and treatment of pneumonia patients receiving mechanical ventilation (MV) in the intensive care unit.

Methods: A phase 2, double blind randomized controlled trial stratified for study center and patient type (non-operative, post-operative) was conducted in three university-affiliated intensive care units. Patients aged ≥18 years and requiring invasive MV for more than 48 hours were randomised to usual care, nebulization of unfractionated sodium heparin (5000 units in 2 mL) or placebo nebulization with 0.9% sodium chloride (2 mL) four times daily with the main outcome measures of the development of ventilator associated pneumonia (VAP), ventilator associated complication (VAC) and sequential organ failure assessment scores in patients with pneumonia on admission or who developed VAP. Trial Registration: Australian and New Zealand Clinical Trials Registry ACTRN12612000038897.

Results: Two hundred and fourteen 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=0.85). There was no difference in the clinical consistency (P=0.70), number (P=0.28) or the total volume of secretions per day (P=0.54). The presence of blood in secretions was significantly less in the usual care group (P=0.005).

Conclusion: 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 sulphated glycosaminoglycan [1] which promotes mucociliary clearance [2], decreases sputum viscidity, [2] displays antibacterial effects on 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 unit dose found in blood. [7] Doses of 30,000 units 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 endpoints were the incidence, severity and time to develop VAP. The incidence of ventilator associated complications (VAC), rate of resolution of pneumonia, and incidence and time to bacterial airway colonization were secondary endpoints.

2. Materials and Methods:

2.1 Study Population

Patients aged ≥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 units of unfractionated heparin 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 (non-operative compared to post-operative) was employed. The three groups included: (A) Intervention group - nebulized unfractionated sodium heparin (2 mL, 5000 units) 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 units (1 mL) made up to 2 mL with sterile 0.9% sodium chloride. 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 hrs, 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 Data Collection

The study sample was defined by criteria including age, sex, Acute Physiologic And Chronic Health Evaluation (APACHE) II score [10], McCabe comorbidities [11], admission Sequential Organ Failure Assessment score (SOFA)[12], 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(ANZICS-CORE). Chronic obstructive pulmonary disease (COPD) diagnosis used the criteria of the American Thoracic Society. [13] Antibiotic use and clinical indications were recorded. Community acquired pneumonia (CAP)[14], health care associated pneumonia (HCAP)[15], and aspiration pneumonia (AP) were determined by the treating clinicians at ICU discharge. In addition, a Clinical Pulmonary Infection Score (CPIS)[16] was calculated at the time of diagnosis. Patients were screened daily for the development of ARDS [17] and improvement monitored by the rate of change in daily PaO_2/FiO_2 ratios and chest X-ray scores.[18] Smoking history was collected. 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. Sequential Organ Failure Assessment (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.

2.5 Clinical Interventions

Interventions with known risks for VAP were standardized. [19] Management of VAP followed a suggested therapeutic guideline. [20] Pneumonia treatment was determined by the treating clinician according to unit antibiograms, surveillance cultures or diagnostic culture results. The minimum duration of pneumonia treatment (including VAP) was 5 days. For *Pseudomonas aeruginosa*, 7-days of therapy was provided consistent with the minimum duration of treatment recommended in Australia and New Zealand. [21]

Semiquantitative bacterial surveillance cultures of endotracheal aspirates (ETA) using routine laboratory processing were performed on admission and then twice weekly. Patients with AP, CAP, HCAP or who developed VAP had additional ETA surveillance cultures for 10 days or until the patient no longer had an artificial airway.

Patients were screened daily using the validated modified Centre for Disease Control criteria for VAP of Klompas [22] with date of onset when all criteria were met. The lead site assessed the effect of inhaled heparin on the development of VAC as defined by Klompas and the National Institutes of Health [23]. Only the first episode of VAC and VAP was included in the analysis.

The definitions for clinical progress of pneumonia (resolution, cure, or treatment failure) [24] and microbiological outcome (eradication, persistence, superinfection) [25] are summarized in the Supplementary Material (eTable 1).

2.6 *Safety Monitoring and Cessation Criteria*

Daily assessment as per usual unit protocol was made of peripheral platelet counts and coagulation profiles. Prolongation of the Activated Partial Thromboplastin Time (APTT) greater than 50%, or a fall of the platelet count <100 X 10^9/L suspended study drug delivery until clinical resolution in the absence of other clinical explanations. Thrombocytopenia < 100 X 10^9/L triggered screening for heparin induced thrombocytopenia syndrome (HITTS) if not previously investigated. Episodes of clinical bleeding were managed with suspension of the study drug with a local clinical decision made to recommence the study drug when bleeding had resolved. All adverse events and protocol violations were recorded.

2.7 Sample Size, Data Management and Analysis Approach:

Previous work by our group established the VAP rate in Australia to be 12% (range 4%-21%).[26] IPHIVAP was powered to reduce the VAP rate from 12% to 6% using uncorrected chi square test for difference between proportions, an alpha of 0.05, power of 80% and a ratio of 2 placebo groups to treatment. 277 patients were needed per group. Allowing for a 10% loss rate from the study, mainly from failure to complete a minimum of 48 hours of MV, 914 patients were required for the study. This proposed sample size encompassed the secondary hypothesis of a reduction in bacterial colonization. For a reduction of bacterial colonization from 80 to 40%, the number per group needed was 35 using a Bonferroni correction for multiple comparisons, an alpha of 0.05 and a power of 80%.

A pragmatic decision was made to cease trial recruitment in December 2013 on the basis of both a revised sample size calculation (November 2013) and the observed recruitment rate between April 2011 and November 2013. The primary endpoint using Klompas criteria for VAP was close to 6% in all study groups (November 2013). Therefore, to demonstrate a 1% difference between groups approximately 22,000 patients would be required, and as such the trial was ceased on the basis of futility.

An intention-to-treat analysis was performed. Continuous data were analyzed using ANOVA and Kruskall-Wallis tests. Categorical data were analyzed using Pearson's chi-squared and Fisher's exact tests as appropriate. Analysis included repeated measures mixed linear models with mean changes of scores, standard deviations and 95% confidence intervals (CI) calculated between groups. All tests of significance were two-tailed, and probability values less than 0.05 were considered significant. [27 28] Results were reported as means (range) and medians (interquartile range) and 95% CIs where appropriate. Data were analyzed using STATA 12 (College Station, Texas. United States) statistical software.

2.9 Ethical Considerations:

Institutional ethical consent was granted by each of the study sites. The study conformed with the CONSORT guidelines for randomized controlled trials. [29] Informed consent was obtained for all participants. The trial was registered with the appropriate jurisdictions for Guardianship in all regions. The trial was also registered with the Australian and New Zealand Intensive Care Society Clinical Trials Group (CTG 09-003) and the Australian and New Zealand Clinical Trials Registry (ACTRN12612000038897).

3.0 Results

The CONSORT diagram of patient enrolment is presented in Figure 1. The demographics of all patients are summarized in Table 1. Study participants had a mean (range) age of 56 (18-86) years with a mean admission APACHE II score of 18.9 (0-46) and an admission SOFA score of 6 (0-18). 141 (66%) were males and 90 patients (42%) had a diagnosis of pneumonia on ICU admission with the causative organisms detailed in Table 2. Medical patients accounted for 64% with 45 (21%) having a history of COPD. The severity of McCabe comorbidities are detailed in the supplementary material (eTable 2). There were no significant differences in the characteristics of the study groups.

Randomization was successful with approximately 33% of patients assigned to each study group. The failure to meet minimum ventilation times of 48 hours was similar in all groups (11-13%). Ventilation times were also similar with a median of 5.5 days (Table 3). Those receiving 0.9% Sodium chloride had higher use of antibiotics on admission (heparin 61%; 0.9% sodium chloride 80%; usual care 67%, P=0.03) and developed ARDS more frequently during their ICU admission (heparin 14%; 0.9% sodium chloride 25%; usual care 8%, P=0.03).

There was no difference in the development of VAP whether diagnosed clinically (heparin 28%; 0.9% Sodium chloride 24%; usual care 26%, P=0.85) or by Klompas criteria (heparin 7%; 0.9% Sodium chloride 6%; usual care 7%, P=1.00) . Time to develop VAP (approximately 7 days, P=0.34) was not different between the groups (Table 4.). There were no significant differences in the organisms causing VAP. VAC rates were similar in all groups, heparin 38%; 0.9% Sodium chloride 28%; usual care 32 %, P=0.59), (Table 4).

For patients with pneumonia on admission or who developed VAP, there were no differences between the groups in organ specific SOFA scores over the first 5 days from the onset of pneumonia (P=0.56-0.96, eTable 3 in Supplementary Material). No differences were found when CAP, HAP or VAP were assessed separately.

Although there were some baseline differences in airway colonization with more *Candida spp* colonization in the 0.9% sodium chloride group (27% compared to 11-15%, P=0.05) and *Staphylococcus aureus* in the heparin group (23% compared to 6-11%, P=0.01, eTable 4 in Supplementary Material), there were no differences in subsequent airway colonization after initiating mechanical ventilation (eTable 5 in Supplementary Material).

The number of suctions per day (P=0.28) and the total volume of secretions per day (P=0.54) were similar for all groups but the presence of blood was significantly less in the usual care group (P=0.005, eTable 6 in Supplementary Material).

There were no significant differences in adverse events between the groups (Table 4). There were similar prolongations of APTT and decrements in platelet counts. Their associated timing with HITTS was suspected in 2 patients although not confirmed; one each in the heparin and saline groups.

4.0 Discussion

In this general cohort of ICU patients, inhaled heparin did not have any significant effect on decreasing rates of VAP or VAC, time course for resolution of pneumonia, airway colonization or airway secretion volume. However, use of inhaled heparin was not associated with any significant adverse events.

Published data of the possible effect of inhaled heparin for prevention and treatment of pneumonia in ICU supported further investigation. In the current trial, doses of heparin used were consistent with previous studies in burns, [1] asthma, [30] bronchiectasis [31] and cystic fibrosis. [6] The lack of effect of heparin in this study compared to previous studies may have been due to different patterns of airway inflammation seen in acutely ventilated patients or a low baseline VAP rate.

We did not see a reduction in days of MV compared with studies using much higher doses of heparin and a more sophisticated nebulization regimen. [9] However, the latter trial investigated a defined group of patients who had a high predilection score for ARDS, perhaps reflecting a more defined patient group who may benefit from inhaled heparin. A similar example would be post cardiac surgical patients, where the extracorporeal circuit has been associated with intrapulmonary clots. [32] These patient groups were not included in the current trial.

It was unlikely that inhaled heparin would have a systemic effect on inflammatory processes or coagulation. Indeed, no differences were seen between the groups on coagulation tests or platelet counts consistent with other studies using similar doses of inhaled heparin. [33-35] The lack of any anti-inflammatory effect of inhaled heparin with severe pneumonia has been seen in animal models. [36]

We did find that ARDS was more common in the nebulized 0.9% sodium chloride group but this group also had a higher prevalence of infections on admission to the ICU. ARDS rates were however similar in the nebulized heparin and usual care groups.

Inhaled heparin has been shown to improve the rheological properties of sputum in airway inflammatory disease. [2] However, given controlled airway humidification and the predominant use of hot water humidification in this trial, perhaps the effects of inhaled heparin or indeed inhaled sodium chloride are mitigated by adequate humidification.

Although burns patients were included in the study, none had associated airway injury. Some studies recommend the use of inhaled heparin to resolve airway burns but definitive trials are yet to be published. [5]

This study had several limitations. Despite being small, there were no significant trends in the incidence of VAP or VAC, pneumonia resolution or effects on airway colonization or airway secretions to justify continued recruitment to the a priori sample size. This trial used robust definitions of VAP [22] and VAC [23] concordant with clinician determined "highly likely" VAP. The random permuted block design for randomization was successful despite the early cessation of the trial. The ARDS definition was consistently applied although the study design predated currently accepted definitions. Two placebo groups were included in order to eliminate the potential confounding effect of nebulized saline on the outcomes of interest. [37] It is possible that a higher dose is required but a pragmatic decision was made to use dosages consistent with other airway inflammatory diseases where some benefit of inhaled heparin has been noted. [2], [3], [4], [5], [6] Importantly, the majority of patients were recruited from a single center.

In summary, a dose of 5000 units of unfractionated heparin administered 4 times daily using commonly available nebulizers cannot be recommended for prophylaxis against nosocomial pneumonia or to improve recovery from pneumonia in patients receiving mechanical ventilation.

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Figure 1. CONSORT Diagram of Patient Randomization

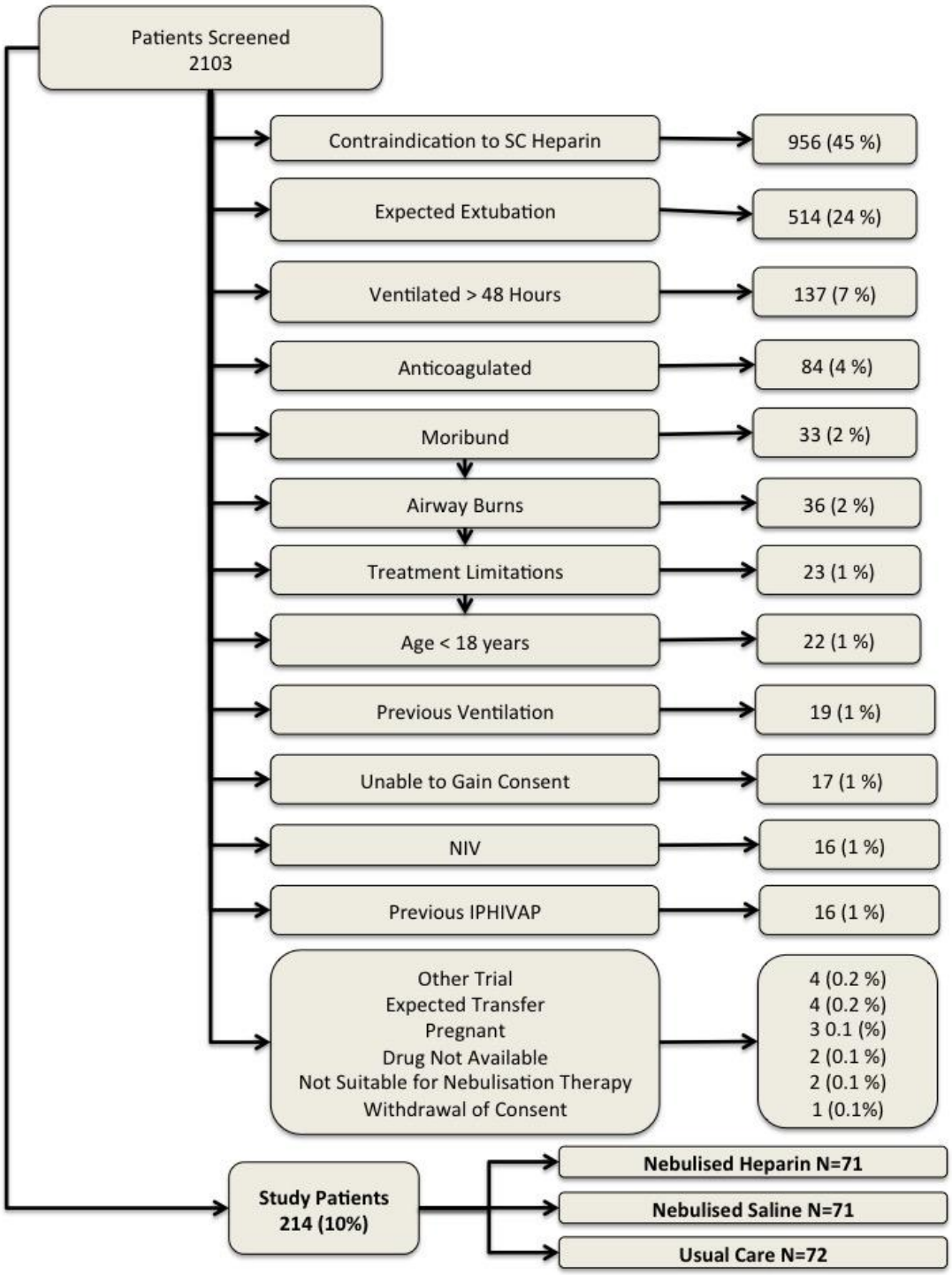

Figure 1

Table 1. Demographics of Study Patients

Variable	Heparin Median/N (%/IQR)	0.9% Sodium chloride Median/N (%/IQR)	Usual Care Median/N (%/IQR)	Total Median/N (%/IQR)	P
N	71(33.1)	71 (33.1)	72 (33.2)	214 (100)	1.00
Age*	57 (35-69)	59 (41-69)	62 (49-71)	59 (42-70)	0.29
Male	45 (63)	49 (69)	47 (65)	141 (66)	0.77
Patient Type *Non-Operative*	52 (73)	53 (75)	53 (74)	158 (74)	0.98
Operative	19 (27)	18 (25)	19 (26)	56 (26)	
Admission Pneumonia#					
Community Acquired	8 (11)	18 (25)	17 (24)	43 (20)	0.07
Health Care Associated	7 (10)	9 (13)	3 (4)	19 (9)	0.15
Aspiration	10 (14)	13 (18)	5 (7)	28 (13)	0.10
All	25 (35)	40 (56)	25 (35)	90 (42)	0.02
Clinical Pulmonary Infection Score	8.2 (4-12)	7.4 (3-12)	6.6 (2-10)	7.4 (2-12)	0.09
APACHE II#	18.8 (0-46)	18.2 (3-38)	19.6 (0-44)	18.9 (0-46)	0.63
Sequential Organ Failure Assessment	6.3 (0-18)	5.4 (0-17)	6.1 (0-19)	6 (0-18)	0.65
Admission Type					0.46
Medical	41 (58)	47 (66)	48 (67)	136 (64)	
Surgical	20 (28)	29 (27)	20 (28)	59 (28)	
Trauma	10 (14)	5 (7)	4 (6)	19 (9)	
McCabe Co-morbidities					
Non-metastatic cancer	2 (3)	1 (1)	7 (10)	10 (6)	0.13
Metastatic Cancer	4 (4)	1 (1)	1(1)	5 (2)	0.48
Hematological Malignancy	1 (1.4)	1 (1.4)	3 (4)	5 (2)	1.00
Bone marrow transplant	0 (0)	1 (1.4)	4 (6)	5 (2)	0.07
Immunocompromised	2 (3)	4 (6)	8 (11)	14 (6.5)	0.32
Chronic Renal Failure	3 (4)	5 (7)	8 (11)	16 (7.2)	0.59
COAD	9 (13)	15 (21)	21 (29)	45 (26)	0.17
Chronic Heart Failure	5 (7)	8 (11)	10 (14)	23 (11)	0.16
Cirrhosis	2 (3)	2 (3)	3 (4)	7 (3)	0.90
Diabetes mellitus	8 (11)	8 (11)	9 (12)	25 (12)	0.95
Chronic Respiratory Failure	5 (7)	1 (1)	7 (10)	13 (6)	0.28
Alcoholism	5 (7)	8 (11)	10 (14)	23 (11)	1.00
Homelessness	1 (1)	3 (4)	3 (4)	6 (3)	0.46
Drug Abuse	6 (8)	2 (3)	5 (7)	13 (7)	0.14
Acquired Immune Deficiency Syndrome	0 (0)	1 (1)	3 (4)	4 (3)	0.50
Smoking					0.36
Non-smoker	8 (12)	10 (15)	9 (13)	27 (13)	
Ceased < 3 months	2 (3)	2 (3)	2 (3)	6 (3)	
Ceased ≥ 3 months	8 (12)	12 (18)	16 (23)	36 (17)	
Presently Smoking	24 (35)	27 (40)	31 (44)	82 (40)	
Not Known	26 (38)	16 (24)	13 (18)	55 (27)	
Hospital Outcome					0.91
Death	10 (14)	13 (18)	13 (18)	11 (16)	
Discharge	56 (79)	53 (75)	53 (75)	55 (80)	
Transfer	5 (7)	5 (7)	5 (7)	3 (4)	
ICU Outcome					
Death	6 (8)	7 (10)	4 (6)	17 (8)	0.88
Discharge	60 (85)	59 (83)	64 (89)	183 (86)	

Transfer	5 (7)	5 (7)	4 (6)	14 (7)	
ICU Length of Stay* (Days)	6.8 (4.0-13.3)	8.2 (4.0-12.0)	6.8 (3.6-13.6)	7.3 (3.9-13.0)	0.81
Hospital Length of Stay* (Days)	21.3 (10.4-42.3)	17.7 (9.9-42.9)	21.3 (10-37.5)	19.9 (10.4-41.7)	0.15
* Median and IQR # Acute Physiologic and Chronic Health Evaluation (APACHE)					

Table 2. Causative Organisms of Admission Pneumonia

Organism	N (%)
Nil	29 (34.5)
Gram Negative	19 (22.6)
Staphylococcus aureus	14 (16.6)
Viral	7(8.3)
Streptococcus pneumoniae	5 (6)
Haemophilus influenzae	3 (3.6)
Chlamydia spp.	2 (2.4)
Legionella spp.	2 (2)
Fungal	2 (2)
Mycoplasma spp.	1 (1.2)
Streptococcus pyogenes	1 (1.2)

Table 3. Treatment Events During Admission

Variable	Heparin N=71 Median/N (%/IQR)	0.9% Sodium chloride N=71 Median/N (%/IQR)	Usual Care N=72 Median/N (%/IQR)	Total N=214 Median/N (%/IQR)	P
Tracheostomy	15 (21)	7 (10)	7 (10)	29 (14)	0.09
Time to Tracheostomy (days)	11.8 (8.0-15.8)	10.9 (6.5-14.2)	10.5 (5.2-11.9)	11.2 (7.1-15.5)	0.89
Humidification[t]					0.15
HME	1 (1)	2 (3)	1 (1)	4 (2)	
HW	68 (96)	68 (96)	64 (89)	200 (93)	
Both	2 (3)	1 (1)	7 (10)	10 (5)	
Antibiotics Day 1 ICU	43 (61)	57 (80)	48 (67)	148 (69)	0.03
ARDS[tt]					0.04
Mild	0 (0)	2 (3)	0 (0)	2 (1)	
Moderate	2 (3)	0 (0)	1 (1)	3 (1)	
Severe	11 (15)	16 (23)	6 (8)	33 (15)	
Dialysis Therapies[*]					0.81
CRRT	10 (14)	8 (11)	12 (17)	30 (14)	
IHD	2 (3)	1 (1)	0 (0)	3 (1)	
Both	1 (1)	1 (1)	2 (3)	4 (2)	
Method of Nebulization					<0.001
Jet[ttt]	23 (32)	13 (18)	11 (15)	47 (22)	
Vibrating sieving mesh[ttt]	16 (23)	24 (34)	12 (17)	52 (24)	
Jet & Vibrating sieving mesh[ttt]	32 (45)	34 (48)	27 (38)	93 (44)	
None	0 (0)	0 (0)	22 (31)	22 (10)	
Additional Nebulizer Therapy					0.38
Bronchodilators alone	23 (32)	31 (44)	37 (51)	91 (43)	
Bronchodilators & Corticosteroid	2 (3)	2 (3)	2 (3)	6 (3)	
Bronchodilators & Other	1 (1)	2 (3)	2 (3)	5 (2)	
Other#	1 (1)	0 (0)	1 (1)	2 (1)	
None	44 (63)	36 (51)	30 (42)	110 (51)	
Duration of Mechanical Ventilation (days)	5.5 (2.4-11.0)	5.7 (2.2-9.7)	5.1 (2.2-10.0	5.5 (2.3-9.9)	0.81
Patients not reaching 2 days Mechanical Ventilation	8 (11)	9 (13)	8 (11)	25 (12)	0.93
Duration Antibiotic Use –all infection episodes (days)	6 (4-9)	6 (4-10.5)	6 (4-10)	6 (4-10)	0.87
Duration Antibiotic Use – Admission CAP[#] (days)	10 (7-24)	8.5 (5-12)	7 (5-9)	8 (5-11)	0.11
Duration Antibiotic Use – Admission HAP[##] (days)	7 (4-8)	9 (5-13)	8 (4-19)	8 (5-13)	0.59
Duration Antibiotic Use – Admission AP[###] (days)	3 (2-4)	7 (4-11)	7 (4-10)	5 (3-10)	0.17
Duration Antibiotic Use – Admission VAP[$] by criterion (days)	10 (6-18)	8.5 (5.5-20.5)	14 (7-21)	9 (7-21)	0.74
Days antibiotics/Days LOS[$$]	0.9 (0.6-1.1)	0.9 (0.7-1.1)	0.9 (0.6-1.1)	0.9 (0.7-1.1)	0.72

[t] HME – heat and moisture exchanger (BB100, Pall Corporation, New York. USA)
HW - hot water (MR850AEA. Fisher & Paykel Health Care. New Zealand)
[tt] Acute Respiratory Distress Syndrome (ARDS)
[ttt] Nebulizers: Jet-Hudson RCI jet nebulizer
Vibrating sieving mesh-Aeroneb Pro/Pro X (Phillips. Amsterdam. Netherlands)

[#] Other nebulizations – lignocaine for cough/N-acetylcysteine
[*] Continuous Renal Replacement Therapy (CRRT) Intermittent Hemodialysis (IHD)
[**]median IQR[#] Other nebulizations – lignocaine for cough/mucomist
[*] Continuous Renal Replacement Therapy (CRRT) Intermittent Hemodialysis (IHD)
** Usual care patients were able to receive nebulized therapy as clinically directed but were not permitted to receive nebulized saline or heparin.
# CAP-community acquired pneumonia
HAP-hospital acquired pneumonia
AP-aspiration pneumonia
$ VAP-ventilator associated pneumonia
$$ LOS-length of stay

Table 4. Ventilator Associated Pneumonia by Clinical Diagnosis and Klompas Criteria

	Heparin N=71 N/Median (%/IQR)	0.9% Sodium chloride N=71 N/Median (%/IQR)	Usual Care N=72 N/Median (%/IQR)	Total N=214 N/Median (%/IQR)	P
Clinically Diagnosed VAP[t]					
All	20 (28)	17 (24)	19 (26)	56 (26)	0.85
High/Moderate	12 (17)	6 (8)	7 (10)	25 (12)	0.27
High	6 (8)	5 (7)	4 (6)	15 (7)	0.76
VAP Klompas Criteria	5 (7)	4 (6)	5 (7)	14 (7)	1.00
First episode of bacterial VAP	5 (7)	4 (6)	4 (6)	13 (6)	1.00
Time to VAP-Klompas (Days)**	7 (5-8)	7.5 (4-19)	8 (6-14)	7 (5-10)	0.35
VAP Microorganisms					
Staphylococcus aureus	1 (20)	2 (50)	1 (20)	4 (29)	
Haemophilus influenza	1 (20)	1 (25)	1 (20)	3 (21)	
Stenotrophomonas maltophilia	0 (0)	0 (0)	0 (0)	2 (14)	
Serratia marcescens	1 (20)	0 (0)	0 (0)	1 (7)	
Enterobacter cloacae	1 (20)	1 (25)	0 (0)	2 (14)	
Klebsiella pneumoniae	1 (20)	0 (0)	1 (20)	2 (14)	
Proteus mirabulus	0 (0)	1 (25)	0 (0)	1 (1)	
Herpes simplex	0 (0)	0 (0)	1 (20)	1 (1)	
Streptococcus pneumoniae	0 (0)	1 (25)	0 (0)	1 (1)	
					0.09
1 organism	5 (100)	1 (25)	3 (60)	9 (64)	
2 organisms	0 (0)	3 (75)	2 (40)	5 (36)	
					0.42
*Gram negative**	4 (80)	1 (25)	3 (75)	8 (62)	
Gram positive	1 (20)	1 (25)	0 (0)	2 (15)	
Both	0 (0)	2 (50)	1 (25)	3 (23)	

Ventilator Associated Complication	Heparin N=68	Saline N=67	Usual Care N=67	Total N=202	P
	20 (29)	15 (22)	18 (23)	53 (25)	0.59

[t] Ventilator Associated Pneumonia (VAP)

* only bacterial isolates included ** median and IQR

Table 5. Adverse Events

Variable	Heparin N=71 Median/N (%/IQR)	0.9% Sodium chloride N=71 Median/N (%/IQR)	Usual Care N=72 Median/N (%/IQR)	Total N=214 Median/N (%/IQR)	P
Highest Activated Partial Thromboplastin Time* (sec)	50 (36-48)	47 (35-48)	46 (31-49)	48 (34-48)	0.20
Lowest Platelet Count (X 10^9/l)	164 (9-580)	183 (27-664)	167 (10-369)	172 (9-664)	0.40
Adverse Events	5 (7)	4 (6)	1 (1)	10 (5)	0.27
Unrelated	4 (6)	4 (6)	1 (1)	9 (4)	0.34
Possible related	1 (1)	0 (0)	0 (0)	0 (0)	1.00
Definitely related	0 (0)	0 (0)	0 (0)	1 (0.5)	1.00
Serious	1 (1)	0 (0)	1 (1)	2 (1)	1.00
Confounding Factors	4 (6)	4(6)	1(1)	9 (4)	1.00
Cessation Study Drug Permanent	3 (4)	2 (3)	0 (0)	5 (2)	0.21

Heparin.

1. Discomfort experienced by patient during nebulization of study drug: rigors, choking sensation.
2. Possible HITTS
3. Rectal ulcer bleed requiring cessation of study drug
4. Bleeding from intercostal catheter. Settled with bronchoscopy
5. Surgical Drain Bleeding-study drug had not commenced

Saline

1. Melena with fall of hemoglobin by 1 gram/dL
2. Worsening coagulopathy and blood stained sputum
3. Hemoptysis due to suction trauma. No fall in hemoglobin. SC heparin continued. Bleeding settled despite continuing study drug
4. Bleed from surgical tracheotomy. Though by treating team to be a surgical bleed. Normal coagulation profile but on aspirin and clopidogrel, 1 g/L HB loss

Usual Care – usual care

1. Significant thrombocytopenia 15x10^9/L from baseline of 60x10^9/L

* median and interquartile range