Inhaled nebulised unfractionated heparin (UFH) for the treatment of hospitalised patients with COVID-19: A randomised controlled pilot study☆

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ABSTRACT

There is a strong scientific rationale to use nebulised unfractionated heparin (UFH) in treating patients with COVID-19. This pilot study investigated whether nebulised UFH was safe and had any impact on mortality, length of hospitalisation and clinical progression, in the treatment of hospitalised patients with COVID-19. This parallel group, open label, randomised trial included adult patients with confirmed SARS-CoV-2 infection admitted to two hospitals in Brazil. One hundred patients were planned to be randomised to either “standard of care” (SOC) or SOC plus nebulized UFH. The trial was stopped after randomisation of 75 patients due to falling COVID-19 hospitalisation rates. Significance tests were 1-sided test (10% significance level). The key analysis populations were intention to treat (ITT) and modified ITT (mITT) which excluded (from both arms) subjects admitted to ITU or who died within 24 h of randomisation.

In the ITT population (n = 75), mortality was numerically lower for nebulised UFH (6 out of 38 patients; 15.8%) versus SOC (10 out of 37 patients; 27.0%), but not statistically significant; odds ratio (OR) 0.51, p = 0.24. However, in the mITT population, nebulised UFH reduced mortality (OR 0.2, p = 0.035).

Length of hospital stay was similar between groups, but at day 29, there was a greater improvement in ordinal score following treatment with UFH in the ITT and mITT populations (p = 0.076 and p = 0.012 respectively), while mechanical ventilation rates were lower with UFH in the mITT population (OR 0.31; p = 0.08). Nebulised UFH did not cause any significant adverse events. In conclusion, nebulised UFH added to SOC in hospitalised patients with COVID-19 was well tolerated and showed clinical benefit, particularly in patients who received at least 6 doses of heparin.

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1. Introduction

Since December 2019, the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has affected millions of people globally, with many patients requiring hospitalisation and ventilatory support. The pathophysiology of COVID-19 is characterised by microvascular thrombosis and coagulopathy accompanied by diffuse alveolar damage, inflammation, DNA neutrophil extracellular traps (NETS) and hyaline membrane formation [1]. We previously described the scientific rationale for nebulised unfractionated heparin (UFH) to be a potentially effective treatment for COVID-19 because of its broad anti-inflammatory activity combined with its anti-coagulant and anti-viral effects [1].

In early-phase trials in patients with acute lung injury, nebulised UFH reduced microvascular thrombosis and hypercoagulation, improved pulmonary dead space and reduced lung injury, with increased time free of ventilatory support [2–4]. Furthermore, in a pre-pandemic, multicentre, double-blind, randomised controlled study in 256 critically ill ventilated patients, nebulised UFH limited survivors' lung injury and accelerated their return to home [5]. Nebulised heparin has also been shown to benefit patients with a number of other respiratory conditions including ARDS [6] and COPD [7], importantly without major safety concerns.

We and others have shown that heparin is able to bind the spike protein expressed by the SARS-CoV-2 virus [8,9] and that UFH in particular reduced the ability of the virus to infect cells in vitro. SARS-CoV-2 Spike protein binding to human epithelial cells requires the engagement of both cell surface heparan sulfate (HS) and angiotensin-converting enzyme 2 (ACE-2), with HS acting as a co-receptor for ACE-2 interaction. UFH has the ability to compete for binding of the SARS-CoV-2 S protein to cell surface HS, and thus reduce infectivity [8]. Additionally, the SARS-CoV-2 Spike S1 protein receptor-binding domain attaches to UFH and undergoes a conformational change that blocks the binding to the AC2 receptor and infectivity of SARS-CoV-2 to Vero E6 cells [9]. This inhibition of SARS-CoV-2 infection of Vero E6 cells by UFH is concentration-dependent, occurs at therapeutically relevant concentrations likely to be achieved following inhalation, and exhibited a significantly stronger anti-viral effect compared to low molecular weight heparins (LMWHs) [8,9].

These observations suggest that UFH uniquely possesses anti- coagulant, anti-inflammatory, and anti-viral activity [1,10,11] of relevance to the treatment of COVID-19. At the time of this study starting, systemic heparin was being widely used in the treatment of patients with COVID-19 [12]. The rationale for investigating nebulised UFH is that when administered by this route, the drug is retained within the lung and therefore could provide local anti-inflammatory, anticoagulant, and

antiviral activity on top of the effect of systemic heparin and other treatments recognised as standard of care; thus, local availability of heparin in the lung following nebulisation may ensure sufficient airway luminal concentrations capable of reducing viral infection, alveolar coagulation and inflammation above that achieved with systemic administration of heparin.

Given the low cost of heparin, this could provide an accessible treatment for patients with COVID-19 in low- and middle-income countries.

Here, we report the safety and efficacy of nebulised UFH in a pilot study in patients with COVID-19 admitted to two hospitals in the state of Sao Paulo, Brazil during the regional peak of the pandemic with the delta variant of SARs-CoV-2. This trial also forms part of a larger meta- trial established to investigate the potential benefit of nebulised UFH in hospitalised COVID-19 patients [13].

2. Methods

This pilot trial was an open, randomised, parallel group study investigating the effect of nebulised unfractionated sodium heparin (Cristalia Ltda; Brazil, 25,000 IU) in patients admitted to two hospitals in the state of Sao Paulo, Brazil (Sao Roque Hospital and Santa Casa de Sorocaba Hospital) between February 25th, 2021, and July 14th, 2021. The trial identification UTN code is U111-1263-3136 and all patients gave their written informed consent to participate in this study which was approved by the Ethics Committee of the University of Sao Paulo – Biomedical Sciences Institute.

3. Study treatment

Nebulised UFH was administered through a vibrating mesh nebuliser (NebZmart, Glenmark, Taiwan) with 1.25 ml of the sodium heparin (5000 IU/0.25 mL) being diluted with 4 ml of 0.9% saline at 6 hourly intervals in addition to standard of care, with other patients randomised to receive only standard of care as the control arm of the study. Ran- domisation was 1:1 without any adjustment for any clinical characteristics. Randomisation was produced by using a computerized random list generator. The selection of the dosing regime in this study was based on the earlier clinical study using nebulised UFH in treating patients with acute lung injury that showed some clinical benefit that importantly was not associated with any major adverse events (5).

The UFH used was formulated as ampules containing 5000 IU/0.25 mL, from Cristalia Ltda, meeting all the requirements of the USP and Brazilian Pharmacopeia (BP). The heparin samples

were analysed by 1D ^{1}H-NMR spectroscopy, gel permeation and anion exchange chromatography and had their anticoagulant potencies determined with anti-FIIa and anti-FXa activity assays, as required by both the USP and BP. The molecular mass distribution parameters of the formulations also met the requirement of USP. Besides certified as being from porcine origin, the formulations showed no contamination with heparins from other animal sources, as recommended by the BP. The 1D ^{1}H-NMR spectrum showed no signal at 7.4 ppm, assuring the absence of benzyl alcohol commonly added as a preservative in multiuse vials for intravenous administration, but not in formulations intended for subcutaneous use. Furthermore, the formulations used showed no contamination with oversulfated chondroitin sulfate after analyses by NMR and anion exchange chromatography.

4. Study population

Patients with a positive SARS-CoV 2 RT PCR test who required hospitalisation were included in the trial. Patients were required to have a WHO modified ordinal clinical scale (MOCS) score (Table 1) of 3–5; subjects requiring mechanical ventilation were not eligible for randomisation. Exclusion criteria included known hypersensitivity to heparin or related compounds, or the diagnosis of a pulmonary obstructive disease. Any patients requiring admission to ICU ceased to receive any further treatment with nebulised UFH.

We collected the following baseline demographic and clinical data: age, sex, co-morbidities, WHO modified ordinal clinical scale (MOCS) for COVID-19, as shown in Table 1, level of respiratory support, other treatments reflecting the standard of care in use during the time of the trial, including the use of any prophylactic or therapeutic anti-coagulant treatment.

Most patients who were on the standard of care arm at the two hospitals received a range of treatments, including corticosteroids (dexamethasone), antibiotics (ceftriaxone and azithromycin) and anti- coagulants (typically, enoxaparin sodium intravenous, IV or subcutaneous, SC), either in prophylactic or therapeutic doses.

We also collected the following treatment-related variables: nebulised UFH dose (daily and cumulative), treatment duration, missed doses and reasons for this. The following safety outcomes were also assessed: baseline and peak activated partial thromboplastin time (APTT), the incidence of epistaxis, blood-stained sputum, pulmonary bleeding, major bleeding, heparin-induced thrombocytopenia, and any other serious adverse events.

5. Outcomes

Two primary outcomes were measured in this pilot study: the mortality rate and the length of stay in hospital (in days) in each arm. The secondary outcomes were: modification of the WHO ordinal scale (clinical parameters) on every day, but analysis was performed only at days 1 (baseline), 7, 15 and 29 (or until the end of hospitalisation), oxygen-free survival days and mechanical ventilation rates.

6. Statistical analysis

Since this was a pilot study, no sample size or power calculations were used; We aimed to recruit 100 patients as a pragmatic approach to evaluate efficacy signals that could lead to larger studies of nebulised UFH for the treatment of hospitalised patients with COVID-19. As this pilot study was not powered for definitive efficacy analysis, significance tests were 1-sided with a 10% significance level, an approach often used in early phase clinical trials [14].

Treatment effects on survival rate were analysed by Fisher's exact text, while length of stay was analysed by the Wilcoxon signed ranked test. In case of death during the study, a value of 29 days was assigned for the number of days of hospitalisation. The time to hospital discharge was estimated by use of the Kaplan-Meier method and Hazard Ratio risk estimates by the Cox model proportional risk analysis. The change in MOCS was analysed by a Mann-Whitney test. The number of days that each subject was both oxygen free and alive up to day 29 was deter- mined. Fisher's exact text was also used to assess the effect of UFH on the requirement for mechanical ventilation.

Both primary and secondary outcomes were measured using 3 data sets, with the ITT and mITT being the primary populations of interest.

- ITT (Intention-to-treat), corresponding to all subjects who were randomised and, for those in the active treatment group, received at least one dose of nebulised UFH, and participated in at least one post- baseline assessment.
- A modified ITT (mITT) population which excluded (from both arms of the ITT population) subjects admitted to ITU within 24 h of randomisation and subjects who died within 24 h of randomisation. Patients randomised to active treatment were required to have received at least 4 administrations of nebulised UFH, corresponding to 24 h after randomisation.
- PP (Per protocol), corresponding to all subjects who adhered to the major criteria in the

protocol (e.g. all subjects who completed efficacy analyses, whose study drug compliance was between 75% and 125%), and all subjects who did not substantially deviate from the protocol. In addition, a post hoc analysis of the sub-group of PP patients who received at least 6 administrations of UFH was analysed; this group was called PP6.

7. Safety outcomes

Baseline activated partial thromboplastin time (APTT) levels before, and on days 3 and 5 following initiation of treatment with nebulized UFH, were measured, as well as recording of any adverse events in all randomized subjects.

8. Results

Seventy-six patients were recruited when admitted to the hospital. Seventy-five patients were randomised, according to Fig. 1 - Consort statement and patient allocation.

The baseline characteristics of the patients are summarised in Table 2. Patients were on average 51.5 years old and 63.2% were males. The majority of patients enrolled in the trial were Caucasian. No significant differences were observed between groups at baseline for age or body mass index. There were also no significant differences observed between groups at baseline for time from symptom onset, time from hospital admission and with the WHO modified ordinal scale at admission (see Table 3).

The time to commencement of inhaled nebulised UFH ranged from a minimum of 1 h to a maximum of 27 h following hospital admission, with a median time of 4 h. Most patients at the two hospitals received a range of other treatments as standard of care, including corticosteroids (dexamethasone), antibiotics (ceftriaxone and azithromycin) and anti- coagulants (typically, enoxaparin sodium intravenous (IV) or subcutaneous (SC), either in prophylactic or therapeutic doses). The standard of care treatment was not different between the two arms of the trial.

The trial was stopped when no patients had been hospitalised with COVID-19 for 60 consecutive days in either of the two sites engaged in this trial.

8.1. Mortality

In the ITT population (n = 75), mortality was numerically lower for nebulised UFH on top of

standard of care (6 out of 38 patients; 15.8%) versus standard of care (10 out of 37 patients; 27.0%), but this difference was not statistically significant (odds ratio 0.51, p = 0.2349), with similar results observed for the per-protocol-population (odds ratio 0.31, p = 0.1482) (Table 4). However, there were statistical differences be- tween treatments in favour of nebulised UFH in the mITT population (odds ratio 0.2, p = 0.0353), and the post-hoc analysis of PP6 population (odds ratio 0.1, p = 0.0184), (see Table 4, Table 5).

All deaths occurred only in patients who scored 4 or 5 on the WHO ordinal scale on the day of hospital admission.

8.2. Days of hospitalisation

Subjects receiving nebulised UFH showed a similar time to discharge compared to the standard of care group.

8.3. Oxygen-free survival days

Subjects receiving nebulised UFH had a similar number of oxygen free survival days compared to the standard of care group (Table 6).

8.4. WHO MOCS

There was a significant treatment benefit for patients receiving nebulised UFH on top of standard of care versus patients treated with standard of care only as assessed by the WHO MOCS (Table 6). At day 29, the treatment difference reached significance in all analysis populations ($p < 0.1$).

8.5. Mechanical ventilation rates

The rates of mechanical ventilation were not significantly different between the two treatment arms in the ITT population, although the nebulised UFH treatment arm showed numerically lower rates of intubation (ITT population; odds ratio 0.51, 95% CI 0.16–1.57) (Table 7).

For the MITT and PP populations, the treatment effects reached the pre- defined level of significance ($p < 0.1$).

9. Safety outcomes

No laboratory measurements showed abnormal findings that could be attributable to treatment with nebulised UFH and in particular, there were no significant differences in APTT between the two treatment groups (Fig. 2).

There were no cases recorded of pulmonary bleeding, heparin induced thrombocytopenia, or anaphylaxis during or immediately after administration of nebulised UFH, or any other adverse events.

10. Discussion

This exploratory study showed clinical benefit for nebulised UFH on top of standard of care for patients hospitalised with COVID-19. The primary endpoints showed a reduction in mortality, reaching significance in the mITT population, but no difference in duration of hospital stay. For the secondary endpoints, positive effects of nebulised UFH were observed on MOCS change and rates of mechanical ventilation. Overall, nebulised UFH appeared to be well tolerated.

As this was a pilot study we also performed a post-hoc analysis of the data obtained, as it was clear that some patients who were recruited into the trial died within the first 24h of hospitalisation which was not considered to be related to any nebulised heparin they had received, but rather a reflection of the severity of their COVID-19 at the time of hospitalisation. We firstly investigated the effect of the number of doses of heparin patients received. In patients that were administered at least 6 administrations of nebulised heparin, there was a statistically significant difference for the primary outcome of mortality in favour of nebulised heparin added to standard of care in comparison with standard of care. There was however no difference seen in the time until hospital discharge, with the nebulised heparin group taking longer than the standard of care.

The two analysis populations of key interest were the ITT and mITT. The purpose of the mITT was to exclude subjects from both treatment arms with rapid disease progression within 24 h of admission, resulting in mechanical ventilation or death. There was limited scope for nebulised UFH to alter the disease trajectory in these subjects, as their disease trajectory implied a poor prognosis. Furthermore, these subjects received few (<4) or no UFH doses before ventilation or death; the potential benefits of nebulised UFH are unlikely to be realised after such short treatment duration is subjects with rapidly progressive disease. While the mortality benefit in this study was greatest (and significant) in the mITT population (odds ratio 0.20), a numerical (non-significant)

trend was observed in the ITT population (odds ratio 0.51). A post-hoc analysis of subjects who received at least 6 nebulised UFH doses showed a greater benefit (odds ratio 0.1, p = 0.0184), compatible with the concept that at least 24 h UFH treatment allows a greater possibility for the clinical benefit of this treatment to be realised.

The secondary endpoints for MOCS change and rates of ventilation also showed evidence for efficacy of nebulised UFH in this patient population. Taken together with the mortality efficacy signals observed, these results support the need for larger studies to be undertaken to further investigate the potential benefits of nebulised UFH in patients with COVID-19. To this end the results from our study will also be used as part of an ongoing meta-trial involving a higher number of patients with COVID-19 being carried out in a number of other countries than Brazil [13]. The results of the current study are consistent with a recently published case series of 98 patients showing that nebulised UFH administration in hospitalised patients with COVID-19 is safe and potentially beneficial [15], and with the results of earlier studies reporting a beneficial effect in patients with ARDS pre the COVID-19 pandemic [5].

The duration of hospital stay (the co-primary endpoint) however, did not show any differences between groups. This outcome measure can be influenced by a variety of factors including age, co-morbidities and rate of recovery from COVID-19. Therefore, it is probable that our study was too small to detect any difference in this outcome measure. Additionally, this endpoint was likely influenced by other pressures on hospitals during the peak of the pandemic to create space for newly diagnosed COVID-19 patients by the rapid (subjective) discharge of improving patients.

We had planned to recruit a sample size for this trial of 100 study subjects. However, we only managed to recruit 76 patients into the study due to changes in the prevalence of COVID-19 patients in the state of Sao Paulo between February 25th, 2021, when the study started and July 14th, 2021 when the Steering Committee decided to end recruitment and analyse the data. The smaller than anticipated study size therefore prevented the possibility to conduct sub-group analysis. Other limitations of our study included the heterogeneity of the clinical status of patients on admission to hospital, the change in vaccination status through the progress of the trial and the open label status of the treatment arms, hence we used a conservative level of significance set at 10%.

Whilst this was a pilot study in a limited number of patients, our results suggest that use of nebulised UFH is safe and may provide additional benefit in reducing mortality in patients hospitalised with COVID-19 on top of standard of care, including patients who were also receiving

systemic heparin, and providing at least 6 doses of UFH were adminstered [12,16]. Whilst a number of effective treatments have now been identified to treat hospitalised patients with COVID-19 [15], the recent emergence of new variants of SARs-CoV-2, that appear to be highly transmissible and possibly escape the impact of many of the available vaccines, shows that there is still a need to continue to seek effective treatments for this and future virally mediated pneumonias. The ability of heparin to prevent infection of mammalian cells with SARs-CoV [1,11], coupled with its well-recognised ability to reduce inflammation by binding various cytokines implicated in the cytokine storm often associated with COVID-19 [1,10], as well as the well-recognised anti-coagulant effect of this drug of benefit in dealing with the alveolar coagulation seen in such patients, suggests that further controlled, larger studies of nebulised UFH are warranted, given that this a widely available and low cost medicine.

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Author statement

We confirm that the manuscript has been read and approved by all named authors and that there are no other persons who satisfied the criteria for authorship but are not listed. We further confirm that the order of authors listed in the manuscript has been approved by all of us.

The corresponding author is responsible for ensuring that the descriptions are accurate and agreed by all authors.

We confirm that we have given due consideration to the protection of intellectual property associated with this work and that there are no impediments to publication, including the timing of publication, with respect to intellectual property. In so doing we confirm that we have followed the regulations of our institutions concerning intellectual property. We further confirm that any aspect of the work covered in this manuscript that has involved either experimental animals or human patients has been conducted with the ethical approval of all relevant bodies and that such approvals are acknowledged within the manuscript.

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communicating with the other authors about progress, submissions of revisions and final approval of proofs. We confirm that we have provided a current, correct email address which is accessible by the Corresponding Author.

Declaration of competing interest

TW reports receiving fees and grant support from Synairgen, Bergenbio, AstraZeneca, Janssen, UCB and Valneva in the area of the sub- mitted work, and from GSK, Boehringer-Ingelheim, AZ, and Roche outside the area of the submitted work. CP reports receiving personal fees and grant support from EpiEndo, Eurodrug, Recipharm and Gly- cosynnovation, and has equity in Verona Pharma, outside of the sub- mitted work. AW reports receiving fees from Theravance in the area of work, and personal fees from Boehringer-Ingelheim, GSK and Novartis outside the submitted work. JS has equity in Ockham Biotech Ltd. who are developing inhaled heparin for the treatment of respiratory diseases. DS has received personal fees from Aerogen, AstraZeneca, Boehringer Ingelheim, Chiesi, Cipla, CSL Behring, Epiendo, Genentech, GlaxoSmithKline, Glenmark, Gossamerbio, Kinaset, Menarini, Novartis, Pulmatrix, Sanofi, Synairgen, Teva, Theravance and Verona.

Data availability

Data will be made available on request.

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Figures and Tables

Table 1

WHO modified ordinal clinical scale (MOCS) for COVID-19.

Level	Description
1.	Not hospitalised
2.	Hospitalised, not requiring supplemental oxygen and no longer requiring medical care for COVID-19
3.	Hospitalised not requiring supplemental oxygen, but in needing medical care for COVID-19
4.	Hospitalised requiring supplemental oxygen
5.	Hospitalised requiring non-invasive ventilation or high-flow oxygen
6.	Hospitalised requiring intubation and mechanical ventilation or ECMO
7.	Death

Table 2

Baseline characteristics and additional characteristics.

	All patients (n = 75)	**Standard of care (n = 37)**	**Heparin (n= 38)**	**P- value**
Age (y)	51.95 ± 12.39	52.63 ± 12.48	51.26 ± 12.27	0.688
Male n, (%)	48 (63%)	25 (67%)	23 (60%)	N/A
Caucasian n, (%)	65 (85%)	35 (97%)	30 (79%)	N/A
Body Mass Index (kg/m2) ±SD	30.65 ± 6.19	29.79 ± 6.02	31.44 ± 6.23	0.389
Time from symptom onset (days) ±SD	8.61 ± 4.15	8.97 ± 5.10	8.26 ± 2.85	0.933
Time to commencement of inhaled UFH (hours)	N/A	N/A	4	N/A
Modified ordinal scale at baseline (average) ±SD	4.23 ± 0.57	4.14 ± 0.58	4.32 ± 0.61	0.205
WHO SCORE	Number of patients			
1	0	0	0	N/A
2	0	0	0	
3	8	4	4	
4	44	24	20	
5	24	9	15	
6	0	0	0	
7	0	0	0	

N/A = not applicable.

Table 3

-Mortality comparison between the two groups).

	Control		Heparin		p value
	n	%	n	%	
Did the patient die?					
ITT					0,2707[a]
No	27	73,0%	32	84,2%	
Yes	10	27,0%	6	15,8%	
MITT					0,0341
No	27	73,0%	27	93,1%	
Yes	10	27,0%	2	6,9%	
PP					0,1451[a]
No	27	73,0%	32	86,5%	
yes	10	27,0%	5	13,5%	
PP6					0,0138
No	27	73,0%	26	96,3%	
yes	10	27,0%	1	3,7%	

Exact Fisher Test one sided.

[a] Chi-squared one sided.

Table 4

Days of hospitalisation comparison.

Days of hospitalisation	Control n	Heparin n	p-value
ITT			0,4032
Mean (std)	12.6(11.2)	12.0(9.7)	
Median (IQR)	6(4–29)	7(5–17)	
MITT			0,4499
Mean (std)	12.6(11.2)	10.4(8.0)	
Median (IQR)	6(4–29)	7(5–13)	
PP			0,4558
Mean (std)	12.6(11.2)	11.5(9.4)	
Median (IQR)	6(4–29)	7(5–16)	
PP 6			0,4556
Mean (std)	12.6(11.2)	9.7(7.5)	
Median (IQR)	6(4–29)	7(5–13)	

Wilcoxon (or Mann-Whitney) one sided.

Table 5

Days of oxygen use in all datasets.

Oxygen free survival days	Control		Heparin		p-value
	n	%	n	%	
ITT					0,3783
Mean (std)	18.1(12.3)		18.9(10.4)		
Median (IQR)	25.5(0–27)		24.5(13–27)		
MITT					0,4394
Mean (std)	18.1(12.3)		20.7(8.4)		
Median (IQR)	25.5(0–27)		25(18–26)		
PP					0,4296
Mean (std)	18.1(12.3)		19.4(10.0)		
Median (IQR)	25.5(0–27)		25(14–27)		
PP6					0,4694
Mean (std)	18.1(12.3)		21.5(7.7)		
Median (IQR)	25.5(0–27)		25(18–27)		

Mann-Whitney, P-values based on median.

Table 6

Evolution of the MOCS WHO scale following treatment with standard of care or heparin plus standard of care.

Score/Day	Control	Heparin	Control	Heparin	Control	Heparin	Control	Heparin
	D1		D7		D15		D29	
ITT								
Mean (std)	4,14(0,59)	4,32 (0,62)	3(2,50)	3,05(2,32)	2,78(2,73)	2,45(2,40)	2,75(2,72)	1,95(2,22)
Median (IQR)	4(4–4)	4(4–5)	1(1–6)	1(1–5)	1(1–6,5)	1(1–4)	1(1–7)	1(1–1)
p-value	0,0933		0,5000		0,3437		0,0765	
MITT								
Mean (std)	4,14(0,59)	4,32 (0,62)	3(2,50)	2,76(2,1)	2,78(2,73)	1,90(1,90)	2,75(2,72)	1,41(1,55)
Median (IQR)	4(4–4)	4(4–5)	1(1–6)	1(1–4)	1(1–6,5)	1(1–1)	1(1–7)	1(1–1)
p-value	0,0507		0,3427		0,1172		**0,0118**	
PP								
Mean (std)	4,14(0,59)	4,30(0,62)	3(2,50)	2,97(2,30)	2,78(2,73)	2,32(2,31)	2,75 (2,72)	1,81(2,08)
Median (IQR)	4(4–4)	4(4–5)	1(1–6)	1(1–5)	1(1–6,5)	1(1–4)	1(1–7)	1(1–1)
p-value	0,1187		0,4567		0,2739		**0,0469**	
PP6								
Mean (std)	4,14(0,59)	4,33(0,56)	3(2,50)	2,56(1,99)	2,78(2,73)	1,74(1,68)	2,75 (2,72)	1,22(1,15)
Median (IQR)	4(4–4)	4(4–5)	1(1–6)	1(1–4)	1(1–6,5)	1(1–1)	1(1–7)	1(1–7)
p-value	0,0956		0,2259		0,0801		**0,0052**	

Wilcoxon (or Mann-Whitney) one sided.

Table 7

Rates of Mechanical ventilation

Did patients require mechanical ventilation?	Control		Heparin		p-value
	n	%	n	%	
ITT					0,2331[a]
No	27	73,0%	32	84,2%	
Yes	10	27,0%	6	15,8%	
MITT					0,0802
No	27	73,0%	26	89,7%	
Yes	10	27,0%	3	10,3%	
PP					0,1235
No	25	71,4%	32	86,5%	
Yes	10	28,6%	5	13,5%	
PP6					0,1045
No	27	73,0%	24	88,9%	
Yes	10	27,0%	3	11,1%	

Fisher exact test.

[a] Chi-squared one sided.

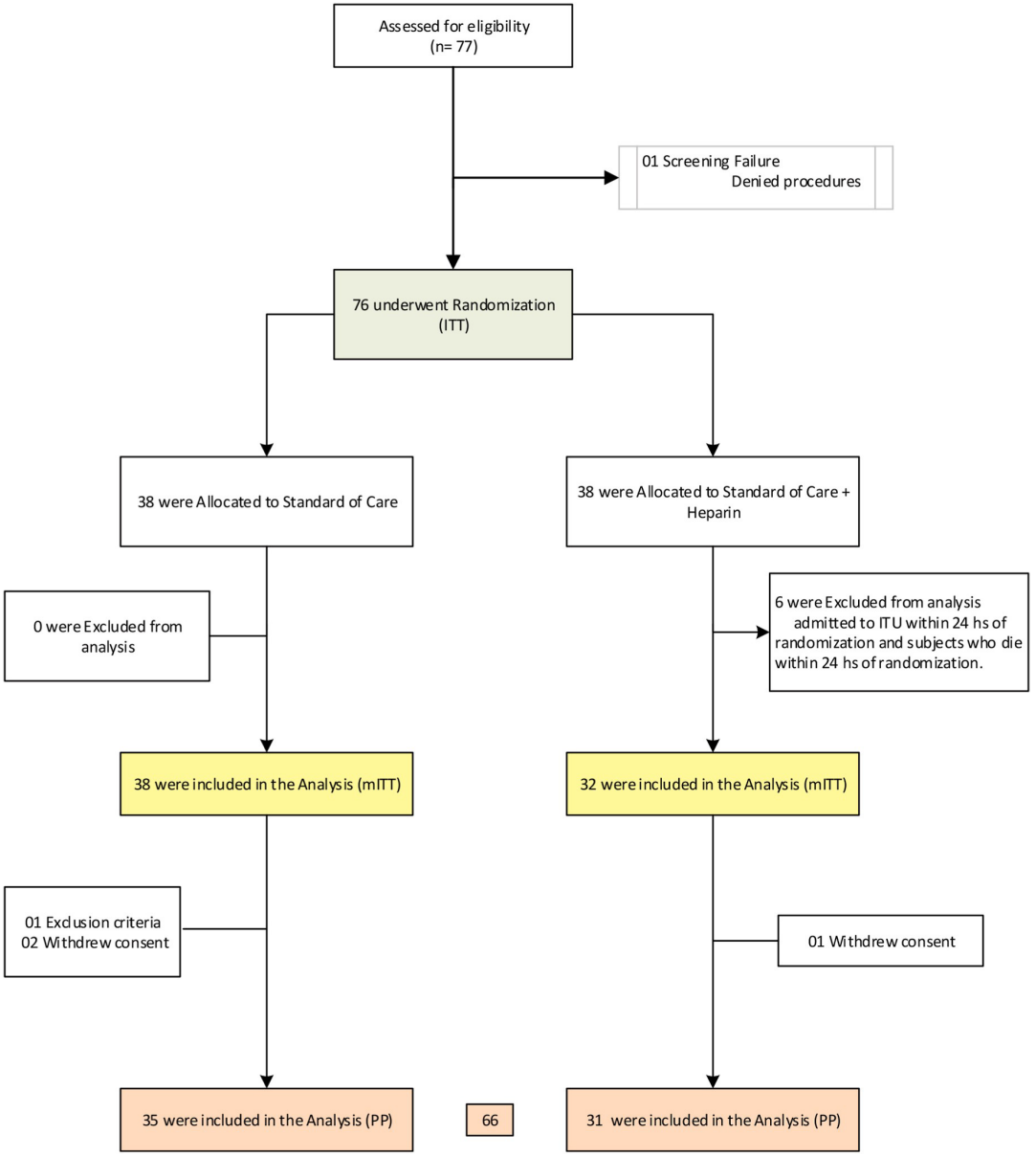

Fig. 1. Consort statement and patient allocation.

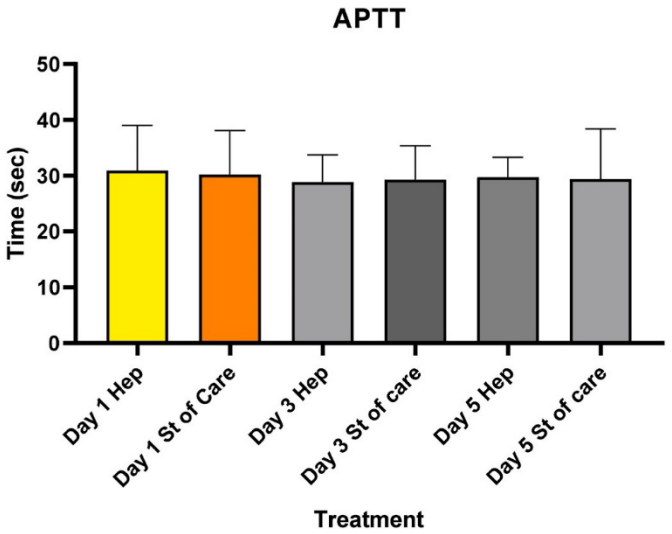

Fig. 2. APTT values at days 1, 3 and 5 for Heparin and Standard of Care arms.