

# Covid-19 and low molecular weight heparin therapy: retrospective study of 257 patients.

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## Short Report

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# Abstract

**Objective** To evaluate the role of low molecular weight heparin in COVID-19 treatment.

**Design** Retrospective cohort study

**Setting** Patients with COVID-19 pneumonia consecutively admitted to Castel San Giovanni COVID-Hospital from February 29, to April 7, 2020.

**Main outcome measure** Hospital mortality and safety in patients treated with low molecular weight heparin.

**Results** Of the 257 patients enrolled, 49 (19.1%) died during the hospitalization. Hospital mortality was significantly lower in patients treated with therapeutic dose of low molecular weight heparin (T-LMWH) (17/126, 13.5%), compared with patients treated with prophylactic dose (P-LMWH) (32/131, 24.4%;  $\chi^2=4.98$ ,  $p = 0.02$ ). Crude and adjusted odds ratios of mortality for patients treated with T-LMWH were  $OR=0.483$ , 95% CI 0.252-0.923 and  $OR=0.374$ , 95% CI 0.177-0.792. In a stratified analysis by ventilation type, the only subgroup of patients who benefited from therapeutic doses of heparin were those receiving non-invasive mechanical ventilation ( $OR=0.099$ , 95% CI 0.028-0.354,  $p<0.001$ ). No fatal bleedings were observed.

**Conclusion** Treatment with therapeutic doses of T-LMWH is safe and seems to reduce mortality in COVID-19 patients with pneumonia, especially among those who need non-invasive mechanical ventilation. We look forward to prospective studies to confirm this observation and evaluate the appropriate dose of LMWH in the treatment of COVID-19 patients.

## Introduction

The coronavirus SARS-CoV-2 infected thousands of people in Wuhan in December 2019 and spread rapidly worldwide. Since February 29, 2020, Castel San Giovanni Hospital in Italy was entirely dedicated to the treatment of coronavirus disease 2019 (COVID-19) patients. Pneumonia is the main clinical feature of COVID-19, however we observed several patients dying with very high D-dimer serum levels, suggesting a hypercoagulability state, as recently reported [1-3].

The relationship between inflammation and thrombosis is well recognized and the anticoagulant and anti-inflammatory activity of heparin may exert a beneficial effect on COVID-19 disease [4-5]. No specific pharmacological protocols with proved efficacy were, and actually are, available for treatment of Coronavirus disease [6]. We therefore hypothesized that treatment with Low Molecular Weight Heparin (LMWH) at a therapeutic dose could benefit COVID-19 patients and we decided, with clinical equipoise, to treat patients with therapeutic doses of LMWH taking advantage of its anticoagulant, anti-inflammatory, and in vitro antiviral properties [7-10].

The aim of this study is to evaluate the hospital mortality of COVID-19 patients treated with LMWH, administered at prophylactic doses (P-LMWH) and therapeutic doses (T-LMWH).

## Methods

Adult patients, consecutively admitted to the Castel San Giovanni Hospital, from February 29, to April 7, 2020 with confirmed COVID-19 pneumonia were included in the study. The diagnosis was consistent with the World Health Organization interim guidelines [11] and was confirmed by RNA detection of the SARS-CoV-2 from oropharyngeal and nasopharyngeal swab sample. In all patients Computed Tomography scan diagnosis of pulmonary pneumonia was performed.

We excluded patients on hemodialysis and patients with a hospital stay  $\leq 7$  days to exclude either mild forms of disease with an early discharge or more advanced forms of disease with early death or early transfer to another hospital for whom heparin treatment would not be appropriate [12-13].

The therapeutic approach included hydroxychloroquine, azithromycin, anti-viral therapy (lopinavir/ritonavir and/or darunavir/cobicistat), corticosteroid, tocilizumab (in selected patients) and LMWH. From 24 February 2020 to 15 March 2020, our patients received P-LMWH corresponding to 4000 IU once a day, as suggested by International guidelines for bedridden patients [14]. On 16 March 2020, during a medical staff briefing, we decided to treat our patients with T-LMWH corresponding to 70-100/kg IU twice a day. The approval of the Healthcare Directorate of Piacenza Local Health Authority was obtained. Patients with a HAS BLED score  $\geq 3$  were excluded from T-LMWH treatment [15].

### *Data Collection*

Data were extracted from electronic medical records and included age, gender, clinical characteristics, in-hospital pharmacological treatments and type of high-flow oxygen needed. The comorbidities recorded were arterial hypertension, diabetes mellitus, cardiovascular diseases (defined as history of myocardial infarction, ischemic stroke, and peripheral atheromasia), atrial fibrillation, chronic obstructive pulmonary disease, chronic kidney disease (Cockcroft-Gault e-GFR < 60 ml/min/1.73m<sup>2</sup>) and the presence of active or previous cancer. Bleeding events also recorded and classified according to International Society of Thrombosis and Hemostasis (ISTH) definition of bleeding [16]. Patients were followed up until discharge, death or April 20, 2020, whichever came first.

### *End points*

The primary endpoint of the study was hospital mortality and the secondary endpoint was safety.

### *Statistical analysis*

The cohorts of patients treated with P-LMWH and T-LMWH were compared on continuous variables using the t-test and on categorical variables using the  $\chi^2$ -test. Crude odds ratios of hospital mortality T-LMWH were obtained using univariate logistic regression analysis. In order to control for the different

proportion of patients receiving concomitant treatments in the two groups, adjusted odds ratios were estimated using multivariable logistic regression. All statistical analyses were performed using IBM SPSS, version 25 [16].

## Results

During the enrolment period, 351 patients were admitted to Castel San Giovanni COVID Hospital. Nine-ty-four patients were excluded from the analysis for the following reasons: 30 were discharged, 43 died and 17 were transferred to other care units (7 to Intensive Care Units outside our province) within 7 days. Three were not COVID-19 confirmed patients and 1 patient was in hemodialysis. The characteristics of the 257 patients included in the analyses are shown in Table 1.

One hundred-thirty-one (51%) received P-LMWH (4000 IU once a day at least 7 days) and 126 patients (49%) received T-LMWH (70-100/kg IU twice a day at least 7 days) treatment.

Two hundred-thirty-two patients (90.3%) received empiric antibiotic treatment (azithromycin 500 mg/day for at least 5 days), 237 patients (92.2%) received hydroxychloroquine (200 mg twice a day for at least 5 days), 146 patients (55.7%) received corticosteroids (methylprednisolone 1 mg twice a day i.v. or dexamethasone 40 mg i.v. once a day for 3 days followed by decreasing dosage), 236 patients (91.8%) received anti-retroviral therapy (darunavir/cobicistat 800 + 150 mg, 1 tablet for 7 days and/or lopinavir/ritonavir 200 + 50 mg, 1 tablet twice a day for 7 days). Twenty-five patients (9.5%) were eligible for treatment with tocilizumab (8mg/kg i.v. in a single or double dose). D-dimer was collected in 93 patients and the mean peak level was 5241 µg/ml, the median level was 1489 µg/ml.

All patients required oxygen therapy: 135 patients (52,5%) needed nasal cannula with oxygen flow  $\leq$  6 l/min or non-rebreather mask with oxygen flow from 10 to 15 l/min (Vent 1); 67 patients (26.1%) required non-invasive mechanical ventilation (Vent 2) and 55 patients (21.4%) required invasive mechanical ventilation (Vent 3).

Patients treated with P-LMWH and T-LMWH had similar demographic and clinical characteristics (Table 1). However, patients in the T-LMWH group received more frequently corticosteroids, hydroxychloroquine and tocilizumab.

### *Hospital mortality in patients treated with T-LMWH vs. P-LMWH*

During hospitalization 49 patients died (49/257, 19.1%). Hospital mortality was significantly lower in patients treated with T-LMWH (17/126, 13.5%) than in those treated with P-LMWH (32/131, 24.4%;  $\chi^2=4.98$ ,  $p = 0.02$ ). The crude odds ratio of mortality in patients treated with T-LMWH was OR=0.483, 95% CI 0.252-0.923,  $p<0.05$ .

When analyses were stratified by type of ventilation, patients with non-invasive mechanical ventilation (Vent-2) were those who mostly benefited from higher doses of heparin, since in these patients the mortality was lower than in those treated with P-LMWH (OR=0.099, 95% CI 0.028-0.354,  $p<0.001$ ). In the other

two types of ventilation, no significant differences in mortality rates were observed (Vent1: OR=0.853, 95% CI 0.309-2.355, p=0.759; Vent 3: OR=0.792, 95% CI 0.220-2.852, p=0.721. Multivaria-

ble linear regression was conducted to determine whether T-LMWH was more effective than P-LMWH in reducing hospital mortality after controlling for concomitant administration of corticosteroids, hydroxychloroquine and tocilizumab. The results indicate a significant 62.6% reduction in the mortality risk among those treated with T-LMWH (OR=0.374, 95% CI 0.177-0.792, p=0.01) (Table 2).

### *Safety of T-LMWH*

Two major and 1 minor bleeding episodes were recorded in group T-LMWH patients (3/126; 2.4 %): two patients had psoas muscle hematoma that required two packed red blood cells transfusion each and one patient had gluteus muscle hematoma that recovered spontaneously. No patient needed invasive treatment.

## **Discussion**

In this retrospective study, T-LMWH appeared to be the only treatment associated with a significant reduction of mortality, after controlling for the concomitant in-hospital treatment.

Very few data exist on the relationship between therapeutic doses of LMWH and the reduction of mortality rate in COVID-19 patients. In a recent retrospective study, Tang et al. treated COVID-19 patients with therapeutic doses of heparin, reporting a low mortality rate at 28 days' follow-up only in a subgroup of patients with SIC score  $\geq 4$  and D-dimer  $> 6$ -fold the upper limit [13]. During the first two weeks of our involvement in this emergency setting, D-dimer was not systematically recorded in all patients and no analysis could be carried out comparing this predictive parameter apart from few patients. In our study, patients who mostly benefited from therapeutic doses of heparin were those included in the Vent-2 group, who needed non-invasive mechanical ventilation with helmet CPAP (p<0.001).

We can speculate that in this specific clinical setting, the hypercoagulability state, which worsens the respiratory clinical picture, can benefit from the administration of therapeutic doses of heparin.

Conversely, in the mechanical ventilated patients' group (Vent-3), a prognostic advantage from heparin at therapeutic doses was not found, probably because in Intensive Care Unit (ICU) patients the disease is too advanced to benefit from the anti-inflammatory and anticoagulant activity of heparin. Our findings are consistent with a recent retrospective analysis of 150 COVID-19 ICU patients, in which a significantly high thromboembolic event rate was found also in those treated with anticoagulant therapy [18]. Probably in such an advanced state of the disease even a therapeutic dose of heparin may not improve the outcome [19].

SARS-Cov-2 infection induces diffuse endothelial inflammatory status due to direct viral infection of the endothelial cells in different organs of the human body [20]. Endothelial damage is the main determinant of microvascular dysfunction that led to vasoconstriction and subsequent organ ischemia, inflammation,

tissue edema and a pro-coagulant state [21]. Hypercoagulability state has been demonstrated in other viral infections [22, 23]. During the epidemic SARS-CoV-2, vascular endothelial damage, in both small and mid-sized pulmonary vessels, was observed and resulted in pulmonary infarction [24, 25]. In COVID-19 patients, the radiological features observed on CT angiography images suggest venous and arterial thrombosis [26] and also in autopsy studies, diffuse thrombosis of the peripheral small vessels has been found [27, 28]. Therefore, the protective effect of T-LMWH is probably due to the prevention/treatment of such thrombotic events, which is in keeping with the benefit of anticoagulation in a particular subset of patients with severe pulmonary involvement.

Apart from its anticoagulant properties, LMWH has an anti-inflammatory effect that reduces the uncontrolled activation of the cytokine cascade by inhibiting the release of IL-6 [29]. High serum IL-6 levels are observed in the advanced stages of COVID-19, significantly and directly correlate with the severity of the disease [30,31,32].

Lastly, no fatal bleeding occurred in the study population and only 2 out of 126 patients (1.6 %) had bleeding requiring transfusions, which indicates that this treatment is safe [33].

Limitations in current retrospective observational study include the potential selection bias and residual confounding associated with a small sample size. It is also possible that the improving learning curve may have produced a non-pharmacological benefit in the management of patients over time. However our observation maybe useful to stimulate prospective studies to evaluate which heparin dose could be optimal in the treatment of Covid-19 patients.

## Conclusion

In this retrospective study T-LMWH treatment reduces in-hospital mortality in COVID-19 patients and seems to be safe and well-tolerated. Future randomized clinical trials are still needed to confirm this observation.

## Declarations

**Funding** No specific funding has supported this study.

**Ethics approval** The Healthcare Directorate of Piacenza Local Health Authority approved the therapeutic protocol.

**Consent to participate** The Healthcare Directorate of Piacenza Local Health Authority granted a waiver of informed consent.

**Consent for publication** No consent for publication was requested, because data are presented in aggregate form and do not include sensitive data.

**Availability of data and material** Data are available upon request from the first author.

**Code availability** A commercial software, IBM SPSS version 25.0, was used for the data analysis.

**Authors' contributions** Marco Stabile, Daniela Aschieri contributed to the design and implementation of the research, Enrico Fabrizi and Paola Rucci to the statistical analysis of the results. Marco Stabile, Daniela Aschieri, Cristina Maestri, Luca Rosato, Paola Novara and Gianluca Lanati contributed to the writing of the first draft of manuscript. Gloria Taliani contributed to the writing and the interpretation of the results. All authors provided important intellectual contents and approved the final version of the manuscript and agreed to the publication of the manuscript. Special thanks to the members of the COVID-19 Castel San Giovanni Group: Francesco Andrani, Angelo Benedetti, Mara Bozzarelli, Carlo Cagnoni, Paolo Cambrini, Esther Centenara, Sara Chiesa, Mauro Codeluppi, Patrizia Colazzo, Donatella Covini, Alessandro Esposito, Angelo Mangia, Demostene Marifoglou, Massimiliano Mazzilli, Samantha Mazzocchi, Monica Pellegrini, Iacopo Pellegrino, Annamaria Pieri, Daria Sacchini, Tiziana Spezzano, Corrado Tosca, Lucia Torretta, Gioacchino Valenti, Ercole Zanotti.

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# Tables

**Table 1.** Demographic, clinical characteristics and treatment of the study population and comparisons between patients treated with P-LMWH (N=131) and T-LMWH (N=126).

	Overall sample	P-LMWH	T-LMWH	p-value
Variables	Mean $\pm$ SD or N(%)	Mean $\pm$ SD or N(%)	Mean $\pm$ SD or N(%)	
Age (years)	69.3 $\pm$ 10.7	69.4 (11.9)	69.2 (9.5)	0.836 <sup>o</sup>
Gender				0.583 <sup>^</sup>
Male	174 (67.7%)	91 (69.5%)	83 (65.9%)	
Female	83 (32.3%)	40 (30.5%)	43 (34.1%)	
Arterial hypertension	162 (63.0%)	83 (63.4%)	79 (62.7%)	0.913 <sup>^</sup>
Diabetes mellitus type 2	46 (17.9%)	25 (19.1%)	21 (16.7%)	0.613 <sup>^</sup>
Cardiovascular disease	44 (17.1%)	28 (21.4%)	16 (12.7%)	0.065 <sup>^</sup>
Dyslipidaemia	37 (14.4%)	19 (15.0%)	18 (14.3%)	0.879 <sup>^</sup>
Obesity	25 (9.7%)	12 (9.2%)	13 (10.3%)	0.754 <sup>^</sup>
Smoke	21 (8.2 %)	12 (9.4%)	9 (7.1%)	0.518 <sup>^</sup>
Chronic or paroxysmal atrial fibrillation	33 (12.8%)	17 (13.0%)	16 (12.8%)	0.966 <sup>^</sup>
Chronic obstructive pulmonary disease	22 (8.6%)	13 (9.9%)	9 (7.1%)	0.426 <sup>^</sup>
Chronic kidney disease	22 (8.6%)	14 (10.8%)	8 (6.3%)	0.207 <sup>^</sup>
History of cancer	18 (7.0%)	11 (8.4%)	7 (5.6%)	0.372 <sup>^</sup>
<b>IN-HOSPITAL TREATMENT</b>				
Azithromycin	232 (90.3%)	108 (82.4%)	114 (90.5%)	0.061 <sup>^</sup>
Hydroxychloroquine	237 (92.2%)	114 (87.0%)	123 (97.6%)	0.002 <sup>^</sup>
Corticosteroid	146 (56.8%)	44 (33.6%)	102 (81.0%)	<0.001 <sup>^</sup>
<i>Anti-viral therapy</i>				
Lopinavir/ritonavir and/or Darunavir/cobicistat	236 (91.8%)	118 (90.1%)	119 (94.4%)	0.191 <sup>^</sup>
Tocilizumab	25 (9.7%)	2 (1.5%)	23 (18.3%)	<0.001 <sup>^</sup>
<i>Oxygen support</i>				0.066 <sup>^</sup>
Vent 1	135 (52.5%)	78 (59.5%)	57 (42.5%)	
Vent 2	67 (26.1%)	28 (21.4%)	39 (31.0%)	
Vent 3	55 (21.4%)	25 (19.1%)	30 (23.8%)	

P-LMWH = Low Molecular Weight Heparin at prophylactic doses 4000 IU once a day; T-LMWH = Low Molecular Weight Heparin at therapeutic doses 70-100 IU twice a day. Vent 1: nasal cannula with oxygen

flow  $\leq$  6 l/min or non-rebreather mask with oxygen flow from 10 to 15 l/min; Vent 2: non-invasive mechanical ventilation; Vent 3: invasive mechanical ventilation. ^Chi-square test. °t-test.

**Table 2.** Odds ratio of mortality in patients treated with T- LMWH vs. P-LMWH, adjusted for concomitant drug intake. Results of multivariable logistic regression model.

	B	S.E.	p	OR	95% C.I.for OR	
					Lower	Upper
T- LMWH vs. P- LMWH	-0.983	0.382	0.010	0.374	0.177	0.792
Corticosteroids	0.763	0.375	0.042	2.145	1.029	4.474
Hydroxychloroquine	0.074	0.603	0.902	1.077	0.330	3.513
Tocilizumab	-0.878	0.780	0.260	0.416	0.090	1.918
Constant	-1.470	0.574	0.010	0.230		