Higher heparin dosages reduce thromboembolic complications in patients with COVID-19 pneumonia

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ABSTRACT

Coronavirus disease 2019 (COVID-19) is a new viral disease complicating with acute thrombophylic conditions, probably also via an inflammatory burden. Anticoagulants are efficacious, but their optimal preventive doses are unknown. The present study was aimed to compare different enoxaparin doses/kg of body weight in the prevention of clot complications in COVID-19 pneumonia. Retrospective data from a cohort of adult patients hospitalized for COVID-19 pneumonia, never underwent to oropharyngeal intubation before admission, were collected in an Internal Medicine environments equipped for non-invasive ventilation. Unfavorable outcomes were considered as: deep venous thrombosis, myocardial infarction, stroke, pulmonary embolism, cardiovascular death. Fourteen clinical thromboembolic events among 42 hospitalized patients were observed. Patients were divided into two group on the basis of median heparin dose (0.5 mg—or 50 IU—for kg). The decision about heparin dosing was patient by patient. Higher enoxaparin therapy (mean 0.62±0.16 mg/kg) showed a better thromboprophylactic action (HR=0.2, p=0.04) with respect to lower doses (mean 0.42±0.06 mg/kg), independently from the clinical presentation of the disease. Therefore, COVID-19 pneumonia might request higher enoxaparin doses to reduce thromboembolic events in hospitalized patients, even if outside intensive care units.

INTRODUCTION

Beyond the pulmonary manifestations, coronavirus disease 2019 (COVID-19), is characterized by a procoagulant state that predisposes to thrombosis in both arterial and venous districts in various organs. It has been reported an incidence of venous thromboembolism of 26% and an incidence of myocardial infarction of 7%–28%.[1 2] The pathogenesis of these coagulative disorders has not yet been completely clarified, but the excess production of proinflammatory cytokines, endothelial dysfunction, platelet activation, and stasis might play a leading role.[3]

Unless contraindicated, hospitalized patients with COVID-19 should be treated with low molecular weight heparin (LMWH).[4 5] Although intermediate LMWH dosage seems to be associated with lower incidence of mortality compared with standard dose prophylaxis,[6] clear information about the optimal dosage for thromboprophylaxis in patients with COVID-19 is still lacking, particularly outside intensive care units (ICUs).[3]

Aim of the present study is to compare thromboembolic outcomes of patients with COVID-19 pneumonia treated with different LMWH dosages in an Internal Medicine environment.

METHODS

Study design

The present is a cohort retrospective study, performed analyzing clinical records of 162 consecutive patients with COVID-19 pneumonia discharged by the Internal Medicine plus Infectious Disease Units of Santa Chiara Hospital in Trento (TN, Italy), and the High Intensity Internal Medicine Unit of "Santa Maria del Carmine" Hospital in Rovereto (TN, Italy), from March to April 2020. Both hospitals belong to the same medical district, sharing medical treatments.

Ethics

In this collection, data were examined and collected anonymously (non-sensitive data) and extracted as aggregated from the electronic health record. Patients had previously provided informed consent for this kind of treatment. This is a retrospective analysis of data routinely registered in our hospital database in compliance with EU GDPR—European Union General Data Protection Regulation; therefore, it does not need of additional permissions from the ethics committee.

Subjects and methods

Inclusion criteria were: evidence of interstitial pneumonia by at least a standard chest X-ray, diagnosis of COVID-19 infection with RNA detection of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) from nasal and/or pharyngeal swab specimens, disease duration <1 month, age >18 years.

Exclusion criteria were: oropharyngeal intubation before admission, patients assuming vitamin K antagonist or direct oral anticoagulants, cancer, chronic kidney disease stage >III, hepatic cirrhosis, heart failure New York Heart Association class >II, chronic obstructive pulmonary disease (COPD), recent surgical intervention or bone fractures, possibly pregnant women.

The grouped cardiovascular endpoint was: deep venous thrombosis (DVT), (non-) ST elevation myocardial infarction (NSTEMI, STEMI), pulmonary embolism, or cardiovascular death if derived from one of previous diagnoses. No autopsies were performed.

All subjects underwent a complete clinical examination. National Early Warning Score (NEWS2), a multiparametric score system, was calculated from respiratory rate, oxygen saturation, temperature, blood pressure, pulse/heart rate, hypercapnic respiratory failure, room air or supplemental O_2, level of consciousness, or new confusion.[7] C reactive protein (CRP), white blood cell (WBC) count, and platelets count, known as related to the clinical impact of the disease, have also been considered. In the first admission day, and whenever clinically indicated, a complete Doppler ultrasound scan of the lower extremities was performed.

Non-invasive ventilation was administered depending on the Brescia-COVID respiratory severity scale.[8] Oxygen level strategy was on clinical needs. All patients underwent to anticoagulant treatment that was defined as receiving enoxaparin as LMWH, with dosages based on body weight. Since an efficacy threshold of heparin treatment in this peculiar and new situation is not yet defined, prescribed LMWH dose/kg was, case by case, on the clinical judgment of every physician at the hospital admission. Dosages were never changed during the hospital stay until discharge or cardiovascular complications intervention. For safety evaluations, apart from the daily physical examination, patients were weekly monitored during the hospital stay with a complete blood cell count. After the discharge, LMWH therapy was suspended, and no additional monitoring was performed.

Statistical analyses

Statistical analyses were performed by PASW 18.0 for Windows. The normality of the distribution was assessed by the Shapiro-Wilk test.

Subjects were divided accordingly to the prevalence of cardiovascular thrombotic events. Student's t-test for unpaired data or Wilcoxon test was used as appropriate to compare variables between groups.

The Cox proportional hazard regression model was used to assess the relationship between cardiovascular endpoint and covariates. The regression model was constructed into two blocks: in a first block (enter) age, gender, body mass index (BMI), diabetes mellitus, hypertension, hyperlipidemia, smoking, previous cardiovascular disease, representing pre-existent clinical status, plus NEWS2 index, CRP, WBC, and platelets, regarding clinical presentation of the disease; heparin therapy was included in a second block (forward), and LMWH dosage was used here as a categorical variable, higher or lower its median value. Results have been displayed as HR and 95% CI.

Statistical significance was set at $p<0.05$.

Table 1 Clinical and biochemical profile of hospitalized patients with COVID-19 pneumonia, divided accordingly to the prevalence of vascular clot events

Variables	Patients with new clots (n. 14)—mean±SD	Patients without new clots (n. 28)—mean±SD	P value
Age (years)	68.1±16.1	62.3±15.2	NS
Male gender (%)	93	79	NS
Body mass index (kg/m^2)	27.0±3.0	26.7±4.1	NS
Diabetes mellitus (%)	14	11	NS
Arterial hypertension (%)	64	43	NS
Hyperlipidemia (%)	21	29	NS
Actual smoking (%)	21	07	NS
Obesity (%)	29	14	NS
History of CVD (%)	21	14	NS
NEWS2	7.4±2.56	7.29±2.0	NS
White blood cells count	7470±3300	9080±4400	NS
Platelets count (×10^3)	145±65	227±142	0.04
C reactive protein (mg/dL)	151±88	105±79.3	NS
NIV (%)	78.6	75.0	NS

COVID-19, coronavirus disease 2019; CVD, cardiovascular diseases; NEWS2, National Early Warning Score 2; NIV, non-invasive ventilation at least in a day during the in-hospital stay.

RESULTS

Retrospectively, 42 patients had complete data and fulfilled recruitment criteria, and they were considered in the present study. Table 1 shows clinical and biochemical characteristics of patients. Among them, 14 had an unfavorable cardiovascular outcome: 6 patients developed DVT, 1 NSTEMI, 1 STEMI, 4 pulmonary embolisms leading or not to oropharyngeal intubation, 2 cardiovascular deaths. Within these 14 patients, 9 patients were then transferred to ICU. No patients presented stroke. Regarding LMWH safety, neither newly detected anemia nor external bleeding events needing for hemotransfusion were recorded.

Enoxaparin (the only LMWH used) daily mean dosage was 0.52±0.16 mg/kg (or 52±16 IU/kg—min–max 0.25–1.1 mg/kg), with a median dosage that was 0.5 mg/kg. Heparin mean doses, up and down the median value, were, respectively, 0.62±0.16 and 0.42±0.06 mg/kg (mean±SD).

Figure 1 shows results of Cox proportional hazard regression model. With respect to lower doses, patients above median heparin dosage (0.5 mg/kg/day) were significantly more protected from cardiovascular accidents, independently from their age, gender, BMI, diabetes mellitus, hypertension, hyperlipidemia, smoking, previous cardiovascular disease, NEWS2 index, CRP, platelets count, and WBC values.

Enoxaparin therapy above its median value showed a better thromboprophylactic action, with an HR=0.2 and a p=0.04 with respect to lower doses, independently from the clinical presentation of the disease.

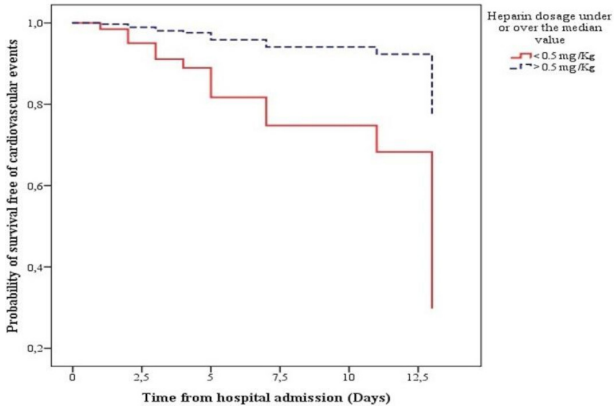

Figure 1 Effects of different doses of enoxaparin therapy (median dose 0.5 mg/kg/day–50 IU/kg/day) on the incidence of cardiovascular events during COVID-19 pneumonia. HR=0.21; 95% CI 0.05 to 0.93; p=0.04. COVID-19, coronavirus disease 2019.

DISCUSSION

The present retrospective study suggests that higher LMWH dosages seem to reduce clot accidents in non-ICU patients hospitalized for COVID-19 pneumonia. This effect was independent from clinical presentations of the disease.

A heparin dose above 0.5mg/kg/day (until 1.1 mg/kg/day), for a duration between 2 and 12 days, was demonstratedmore efficacious in the cardiovascular prevention duringthe hospital stay. No side effects were noted, probably both because patients were carefully selected avoiding several important comorbidities, and because mean enoxaparin dosages were less than a half of those used for acute clotting conditions therapy.

In medical routine, 0.4 mg/kg/day is normally used for thromboprophylaxis, whereas 1.5 mg/kg/day is used for DVT/pulmonary embolism therapy.[9] Looking at present quantitative results of higher LMWH doses on cardiovascular system, after 10 days of hospital stay, prevalence of clot accidents in lower doses LMWH users was 6.2 times higher, with respect to the patients using more LMWH. HR of cardiovascular events was 0.2 at the end of hospital stay among high LMWH doses users.

The present results are emphasized looking at the clinical environment of the hospital. In fact, all patients were in Internal Medicine facilities, where it is known that thrombosis risk is lower compared with environments as ICUs.[10] In ICUs, it has been reported that 31% of the COVID-19 admitted patients had thrombotic complications, with pulmonary embolism as the main cause of death.[11] Furthermore, differently to previous reports,[6] the present study only focused on clot-based endpoints, LMWH doses were standardized for body weight, and it was avoided recruiting patients with several important comorbidities as possible confounding factors as

Chronic Kidney Disease, hepatic cirrhosis, heart failure, COPD, all conditions difficult to be corrected into the statistic analysis with a retrospective approach.

In the statistical analysis, these results have been obtained after correction for several known factors deeply influencing clinical course of COVID-19 pneumonia.[12] Age, male gender together with pre-existent chronic diseases and poor clinical conditions at hospital entrance, obesity, and CRP are the factors influencing COVID-19 severity and have been considered in the present analysis.[13–15] In fact, the protective effect of more elevated LMWH dosages remains significant after the correction of results for clinical presentations.

Limitations

The present is a cohort retrospective study, whereas to finally assess efficacy a randomized control group is mandatory. Even if the study design and statistical analysis take into account several confounding factors of non-randomized controlled studies, it is always possible that unknown and/or uncontrolled factors (other therapies and/or clinical factors) might have played a role influencing the results. The small number of subjects makes difficult to draw definite conclusion about this important topic. Furthermore, our study was conducted in an Internal Medicine setting, and makes it arduous to extend the present results in other settings such as ICUs. Finally, any pathophysiological consideration about heparin improvements of COVID-19 pneumonia cardiovascular outcome is beyond the aims of the study.

CONCLUSION

Our results offer additional insights about the optimal LMWH dosage in non-ICU, hospitalized patients, for COVID-19 pneumonia. Higher LMWH dosages seem to be more effective than standard prophylaxis dosage in preventing serious clot based events. Randomized controlled trials are needed to confirm the present data.

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