Standard prophylactic doses of heparin are not sufficient to mitigate the clinical scenario in patients with COVID-19 and severe pneumonia

HIV Drug Therapy GLASGOW 2020 | VIRTUAL

P136

A. Vergori, DR. Donno, P. Lorenzini, G. Gualano, E. Nicastri, F. Iacomi, L. Marchioni, P. Campioni, V. Schininà, S. Cicalini, C. Agrati, MR. Capobianchi, E. Girardi, G. Ippolito, F. Vaia, N. Petrosillo, A. Antinori, F. Taglietti on behalf of the ReCOVeRI Study Group

National Institute for Infectious Diseases 'Lazzaro Spallanzani' IRCCS, HIV/AIDS Department, Rome, Italy

BACKGROUND

- COVID-19 is commonly complicated with coagulopathy that may predispose to thrombotic events, associated with a higher risk of requiring mechanical ventilation, intensive care unit (ICU) admission, or death [1-4]
- It is yet unknown whether these hemostatic changes are a specific effect of SARS-CoV-2 or are a consequence of a cytokine storm that alters the onset of the systemic inflammatory response syndrome (SIRS), as observed in other viral disease[5]
- Some of the most known non-anticoagulant properties of heparin are its anti-inflammatory activities might be relevant in this setting[6]
- Prophylactic low molecular weight heparin (pLMWH) is currently recommended[7]

AIMS

- To evaluate the role of pLMWH on clinical progression;
- To analyze mean changes of hyperinflammation parameters according to pLMWH exposure.

METHODS

Study design and population: Observational study on consecutive adult patients admitted with SARS-CoV-2 infection diagnosed by means of RT-PCR positive on naso-pharyngeal swabs (at least once) and/or serology with a radiologically confirmed pneumonia from 1st March to 10 May.
Patients on pLMWH were included if they started a standard prophylactic dose of heparin within 48 hours from admission. Patients with confirmed acute pulmonary embolism were excluded from the analysis.

Definitions

Hyperinflammation was defined as the presence of at least two criteria at any time from admission among: a) blood lymphocytes < 1000/mmc; b) ferritin > 500ng/mL; c) LDH > 300 U/L; d) D-dimers > 1000 ng/mL; e) C-reactive protein > 3mg/dL.

Statistical Analysis:

The baseline of the analysis was hospital admission, the follow-up accrued until the occurrence of the outcome or last observation. The follow-up was censored if the patient changes the heparin dose from prophylactic to therapeutic. The primary outcome was the time from hospital admission to orotracheal intubation/death (IOT/death). The secondary outcomes were: i) the time from hospital admission to death, ii) the evaluation of mean changes for each parameters belonging to the hyperinflammation pattern from first to last value during hospitalization, divided for the duration of time. Cumulative probability of experiencing IOT/death or death were estimated by Kaplan-Meier curves and (unweighted and weighted) Cox regression models were used to estimate the effect of the LMWH prophylaxis exposure on the outcome.
The analyses were stratified according to the severity of disease at admission defined as a) PaO2/FiO2 ratio <= or >300 mmHg and b) presence/absence of hyperinflammation. Mean changes of hyperinflammation parameters calculated as difference from first to last value during hospitalization and divided for the duration of time, were compared between exposed and not exposed using t-Student test.

RESULTS

Main characteristics of the study population (n. 422) are shown in Table 1

Table 1 – General characteristics of study population (n.422), according to LMWH prophylaxis status

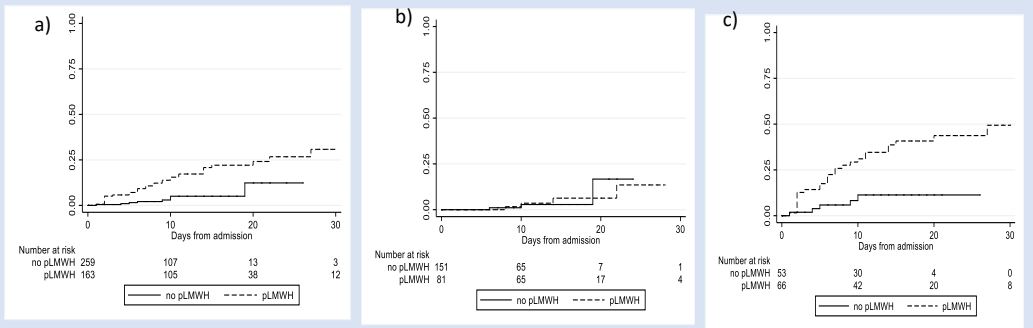
Characteristics	n.259	n.163	
	no pLMWH	pLMWH	p-value
Gender, n (%)			
Male	167 (64.5)	93 (57.1)	0.127
Female	92 (35.5)	70 (42.9)	
Age, years, median (IQR)	57 (46-68)	70 (55-80)	<0.001
Co-morbidities, n (%)			
Diabetes	25 (9.7)	31 (19.0)	0.006
Cardiologic diseases	44 (17.0)	57 (35.0)	<0.001
Hypertension	67 (25.9)	80 (49.1)	<0.001
COPD/asthma	32 (12.4)	41 (25.2)	0.001
Kidney diseases	5 (1.9)	10 (6.1)	0.023
PaO2/FiO2 at admission, mmHg, median (IQR)	358 (300-421)	318 (235-406)	<0.001
Hyperinflammation at admission, n (%)	122 (47.1)	104 (63.8)	0.001
Immunomodulant therapy, n (%)	21 (8.1)	31 (19.0)	0.001
Antiviral therapy (IQC and/or LPV/r), n (%)	201 (77.6)	137 (84.1)	0.107
Padua score, median (IQR)	2 (1.5-3)	2 (1-3)	0.774
Residual normal ventilated lung, volume, (L), median (IQR) (available only for 142 pts)	4.0 (2.9-5.2)	3 (2.2-4.1)	0.003

References: 1.Lippi G, et al. Clin Chim Acta 2020; 2.Zhou F, et al. Lancet 395:1054–1062; 3. Tang N, et al. J Thromb Haemost 18:844–847 6 ; 4. Fan BE, et al. Am J Hematol. https ://doi. org/10.1002/ajh.25774;6 ; 5. Bikdeli B, et al. J Am Coll Cardiol. 2020;S0735-1097(20)35008-7 ; 6.Thachil J. J Am Coll Cardiol. 2020;S0735-1097(20)35008-7.;7. Porfidia A, et al. J Thromb Thrombolysis. 2020;1-4.

RESULTS II

Over 147 person-months of follow-up, 42 patients experienced IOT or death. The estimated probability of IOT/death at 15 days from admission, for patients receiving pLMWH was 22.1% (95%CI 15.6-30.8) and for those who did not receive pLMWH 5.0% (95%CI 2.3-10.8) (Figure 1a). The probability of primary endpoint was very different according to level of PaO2/FiO2 at admission (Figure 1b,c).

Figure 1. a) Estimated probability of mechanical invasive oro-tracheal intubation/death (IOT/death) according to pLMWH exposure in the study population and stratified by PaO2/FiO2 ratio at admission b) >300 mmHg and c) <=300 mmHg



Log-rank p-value <0.001
15-days probability of IOT/death
No pLMWH: 5.0 % (95%CI 2.3-10.8)
pLMWH: 22.1% (95%CI 15.6-30.8

Log-rank p=0.983
15-days probability of IOT/death
No pLMWH: 2.8% (95%CI 0.7-11.3)
pLMWH: 6.3% (95%CI 2.0-18.8)

Log-rank p=0.022
15-days probability of IOT/death
No pLMWH:11.3% (95%CI4.8-25.6)
pLMWH: 40.8% (95%CI 29.3-54.7)

After adjustment for confounders, prophylactic use of LMWH was associated with a 60% increased risk of IOT/death [aHR 1.60 (0.59 to 4.30); p=0.356], but no statistical significance was reached. This risk was different according to PaO2/FiO2 ratio strata (Table2). The mean changes of hyperinflammation parameters are shown in table 3.

Table 2. Hazard Ratio of oro-tracheal intubation/death (IOT/death) in all population and according to PaO2/FiO2.

	Unadjusted and adjusted marginal relative hazards of IOT/death[&]			
	Unadjusted HR (95% CI)	**p-value**	**Adjusted[*] HR (95% CI)**	**p-value**
		All patients		
No pLMWH	1.00		1.00	
pLMWH	1.80 (0.71, 4.57)	0.214	1.60 (0.59, 4.30)	0.356
		Baseline PaO_2/FiO_2 ≤300 mmHg		
No pLMWH	1.00		1.00	
pLMWH	2.51 (0.80, 7.85)	0.113	2.81 (0.82, 9.67)	0.102
		Baseline PaO2/FiO2 >300 mmHg		
No pLMWH	1.00		1.00	
pLMWH	0.36 (0.05, 2.53)	0.303	0.62 (0.10, 3.99)	0.617

[*]adjusted for age (< and >=65 yrs), gender, comorbidities (cardiovascular diseases, hypertension, COPD/Asthma, kidney diseases, neurological diseases), PaO2/FiO2 at admission, time-varying use of immune-therapy, azithromycin and censoring using IPW; [&]Initiation of invasive mechanical ventilation or death; P at interaction test between pLMWH use and baseline PaO2/FiO2 level = 0.134; Abbreviation: pLMWH, prophylactic low molecular weight heparin.

Table 3. Mean changes per day of hyperinflammation parameters

	Parameter	At admission	Last observation	Change/day, mean	p-value
pLMWH	Lymphocytes, cells/mmc	1340	1604	12.3	0.642
No pLMWH		1346	1597	17.5	
pLMWH	D-dimer, ng/ml	2204	1411	-59.9	0.007
No pLMWH		1010	1127	18.4	
pLMWH	CRP, mg/dl	6.4	3.3	-0.28	0.308
No pLMWH		4.6	2.5	-0.13	
pLMWH	Ferritin, pg/ml	638	766	15.4	0.029
No pLMWH		407	515	-5.8	
pLMWH	LDH, U/L	279	249	-1.2	0.612
No pLMWH		256	232	2	

LIMITATIONS

Observational setting: residual confounding bias is likely to be an issue.

CONCLUSIONS

Our results highlight that standard doses of pLMWH did not add any clinical advantage in severe COVID-19 pneumonia supporting the feeling that standard prophylactic doses of anticoagulation might not be sufficient to contrast the hypercoagulable state established in many COVID-19 patients.

FUNDING This work was supported by Line one - Ricerca Corrente 'Infezioni Emergenti e Riemergenti' and by Progetto COVID 2020 12371675 both funded by Italian Ministry of Health

ACKNOWLEDGMENTS The authors gratefully acknowledge nurse staff, all the patients and all members of ReCOVeRI Study Group

Author contact: alessandra.vergori@inmi.it