Hospital survival associated with the use of thromboprophylaxis in patients with severe COVID-19 infection

Survival and thromboprophylaxis in COVID-19

Abstract

Introduction: It has been described that patients with severe or critical infection by COVID-19 suffer an inflammatory state that conditions a high thrombotic risk. However, there is little information on how to address thrombotic risk, coagulopathy, and anticoagulant therapy in these patients. **Objective**: To evaluate the use of thromboprophylaxis in patients with severe COVID-19 infection associated with longer survival. **Material and methods**: Retrospective cohort study, in a 2nd level hospital. 340 records of patients hospitalized for severe COVID-19 infection were reviewed, and 171 were included in the final analysis. Sociodemographic data, previous pathologies, days of hospital stay, respiratory parameters were evaluated; blood gas, hematic cytometry, DHL, C-reactive protein (CRP), antiviral treatment, thromboprophylaxis, use of steroids and use of antibiotics, the study variable was survival associated with the use of LMWH. Descriptive, inferential statistics, univariate and multiple models were used. **Results**: Advanced age, PaO2 / FiO2 index> 200 and high CRP were associated with a higher probability of death. And the greater the number of days of use of thromboprophylaxis; the higher the degree of protection. The PaO2 / FiO2 index> 200 (adjusted HR 0.270; 95%CI;. 0.100-0.727) and greater number of days with thromboprophylaxis (adjusted HR, 0.576; 95%CI;. 0.460 – 0.721) during hospitalization, were factors associated with hospital survival. **Conclusions**: In this study we found evidence to recommend the use of thromboprophylaxis from the first hours of admission in adult patients with severe COVID-19 as long as there are no contraindications for it, due to the increase in hospital survival.

KEY WORDS: Thromboprophylaxis, LMWH, SARS-CoV-2, survival, Severe COVID-19 infection.

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Introduction

It has been described that patients with severe or critical infection by COVID-19 suffer an inflammatory state that conditions a high thrombotic risk.[1,2,3] However, there ,is little information on how to address thrombotic risk, coagulopathy, and a,nticoagulant therapy in these patients.[4]

The host's abnormal inflammatory response to the infection and the cytokine storm may play a crucial role in the endothelial dysfunction that results in a hypercoagulable state.[5]

According to recent data, the risk of thromboembolic events in hospitalized COVID-19 patients increases significantly, which necessitates thrombosis prophylaxis with low molecular weight or unfractionated heparin (LMWH) (UHF).[6] The International Society on Thrombosis and Haemostasis (ISTH) and the American Society of Hematology (ASH) currently recommend that all hospitalized patients for COVID-19 receive thromboprophylaxis with LMWH.[7] This is recommended in place of heparin to reduce contact from healthcare providers.[8] Similarly, the American College of Cardiology recommends that patients hospitalized for COVID-19 with respiratory failure, comorbidities, or who require intensive care should receive thromboprophylaxis, preferably LMWH.[9] The use of heparin was even associated with a reduction in mortality 64.2 vs 40.0% in patients with COVID-19 and induced septic coagulopathy or in those with a baseline D-dimer level > 3 mg,[10] which suggests that thromboembolism prophylaxis is essential in the treatment of COVID-19.[11,12] The objective of this study is to evaluate the use of thromboprophylaxis in patients with severe COVID-19, associated with better survival, without clinically important bleeding.

Materials and methods

Retrospective-comparative cohort study of the month of May 2020 in which the files of hospitalized patients in the emergency area of the HGZ 24 of the IMSS were analyzed. The inclusion criteria were: diagnosis of COVID-19 using real-time polymerase chain reaction (RT-PCR) test,[12] older than 18 years, without distinction of sex, with severe infection criteria, with a report on whether or not they received treatment of thromboprophylaxis with LMWH from the first hours after admission and with complete laboratory results (Leukocytes, lymphocytes, hemoglobin, platelets, albumin, LDH, CPK and CPK MB).

Severe COVID-19 infection was defined as: confirmed case with fever (≥ 37.5º C), respiratory symptoms and tomographic evidence of pneumonia, with dyspnea or respiratory failure.[13] Lymphocytopenia was defined as values less than 800/mm3.[14,] Major bleeding was defined according to the Consensus criteria of the International Society of Thrombosis and Haemostasis.[15]

LMWH was administered under the following scheme: (LMWH-Enoxaparin) 1mg/kg weight every 12 hours SC; and it was adjusted following the glomerular filtration rate (GFR) according to the following scheme: for GFR <30ml/min: 40 to 60mg every 24 hours. SC in> 75 years 0.75 mg/kg every 12 hours.

The following were analyzed: sociodemographic data, presence of previous pathologies, days from the onset of symptoms to medical care, length of hospital stay, respiratory parameters, arterial blood gas, hematic cytometry, DHL, C-reactive protein (CRP), antiviral treatment, thromboprophylaxis, use of steroids and antibiotics. The study variable was hospital survival associated with the use of thromboprophylaxis. The risk of venous thromboembolism (VTE) was calculated using the Padua prediction score (PPS);[14,15] the hemorrhagic one, by the ORBIT scale.[16,17]

The sample size was computed with the formula of a proportion with a confidence level of 95%, an observed frequency in mortality of at least a 10% difference

between the effectiveness of the drug in users and non-users of thromboprophylaxis and a limit of 5% confidence. The sample size was 168 files.

The statistical analysis included descriptive statistics for qualitative variables: frequencies and averages are reported. For the quantitative variables, the Kolmogorov – Smirnov normality test was applied, and the summary measures were mean and standard deviation (if they had a normal distribution); otherwise, median and range were reported.

Two groups were considered: survivors and non-survivors. From this point, the inferential statistics for qualitative variables were applied chi square or Fisher's exact test. For the quantitative ones, if they had a normal distribution, the Student's t-test was applied; if they did not present normality, the Mann–Whitney U test.

To explore the risk factors associated with in-hospital survival, bivariate and multivariate models were used. When considering the total number of deaths in our study, and to avoid an overfitting in the model, six variables were chosen for multivariate analysis based on previous findings and clinical limitations that calculated relative risks (RR), Absolute risk reduction (ARR) and Number Needed to Treat (NNT).

Previous studies indicated an association between survival and the use of thromboprophylaxis adjusted for age and previous pathologies,[17,18] so the use of thromboprophylaxis, steroids, previous diseases, age, lymphocytes and PaO2/ FiO2 ratio were selected as variables for the multivariate model and for the Kaplan–Meier estimator. Their study was considered according to the time of use of prophylaxis, since there are reports that show that the effect on mortality seems to be ≥ 5 days.

Variables were excluded from the bivariate analysis if their differences between groups were not statistically significant, if their precision was not confirmed (for example, imprecise drug doses or treatment days), or if the number of events was too small to calculate relative risks. Those variables that did meet criteria were included in the Cox Proportional Hazards Model. For data processing, the

statistical software SPSS V.24 was used and a value of p≤ 0.05 was estimated as statistically significant.

The study adhered to the Declaration of Helsinki, the basic bioethical principles, the General Health Law and the Regulation of the General Health Law on Research for Health, which in its article 17 classifies this research with minimal risk. The institutional registration F-2020-3511-125 was granted.

Results

During the study period, 558 files were identified, of which 320 were reviewed to finally identify 171 that met the inclusion criteria. Of these, 153 received thromboprophylaxis (89%) and 18 did not (11.1%); the age was 58.5 ± 13.7 years; 123 were men (72%); the most frequent symptoms were cough (64%), fever (62%), and dyspnea (60%). See Table 1.

Of the comorbidities, arterial hypertension and diabetes mellitus were the most frequent (37% and 34% respectively); 46 were current smokers (26.9%), see table 1. 69 patients presented moderate risk and 53 high risk according to the NEWS-2 scale (40.4% and 31% respectively) (Table 2). 99% of the patients had a high thrombotic risk (PPS ≥ 4), while in 94.2% of the sample the bleeding risk score was low (ORBIT <2). At admission, laboratory tests showed that 10 patients had creatinine clearance below 30 ml/min (5.8%) (Table 2).

Only 145 cases had complete laboratory studies; of these, 70 had lymphocytopenia (49%). The initial mean lymphocyte count was significantly higher in survivors than in non-survivors (1300 vs 860 respectively); in the subsequent count, stable levels were maintained in survivors and severe lymphocytopenia was observed in non-survivors. CRP and CPK levels were clearly elevated in deceased patients compared to survivors throughout the clinical course and increased with deterioration of the disease. In both groups, HDL remained high, although with a higher elevation for the deceased (Table 3).

The mean time from hospital admission to discharge was 8.5 days (IQR 2–31), the mean time to death was 6 (IQR 1–50). 36 patients (21%) required invasive mechanical ventilation, of which 36 (100%) died. The median time from the onset of the disease to invasive mechanical ventilation was 12 days (IQR 0-21) and that of days on ventilation was 3 (IQR 1-21) (Table 3). Sepsis was the most frequent complication in 16 patients (9.3%), followed by renal failure in 15 (8.8%) and neurological complications in 6 (3.5%). The frequency of complications was higher in non-survivors 31 (18%) than in survivors 6 (3.5%).

81 patients died during hospitalization and 90 were discharged due to improvement (mortality of 47.3%). 158 received thromboprophylaxis during their hospitalization (92.4%) and of these, 152 took it from the first hours of admission (88.9%). Of 158 people who received LMWH, 70 (44.3%) died, compared with 11 of the 13 (84.6%) who did not receive it (RR = 0.52, 95% CI: 0.39–0.70, p = 0.007) RRR = .47% ARR = 40.3% (95% CI: 26.9–68.27) NNT = 2.4 (95% CI; 1.4–7.8).

In the univariate analysis, the probabilities of in-hospital death with the use of LMWH were significantly lower compared to those in patients who did not receive it. Age over 60, BMI over 30, leukocytosis, lymphocytopenia, elevated CPK, PaO2 / FiO2 less than 300, and high CRP were associated with death. The use of steroids and thromboprophylaxis were factors associated with survival (Table 4). 119 patients with complete data for all variables were included in the multiple logistic regression model (51 non-survivors and 68 survivors). We found that advanced age, PaO2 / FiO2 index <200, and high CRP were associated with a higher probability of death. The greater the number of days of use of thromboprophylaxis, the degree of protection increases (Table 4). In the Kaplan–Meier estimator, a longer survival time was observed among thromboprophylaxis users (Figure 1).

In the Cox Proportional Hazards Model, the variables were included: age, SAH, PaO2 /FiO2, use of steroids and use of thromboprophylaxis, and days of LMWH use. The analysis revealed that the PaO2 / FiO2 index> 200 (adjusted HR .270; 95% CI .100 -.727) and a greater number of days with thromboprophylaxis

(adjusted HR, .576; 95% CI; .460 – .721) during the hospitalization were factors associated with hospital survival (Table 5, Figure 2).

Discussion

The disease caused by the new coronavirus COVID-19 predisposes to both arterial and venous thromboembolic diseases, which increases the risk of mortality in hospitalized patients. In our study, the use of thromboprophylaxis with LMWH at therapeutic doses demonstrated a statistically significant reduction in mortality at 28 days in patients hospitalized for severe COVID-19, with few side effects and few bleeding events. No bleeding or thrombosis events were recorded. Finally, the frequency of mortality was high with respect to what has been published worldwide.

In retrospect, Ning Tang et al.[18] analyzed 449 records of patients hospitalized for severe COVID-19 at Tongji Hospital at Huazhong University of Science and Technology in Wuhan from January 1 to February 13. They studied 28-day mortality among heparin users and non-users, risk of coagulopathy, and D-dimer levels in 94 of 97 patients treated with LMWH (40-60mg enoxaparin / d) and five more with unfractionated enoxaparin. (10000-15000 U / d). Ning et al. found no differences in mortality at 28 days between users versus 29.7%. p = 0.910); however, they did observe divergences in the stratified analysis. They reported an association between lower mortality in patients with heparin treatment, observing an approximate 20% reduction in mortality in patients at high risk of thrombosis. These results support our findings where lower mortality was identified among LMWH users compared to non-users. We found a mortality in the group treated with heparin of 44.3% (70 subjects) compared to the group of non-LMWH users that was 84.6% (11 subjects). Although our sample presented higher mortality than the study population of Ning et al., Our population presented a higher percentage of concomitant diseases, such as diabetes mellitus in 33% compared with 20% of

the Ning population, in addition to other factors that may contribute to increasing this risk.

For their part, Stessel et al.,[19] in their retrospective cohort study, observed a decrease in mortality at 30 days — which was from 39.13% to 3.85% —with the use of 3800IU SC-based nadroparin thromboprophylaxis every 12 hours. Gasometrical clinical parameters were evaluated and severity scales such as SOFA and Apache II were applied. These findings also support the theory of greater protection for the use of prophylactic thromboprophylaxis in patients hospitalized for severe COVID-19.

On the other hand, Fogarty et al.[20] observed in their study that Caucasian patients with COVID-19, who rarely receive low-molecular-weight heparin thromboprophylaxis, develop overt disseminated intravascular coagulation (DIC). Like other studies,[21] they suggest that race and ethnicity have important effects on thrombotic risk; in particular, epidemiological studies have shown that the incidence of venous thromboembolism (VTE) is approximately 3-4 times lower in Chinese compared to Caucasians.

The dose of LMWH in thromboprophylaxis for COVID-19 infection is still controversial. Due to the high risk of VTE in severely to critically ill COVID-19 patients, adequate VTE prophylaxis appears to be an important part of the management of these patients. Many critically ill patients have high Padua scores and it is associated with lower mortality rates when given LMWH or heparin. Aryal et al.[22] suggest that all severe COVID-19 patients undergo weight-based thromboprophylaxis. Although the use of standard-dose thromboprophylaxis in hospitalized patients is acceptable, the high incidence of VTE (25-31%) suggests that higher doses, i.e. enoxaparin 0.5 mg/kg twice daily, may be more appropriate.[23,24] Since thrombocytopenia in COVID-19 patients may be less profound than in other sepsis syndromes, prophylactic anticoagulation is likely feasible.

Anticoagulation treatment in patients with severe COVID-19 appears to be associated with better outcomes. COVID-19 infected patients, whether hospitalized or outpatient, are at high risk for venous thromboembolism, therefore early and prolonged drug thromboprophylaxis with low molecular weight heparin is highly recommended.[25]

Empirical anticoagulation should be seriously considered in patients with high suspicion of VTE, but who cannot undergo imaging, in the absence of contraindications to anticoagulant therapy. Patients with physical findings consistent with superficial DVT should also undergo therapeutic anticoagulation. Helms et al.[26] found that despite prophylactic anticoagulation, a large number of ARDS COVID-19 patients developed life-threatening thrombotic complications; therefore, higher anticoagulation goals have been suggested.[27]

Our study has several limitations such as the type of retrospective cohort design which was the most appropriate and immediate to obtain the results base on which subsequent decision-making in our hospital would be based, due to the scarce information at the time on guidelines for prophylactic hospital management in critically ill patients due to COVID-19. Our work also presented different confusing variables that were difficult to control, and which could have influenced the results and the wide margin of mortality in our setting, as well as the multiple pathologies of the patients influenced the outcome. On the other hand, the sample size is small: it only involved patients from one hospital and may not be applicable to patients in other latitudes. A prospective study is needed to confirm the effectiveness and safety of the use of LMWH and the doses for this new SARS-Cov-2 virus.

Conclusions

The use of thromboprophylaxis with LMWH — from the first hours after hospital admission of patients with severe COVID-19 infection — was shown to improve survival in the HGZ 24 of the IMSS. The risk of having a longer survival with the

use of thromboprophylaxis is 48% compared with patients who do not receive it. It is necessary to treat 2 patients to avoid a fatal outcome in at least one of them.

Conflict of interests

The authors declare that they have no conflict of interest.

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Ethical responsibilities

Protection of people and animals. The authors declare that no experiments were performed on humans or animals for this research.

Confidentiality of the data. The authors declare that they have followed the protocols of their work center regarding the publication of patient data.

Right to privacy and informed consent. The authors declare that no patient data appear in this article.

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