International Journal of Basic & Clinical Pharmacology
Bhuta MS et al. Int J Basic Clin Pharmacol. 2022 Sep;11(5):460-464
http://www.ijbcp.com
pISSN 2319-2003 | eISSN 2279-0780

DOI: https://dx.doi.org/10.18203/2319-2003.ijbcp20222143

Original Research Article

Comparative study between effectiveness of low molecular weight heparin injection and unfractionated heparin in terms of morbidity and outcome in COVID-19 cases

Meet S. Bhuta, Sapna D. Gupta*

Department of Medicine, SVP Hospital, Smt. NHL Municipal Medical College, Ahmedabad, Gujarat, India

Received: 25 July 2022
Revised: 15 August 2022
Accepted: 16 August 2022

***Correspondence:**
Dr. Sapna D. Gupta,
Email: sapna_gupta76@yahoo.com

ABSTRACT

Background: The novel coronavirus 2019 presented a variety of disease spectrums that range from asymptomatic to sepsis with multi-organ dysfunction and death. One of the mechanisms being a hypercoagulable state with micro and macro-circulatory thrombosis is found in critically ill COVID-19 patient with ARDS with pathology consistent with a vascular occlusive aetiology of respiratory failure rather than more classic finding of ARDS. Venous thromboembolism, MI, acute peripheral arterial thrombosis is seen in COVID-19. Endothelial cells dysfunction induced by infection causing excess thrombin generation, fibrinolysins shutdown, hypoxia inducible transcription factor dependent signalling pathways, increasing blood viscosity leading to Hypercoagulable state. Early application of anticoagulant therapy in severe COVID-19 was suggested for improving outcome in patients with elevated d-dimer. Aim of study was comparing effectiveness of LMWH with unfractionated heparin in outcome of COVID-19.
Methods: This retrospective observational study including 400 patients meeting inclusion criteria were divided 2 groups out of which 200 patients were treated with inj. LMWH and other 200 were treated with injection heparin and various parameters were compared. A probability value (p value) of less than or equal to 0.05 was considered statistically significant.
Results: Death rate is seen lower with LMWH in critically ill patients with high discharge rate with minimal lab parameter derangement and high efficacy to lower down inflammatory markers (LDH, ferritin, CRP, D-dimer, ESR) in comparison to unfractionated heparin.
Conclusions: Early use of LMWH may be beneficial for the outcome.

Keywords: COVID-19 pneumonia, Hypercoagubility, LMWH, Unfractionated heparin

INTRODUCTION

The novel CORONAVIRUS 2019 presented a variety of disease spectrums that range from asymptomatic to sepsis with multiorgan dysfunction (MODS) and death.[1] Proposed mechanism for MODS in COVID-19 is multifactorial ,one of them being a hypercoagulable state with micro and macro-circulatory thrombosis.[1,2] A prothrombotic coagulopathy is commonly found in critically ill COVID-19 patient with ARDS.A unique feature of COVID-19 respiratory failure is relatively preserved lung compliance and high alveolar-arterial oxygen gradient, with pathology consistent with a vascular occlusive etiology of respiratory failure rather than the more classic finding of ARDS. Venous thromboembolic events, MI, acute peripheral arterial

thrombosis are seen in COVID-19.[2] The dysfunction of endothelial cells which is induced by infection can results in excess thrombin generation and fibrinolysins shutdown, which leads to Hypercoagulable state.[3] In addition, the hypoxia found in severe COVID-19 can stimulate thrombosis through not only increasing blood viscosity, but also hypoxia inducible transcription factor dependent signalling pathways.[2] Higher levels of D-dimer, fibrin degradation product (FDP) level, longer prothrombin time and activated partial thromboplastin time, decreased platelet count, lymphopenia suggesting DIC are commonly seen in patients with COVID-19 pneumonia.[4] Elevated D-dimer (above 1 ug/ml) is a strong and independent risk factor for death in this population.[4] Monitoring PT, D-dimer, platelet count and fibrinogen can be helpful in determining prognosis in COVID-19.[4] Ability of SARS-COV-2-S1 RBD to bind with pharmaceutical heparin leads to significant structural changes. Moreover, molecules of basic amino acid residues, known to contribute heparin binding domain are solvent and accessible on SARS-COV 2-S1 RBD surface and form continuous patch that is suitable for heparin binding.[5] In view of high mortality of severe coronavirus disease 2019 (COVID-19), application of heparin in COVID-19 has been recommended by some expert consensus because of risk of DIC and venous thromboembolism. LMWH also protects critically ill patients against venous thromboembolism. In addition, LMWH has been shown to have anti-inflammatory properties which may be an added benefit in COVID-19 infection where proinflammatory cytokines are markedly raised. Occlusion and microthrombosis formation in pulmonary small vessels of critically ill patients in COVID-19.[6,7] Early application of anticoagulant therapy in severe COVID-19 was suggested for improving outcome. Anticoagulant therapy mainly LMWH appears to be associated with better prognosis in severe Covid 19 in patients with elevated d-dimer.[6,7] A different dose of heparin would be required to produce aPTT ratio of 1.5 times the control value.[8]

METHODS

The present study was conducted in a tertiary care hospital (SVP hospital Ahmedabad Gujarat), From November 2020 to November 2021. The study design is retrospective observational study. Total 400 patients were taken in study meeting inclusion criteria.2 groups out of which 200 patients were treated with inj. LMWH (0.6 cc-sc-bd for weight >50 kg, 0.4 cc-sc bd <50 kg weight) and other 200 were treated with inj. Heparin (5000 iu-iv 6 hourly/25000 iu/50cc iv heparin infusion with aPTT monitoring). All patients were explained about the study. After the institutional review board clearance, the study was started. All data were collected from HIS (software) and case record form. Detailed history, clinical examination and relevant investigations, treatment, complication and outcome according to a predefined diagnostic algorithm were carried out. The patients were followed throughout their hospital stay till discharge or death. The data obtained was coded and entered into Microsoft Excel Worksheet. both groups were compared in different parameter (e.g., total duration of hospital stay, effect on levels of inflammatory markers, discharge rate, death rate etc.), statistical analysis was carried out using statistical package for social sciences (SPSS) version 20.0 for Windows (IBM Corporation, Armonk, NY). The categorical data was expressed as rate, ratio and proportion and Chi-Square or Fisher's exact test was used to compare the data, whichever was applicable. The continuous data was expressed as mean, SD (standard deviation) and the comparison was done using unpaired t test. To estimate the risk factors for death, multinomial regression analysis was applied. A probability value (p value) of less than or equal to 0.05 was considered statistically significant. Group 1: COVID-19 positive patient meeting the inclusion criteria who received unfractionated heparin (Dose: 5000 IU iv 6 hourly or 25000 IU in 50 cc NS iv @ 2.0 ml/hr with aPTT monitoring, infusion rate adjusts according to target aPTT double than controlled value). Group 2**:** COVID-19 positive patients meeting the inclusion criteria who received LMWH (Dose: LMWH 0.6 ml sc 12 hourly if weight >50 kg or 0.6 ml sc 12 hourly if weight <50 kg).

RESULTS

Total 400 patients were included in the study. 200 patients were given ultra-fractionated heparin and 200 patients were given LMWH. Both groups were comparable in terms of age, sex comorbidity and presenting complains.

Table 1: Demography and baseline characteristic of study population (n=200).

Variables	LMWH, N (%)	Heparin, N (%)	P value
Mean age	55.99±15.39	63.15±14.9(	<0.0001
Sex			
Male	122 (61)	132 (66)	0.2983
Female	78 (39)	68 (34)	0.2983
Co-morbidity			
Hypertension	81 (40.5)	110 (55)	0.0037
DM2	80 (40)	90 (45)	0.3125
Hypothyroidism	20 (10)	14 (7)	0.2801
IHD	9 (4.5)	26 (13)	0.0026
CKD	2(1)	8 (4)	0.0548
Others	<1	<1	
Clinical features			
Fever	158 (79)	144 (72)	0.1031
Cough	89 (44.5)	102 (51)	0.1936
Difficulty in breathing	65 (32.5)	32 (16)	0.0001
Headache	29 (14.5)	52 (26)	0.0042
Sore throat	10 (5)	19 (9.5)	0.0818
Asymptomatic	9 (4.5)	1 (<1)	0.0104
Mean duration of symptoms	4.44±2.75	4.43±1.90	0.9663

Table 2: Comparison of lab parameters between two groups (n=200).

Variables	LMWH	Heparin	P value
Total leucocyte count	6,442.1±2,645.5	6,501.5±2,801.4	0.8275
Platelet count	2,50,925±98,628	2,51,820±1,14,859	0.9334
LDH	331.68±161.85	403.24±305.07	0.0036
Ferritin	332.50±315.42	374.04±348.07	0.2118
CRP	39.34±60.40	23.13±50.96	0.0039
D-dimer	1.29±2.03	2.78±1.10	<0.0001
ESR	43.20±32.62	48.13±33.70	0.1379
PCT	0.15±0.24	0.47±1.35	0.0011
Creatinine	0.91±0.71	1.58±0.55	<0.0001
GGO in HRCT chest N (%)	140 (70)	170 (85)	0.0003
CT severity score	14.23±2.22	17.11±3.12	<0.0001

Table 3: Average duration of hospital stay (n=200).

Duration (days)	LMWH, N (%)	Heparin, N (%)	P value
<7	62 (31)	100 (50)	0.0001
7-14	81 (40.5)	79 (39.5)	0.8414
14-21	35 (17.5)	16 (8)	0.0043
>21	22 (11)	5 (2.5)	0.0007

Table 4: Comparison discharge and death rate (n=200).

Variables	LMWH, N (%)	Heparin, N (%)	P value
Discharge	188 (94)	95 (47.5)	0.00001
Death	12 (6)	105 (52.5)	0.00001

All cases were of severe COVID-19 in study at presentation. Most common age group was 51-60 year followed by 61-70 year in LMWH group and 51-60 year followed by 61-70 year in unfractionated heparin group.

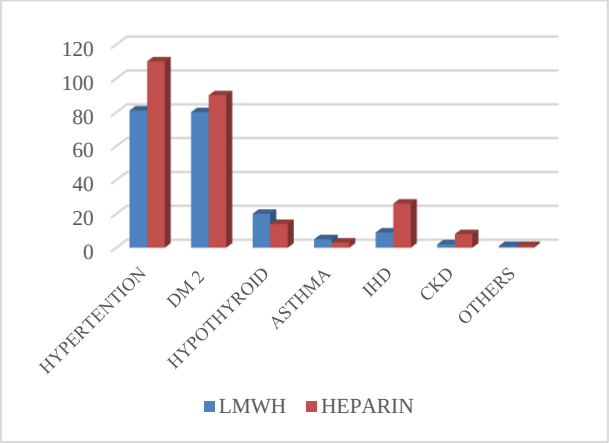

Figure 1: Comorbidity of study population.

Most common symptoms were fever (158/200) followed by cough (89/200) in the LMWH group and fever (144/200) followed by cough (102/200) in the unfractionated heparin group. Maximum number of patients presented to hospital within 3 days LMWH group and 4 days in unfractionated heparin group. Patients with Decreased platelet counts and severe anaemia during hospital stay were significantly high with unfractionated Heparin in comparison to LMWH. Higher inflammatory markers (LDH, Ferritin, CRP, D-dimer, ESR) and electrolyte derangements are seen more in group with unfractionated heparin than LMWH.

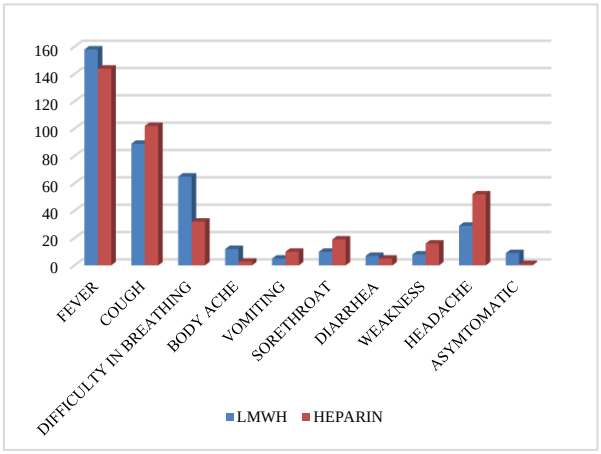

Figure 2: Presenting symptoms of COVID-19.

Ground glass opacities on X-ray and higher CT severity were seen more in group with unfractionated heparin than LMWH. Duration of hospital stay was higher in LMWH (mean day 14) group than unfractionated heparin (mean day 9). Discharge rate was higher with LMWH group (92%-184/200 patients) in comparison with unfractionated Heparin (47%- 95/200 patients). Mortality

is significantly low in patients receiving LMWH in comparison to unfractionated Heparin.

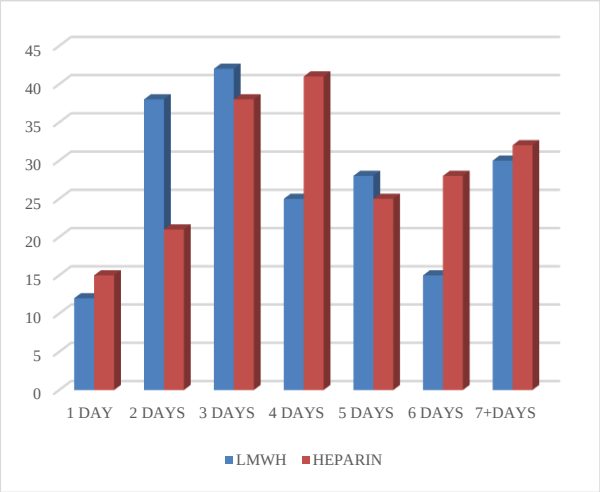

Figure 3: Average duration of symptoms on presentation.

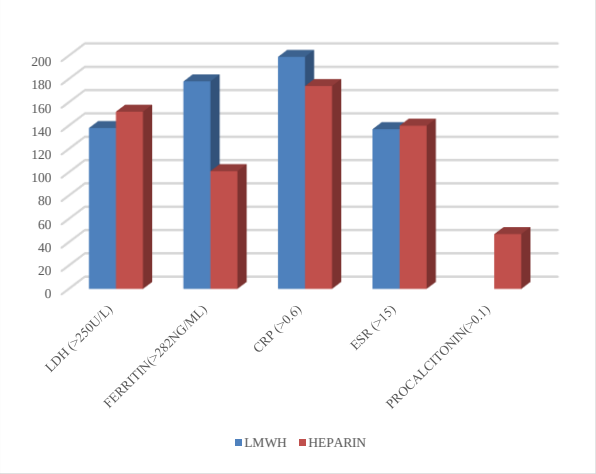

Figure 4: Comparison inflammatory markers.

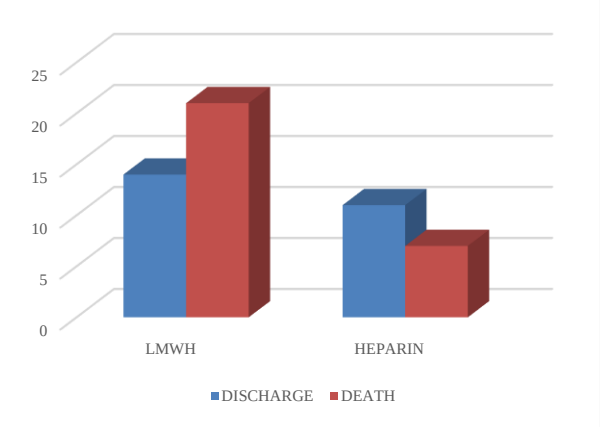

Figure 5: Average days of hospital stay in discharged and expired patient in two groups.

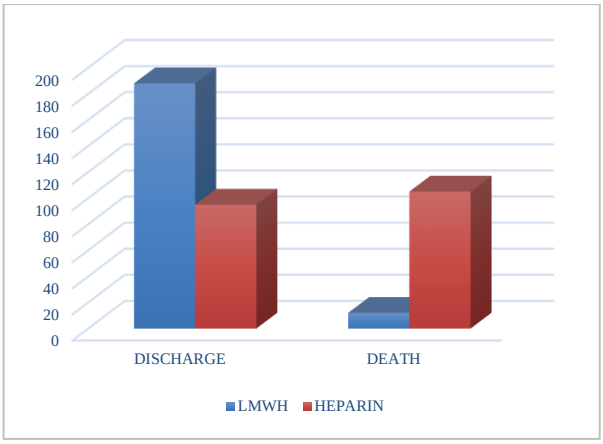

Figure 6: Final outcome in two groups.

DISCUSSION

This retrospective study highlights interesting differences in the outcomes associated with the administration of LMWH vs. unfractionated heparin in COVID -19 patients. LMWH ($t_{1/2}$: 4.5-7 hr) is easier to give in terms of dose calculation, administration and not required monitoring of aPTT, less chances of bleeding, but it is costly and in altered renal function test it cannot be given. Unfractionated Heparin ($t_{1/2}$: 1-2 hr) is cheaper, can be given in altered renal function test, but needs proper dose calculation, intravenous administration, higher chances of bleeding and required frequent aPTT monitoring.[8] In our study we found that the LMWH cohort had favourable outcomes compared to the unfractionated Heparin cohort, in the setting of anticoagulant treatments for COVID-19 without increasing risk of bleeding which is comparable to previous study.[9] We have observed the outcome is more favourable in LMWH group, but at the same these patients were comparatively less severe in terms of covid disease and value of inflammation markers .The Heparin group had renal dysfunction along with other comorbidities, that can add to poor outcome. In Heparin group, presentations were late by almost 24 hours, which again led them prone to more complications. Longer duration of hospital stay was seen with LMWH groups suggesting more survival of patients in LMWH group. In retrograde data collection, it was found that inflammatory markers derangement was significantly higher in Heparin group. Due to such findings, it becomes mandatory for clinicians to ensure full anticoagulation which is measurable by aPTT target while using Heparin whereas in case while using LMWH, we can't measure the level of anticoagulation. Due to the relatively short time period of this study, bias due to changing eligibility criteria over time is unlikely because the medication codes to identify the cohorts of patients who were administered with LMWH and unfractionated Heparin has remained constant over the course of the study. Overall, the results of this study motivate future studies to investigate biological mechanisms underlying differences in the outcomes and enable the development of a more

efficacious standard of practice in regards to administration of anticoagulants in COVID-19 patients.

Limitations

Limitations of current study were cases were randomly selected and divided in two groups. All cases were of severe disease. The results of this study may be influenced by unmeasured confounding variables which are not recorded in this dataset. In addition, there may be misclassification bias if the anticoagulant medications for some of these patients were entered incorrectly into the study. These cases were collected during first wave of covid in Gujarat, India. As we all know that disease presentation varies in each wave, so findings of these study need to be evaluated each time with different clinical scenario and common consensus cannot be made.

CONCLUSION

Death rate is seen lower with LMWH in critically ill patients with high discharge rate with minimal lab parameter derangement and high efficacy to lower down inflammatory markers in comparison to unfractionated Heparin.so we emphasise that early use of LMWH may be beneficial for the outcome.

ACKNOWLEDGEMENTS

Authors would like to thank Dr. Anjali Patel and Dr. Harsh Joshi and all other departmental members for their support.

Funding: No funding sources
Conflict of interest: None declared
Ethical approval: The study was approved by the Institutional Ethics Committee

REFERENCES

1. Yang X, Yu Y, Xu J, Shu H, Liu H, Wu Y, et al. Clinical course and outcomes of critically ill patients with SARS-CoV-2 pneumonia in Wuhan, China: a single-centered, retrospective, observational study. Lancet Resp Med. 2020;8(5):475-81.
2. Lin L, Lu L, Cao W, Li T. Hypothesis for potential pathogenesis of SARS-CoV-2 infection–a review of immune changes in patients with viral pneumonia. Emerg Microbes Infect. 2020;9(1):727-32.
3. Thachil J, Tang N, Gando S, Falanga A, Cattaneo M, Levi M, et al. ISTH interim guidance on recognition and management of coagulopathy in COVID-19. J Thromb Haemostat. 2020;18(5):1023-6.
4. Tang N, Li D, Wang X, Sun Z. Abnormal coagulation parameters are associated with poor prognosis in patients with novel coronavirus pneumonia. J Thromb Haemostat. 2020;18(4):844-7.
5. Mycroft-West C, Su D, Elli S, Li Y, Guimond S, Miller G, et al. The 2019 coronavirus (SARS-CoV-2) surface protein (Spike) S1 receptor binding domain undergoes conformational change upon heparin binding. J Thromb Haemostat. 2021;12:132-8.
6. Li J, Li Y, Yang B, Wang H, Li L. Low-molecular-weight heparin treatment for acute lung injury/acute respiratory distress syndrome: a meta-analysis of randomized controlled trials. Int J Clin Exp Med. 2018;11(2):414-22.
7. Tang N, Bai H, Chen X, Gong J, Li D, Sun Z. Anticoagulant treatment is associated with decreased mortality in severe coronavirus disease 2019 patients with coagulopathy. J Thromb Haemostat. 2020;18(5): 1094-9.
8. Heparin sodium, for intravenous use. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/017029s140lbl.pdf. Accessed on 20 September 2021.
9. Laporte S, Liotier J, Bertoletti L, Kleber FX, Pineo GF, Chapelle C, et al. Individual patient data meta-analysis of enoxaparin vs. unfractionated heparin for venous thromboembolism prevention in medical patients. J Thromb Haemostat. 2011;9(3):464-72.

Cite this article as: Bhuta MS, Gupta SD. Comparative study between effectiveness of low molecular weight heparin injection and unfractionated heparin in terms of morbidity and outcome in COVID-19 cases. Int J Basic Clin Pharmacol 2022;11:460-4.