Research, Society and Development, v. 11, n. 10, e375111031821, 2022
(CC BY 4.0) | ISSN 2525-3409 | DOI: http://dx.doi.org/10.33448/rsd-v11i10.31821

The Use of Low Molecular Weight Heparin Among COVID-19 Patients in Udayana University Hospital, Bali

O uso de heparina de baixo peso molecular entre pacientes com COVID-19 no Hospital Universitário de Udayana, Bali

El uso de heparina de bajo peso molecular entre pacientes con COVID-19 en el Hospital Universitario de Udayana, Bali

Received: 06/16/2022 | Reviewed: 07/21/2022 | Accept: 07/27/2022 | Published: 08/04/2022

Saktivi Harkitasari
ORCID: https://orcid.org/0000-0002-2138-1995
Faculty of Medicine, Warmadewa University, Indonesia
E-mail: saktiviharkitasari85@gmail.com
Cokorda Agung Wahyu Purnamasidhi
ORCID: https://orcid.org/0000-0002-1646-3793
Udayana University, Indonesia
Udayana University Hospital, Indonesia
E-mail: purnamasidhi@unud.ac.id
Ni Made Renny Anggreni Rena
ORCID: https://orcid.org/0000-0001-8763-6631
Udayana University, Indonesia
Sanglah General Hospital, Indonesia
E-mail: renny@unud.ac.id
Ni Made Dewi Dian Sukmawati
ORCID: https://orcid.org/0000-0001-7380-0437
Udayana University, Indonesia
Sanglah General Hospital, Indonesia
E-mail: dewi_dian@unud.ac.id
I Ketut Agus Somia
ORCID: https://orcid.org/0000-0003-4168-9572
Udayana University, Indonesia
Sanglah General Hospital, Indonesia
E-mail: agus.somia@unud.ac.id

Abstract
Experts have speculated the potential of heparin administration as COVID-19 treatment modality, although scientific research regarding its effectivity, recommended dosage, and period are still minimal. This study aims to explore the capacity of LMWH as a medicament for COVID-19, in effort to provide scientific reference for further development of COVID-19 possible choice of treatment or medicament. A retrospective study was conducted in Udayana University Hospital, Bali, Indonesia. Data were sourced from laboratory-confirmed COVID-19 patients medical records during March 25 to July 31, 2020. Clinical, laboratory, treatment and use of LMWH data were reviewed and statistically processed. 42 patients we found Use of LMWH. The patient categorizes from moderate to severe COVID-19. 31 patients use of LMWH for prophylaxis and 11 patients use of LMWH for treatment. 7 patients were death in the hospital, and the other was survived. LMWH elevates coagulation dysfunction in COVID-19 patients. We believe that beneficial effects of LMWH as prophylaxis or treatment in COVID-19 patients.
Keywords: COVID-19; Low molecular Weight heparin; Prophylaxis; Treatment.

Resumo
Especialistas especularam o potencial da administração de heparina como modalidade de tratamento da COVID-19, embora as pesquisas científicas sobre sua eficácia, dosagem recomendada e período ainda sejam mínimas. Este estudo visa explorar a capacidade da HBPM como medicamento para COVID-19, em um esforço para fornecer referência científica para o desenvolvimento posterior da possível escolha de tratamento ou medicamento para COVID-19. Um estudo retrospectivo foi realizado no Hospital Universitário de Udayana, Bali, Indonésia. Os dados foram obtidos de registros médicos de pacientes com COVID-19 confirmados em laboratório durante 25 de março a 31 de julho de 2020. Os dados clínicos, laboratoriais, de tratamento e uso de HBPM foram revisados e processados estatisticamente. 42 pacientes encontramos Uso de HBPM. O paciente classifica de moderado a grave COVID-19. 31 pacientes em uso de HBPM para profilaxia e 11 pacientes em uso de HBPM para tratamento. 7 pacientes morreram no hospital e o

outro sobreviveu. HBPM eleva a disfunção da coagulação em pacientes com COVID-19. Acreditamos que os efeitos benéficos da HBPM como profilaxia ou tratamento em pacientes com COVID-19.
Palavras-chave: COVID-19; Heparina de baixo peso molecular; Profilaxia; Tratamento.

Resumen
Los expertos han especulado sobre el potencial de la administración de heparina como modalidad de tratamiento de la COVID-19, aunque las investigaciones científicas sobre su efectividad, dosis recomendada y duración son aún mínimas. Este estudio tiene como objetivo explorar la capacidad de la HBPM como medicamento para la COVID-19, en un esfuerzo por proporcionar una referencia científica para un mayor desarrollo de la posible elección de tratamiento o medicamento para la COVID-19. Se realizó un estudio retrospectivo en el Hospital Universitario Udayana, Bali, Indonesia. Los datos se obtuvieron de los registros médicos de pacientes con COVID-19 confirmados por laboratorio entre el 25 de marzo y el 31 de julio de 2020. Los datos clínicos, de laboratorio, de tratamiento y uso de HBPM se revisaron y procesaron estadísticamente. En 42 pacientes encontramos Uso de HBPM. El paciente categoriza de moderado a severo COVID-19. 31 pacientes usaron HBPM para profilaxis y 11 pacientes usaron HBPM para tratamiento. 7 pacientes fallecieron en el hospital y el otro sobrevivió. LMWH eleva la disfunción de la coagulación en pacientes con COVID-19. Creemos que los efectos beneficiosos de la HBPM como profilaxis o tratamiento en pacientes con COVID-19.
Palabras clave: COVID-19; Heparina de bajo peso molecular; Profilaxis; Tratamiento.

1. Introduction

COVID-19 has been declared a worldwide pandemic by The World Health Organization (WHO) since March 11, 2020. COVID-19 has infected more than a million people globally and a death rate of 70.000 cases. The distinct feature of COVID-19 virus lies in its highly infective nature, long incubation time, and its various way of viral transmission (Ayerbe et al., 2020; Liu et al., 2020). Up to this point, there is no certain medication or vaccine available yet for the treatment of COVID-19, thus, treatments were mainly symptomatic. Although mild cases are usually not life-threatening, severe cases are highly lethal and needs proper and intensive attention. Comprehensive insights on the pathogenesis of COVID-19 is an important factor that will support the discovery of a reliable treatment or medicine from existing medicament presents.

Patients with COVID-19 shows thrombotic events in different tissues, with consistent laboratory and radiological profiles. (Tang et al., 2020; J. Zhang et al., 2020). Perfusion abnormalities in lungs have been observed in patients who underwent dual-energy CTs (Hendriks, 2017). Deceased patients show evidence of platelet-fibrin thrombi inside the small arterial vessels in the lung tissue (L. Zhang et al., 2020). Based on these finding, heparin have been used as treatment and prevention of the coagulation disorder associated with the infection (Paolisso et al., 2020; Tang et al., 2020; J. Zhang et al., 2020). This treatment can be associated with the clinical recovery of the patients, and lowering hospitalization time and mortality of COVID-19.

Low molecular weight heparin (LMWH) is a low-risk, affordable, and practical method as a potential treatment for both inpatients and outpatients of COVID-19. This study aims to explore the capacity of LMWH as a medicament for COVID-19, considering the limited study covering this specific topic. The results of this study would contribute as a scientific reference for further development of COVID-19 possible choice of treatment or medicament.

2. Methodology

A retrospective study was carried out in Udayana University Hospital, Bali, Indonesia. Udayana University Hospital is a COVID-19 referral hospital (appointed by the local government). Data for the study was obtained by analyzing medical records of COVID-19 patients who received LMWH treatment during the period of March 25 to July 31, 2020 as a secondary data source. The Ethics committee of Medical Faculty Udayana University approved this study.

From the medical records, data regarding basic demographic information, complete blood count, coagulation profile, and serum biochemical indicators (including liver function, kidney function and electrolytes) were obtained. After all

necessary data had been collected, a statistical analysis was completed with the help of IBM SPSS Statistics 22 software. Analyzed data were presented in mean mean ± standard deviation (SD) (Dahlan, 2013).

3. Results and Discussion

A total of 42 medical records were reviewed, in which 30 (71.43%) were men, 12 (28.57%) were women, and the mean age was 49 ±15.34. During data collection progress, unfortunately, 7 patients passed away while 35 recovered and discharged from the hospital. Median follow up time was 10 (IQR: 7-14) days.

In our study, 31 patients use of LMWH for prophylaxis. Prophylaxis with LMWH (Enoxaparin) 40 mg subcutaneous were use in 9 patients and 60 mg subcutaneous were use in 22 patients. LMWH for treatment 1 mg/kg subcutaneous twice daily (TBW) were use in 11 patients. (table 1)

From the laboratory data, before use LMWH, we found WBC 9.1629 ± 4.09642, lymphocyte 1.01 ± 0.43158, Hemoglobin (Hb) 13.14 ± 2.08090, ALT 62.00 ± 38.283, AST 65.93 ± 42.79, BUN 11.88 ±11.0, creatinine serum 0.57 ± 0.56, sodium serum 137.67± 11.0, potassium serum 3.8 ± 0.45. After the use of LMWH (in day 7) the result of the labolatory were WBC 9.1629 ± 4.09642, lymphocyte 1.01 ± 0.43158, Hemoglobin (Hb) 13.14 ± 2.08090, ALT 62.00 ± 38.283, AST 65.93 ± 42.79, BUN 11.54 ± 6.59, creatinine serum 0.58 ± 0.14, sodium serum 138.77± 11.0, potassium serum 3.7 ± 0.40. The decrease of D-dimer serum after we gave LMWH were happen in all of the patients with value 0.8 (range 0.4-1.8) vs. 0.4 (range 0.2-1.0) (Table 2 and Figure 1).

Table 1. Characteristics patients.

Characteristics	**n (42)**	**%**
Age (mean ±SD)	49 ± 15.34	
Sex		
Female	12	28.57
Male	30	71.43
Comorbidity		
Hypertension	12	28.57
Diabetes	10	23.80
Cardiovascular disease	8	19.04
Chronic kidney disease	0	0.00
Obesity	7	16,67
Signs and symptoms		
Fever	22	52.38
Cough	24	57.14
Shortness Of Breath	7	16.67
Anosmia	9	21.42
Myalgia	27	64.28
Diarrhoea	0	0.00
Nausea or vomiting	3	7.14
Respiratory rate ≥30 breaths per min	12	28.57
Pulse ≥125 beats per min	7	16.67
Systolic blood pressure <90 mmHg	3	7.14
Therapy		
Azithromycin	15	35.71
Vitamin C	42	100.0
Antivirus (aluvia)	3	11.90
Steroids	37	88.09
Tocilizumab	4	9.52
Disease progression		
Improved	35	83.33
Death	7	16.67
Hospital length of stay, days	15 ± 11.24	

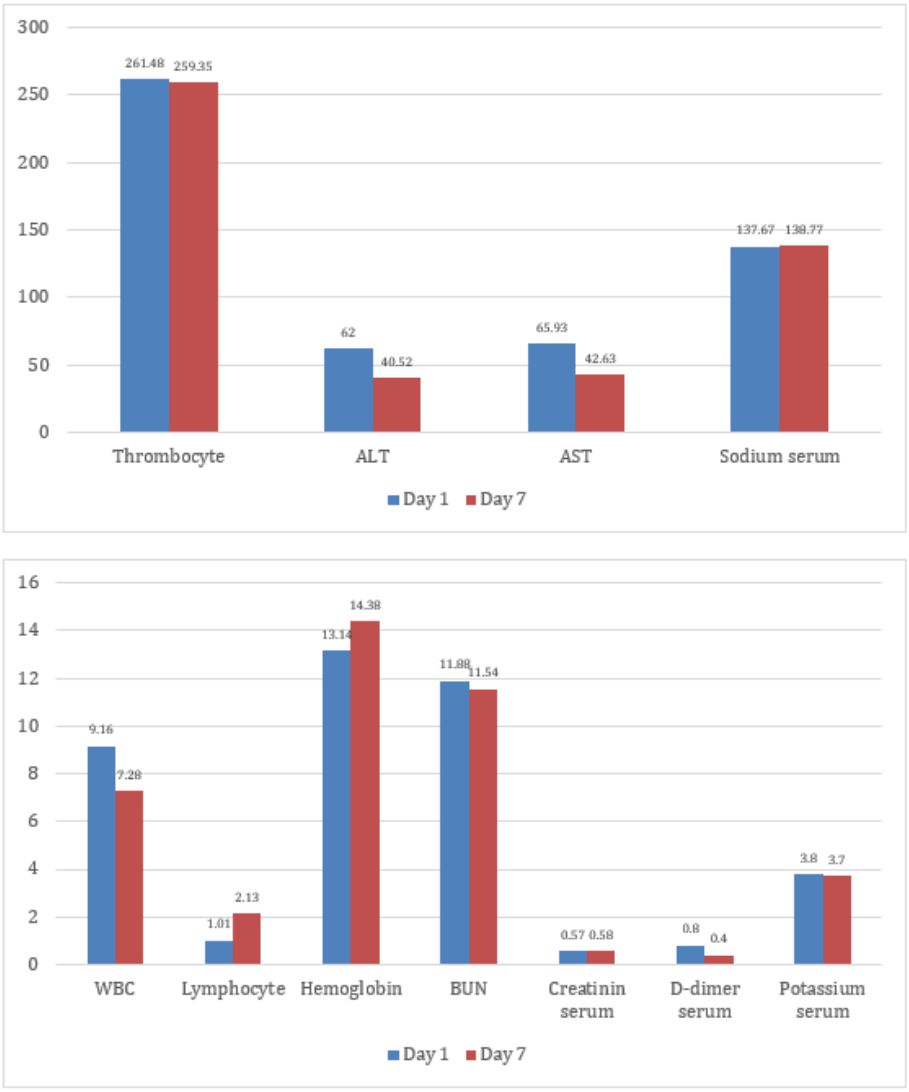
Source: Analysis.

Table 2. laboratories value of patients.

Characteristics	**Day 1**	**Day 7**
WBC (mean ±SD) (× 10^9 cells/L) (normal range 3.5–9.5)	9.16 ± 4.09	7.28 ± 2.22
Lymphocyte (× 10^9 cells/L) (normal range 1.1–3.2)	1.01 ± 0.43	2.13± 0.89
Hemoglobin (Hb) (g/L) (normal range 125.0–175.0)	13.14 ± 2.08	14.38± 1.47
Thrombocyte (Plt) (×10^9 cell/L) (normal range 125.0–350.0)	261.48± 83.85	259. 35 ± 82.73
ALT (U/L) (normal range 0.0–41.0)	62.00 ± 38.283	40.52 ± 30.0
AST (U/L) (normal range 0.0–40.0)	65.93 ± 42.79	42.63 ± 33.5
BUN (mmol/L) (normal range 3.1–8.0)	11.88 ± 11.0	11.54 ± 6.59
Creatinin serum	0.57 ± 0.56	0.58 ± 0.14
D-dimer serum (µg/mL) (normal range 0.0–0.5)	0.8 (0.4-1.8)	0.4 (0.2-1.0)
Sodium serum	137.67± 11.0	138.77± 11.0
Potassium serum	3.8 ± 0.45	3.7 ± 0.40

Source: Analysis.

Figure 1. Laboratories Values Day 1 and Day 7 After LMWH Therapy.



Source: Analysis.

Progressive respiratory default is the primary cause of death in the coronavirus disease 2019 pandemic (COVID-19). Histologic analysis of pulmonary vessels in patients with COVID-19 has shown rife thrombosis with alveolar capillary microthrombi (Ayerbe et al., 2020). Thrombotic phenomena present on pat COVID-19 is known to be associated with thrombotic phenomena that are related to the high mortality of this disease and right treatment can improve the survival of these patients

Heparin treatment was associated with better recovery rate in patients with COVID-19. As an anticoagulant, heparin facilitate reduction of thrombi in pulmonary microcirculation. Therefore, heparin treatment may prevent hypoxia from pulmonary vasculopathy and increased dead space.

Studies showed that heparin affect patients with COVID-19 positively, but noted that uncertainties remained about the heparin dose that would be most effective, and about monitoring of complications (Hosseini & Bahramnezhad, 2020). Inflammatory biomarkers were decreased with heparin treatment, which is effective in reducing the inflammatory status of COVID-19.

To the best of our knowledge, there is no interventional evidence on the management of the coagulopathy associated with Covid-19. Use of LMWH proofed to be positive and could be applied on clinical settings. Future studies with randomized controlled trials might complement this study to assess different therapeutic regimes of heparin and the clinical outcomes.

4. Conclusion

LMWH elevates coagulation dysfunction in COVID-19 patients. We believe that beneficial effects of LMWH as prophylaxis or treatment in COVID-19 patients. LMWH is a practical method that could be implemented to help treat for both inpatients or outpatients. It has effectivity in preventing the necessity of hospital admissions, as well as lowering the hospital stay duration for those who still need it. LMWH could also be considered as a potential effective medicaments by clinicians and future researchers. Further research incorporating larger number of samples with better statistical control quality may help advance knowledge about how LMWH affects COVID-19 patients.

References

Ayerbe, L., Risco, C., & Ayis, S. (2020). The association between treatment with heparin and survival in patients with Covid-19. *Journal of Thrombosis and Thrombolysis*, *50*(2), 298–301. https://doi.org/10.1007/s11239-020-02162-z

Dahlan, S. (2013). *Statistik Untuk Kedokteran dan Kesehatan*. Penerbit Salemba. https://books.google.co.id/books?hl=id&lr=&id=Abh5OaO3qlMC&oi=fnd&pg=PA1&ots=SWVDMa00xU&sig=yEOdMqA_b5Jo3ZKRAGoYNY8s5Ww&redir_esc=y#v=onepage&q&f=false

Hendriks, S. A. (2017). *Understanding The Clinical Course of Dementia*. https://research.vu.nl/ws/portalfiles/portal/42577616/complete+dissertation.pdf

Hosseini, A., & Bahramnezhad, F. (2020). Pulmonary embolism in patients with COVID-19 and its treatment based on low-molecular-weight heparin. *Sao Paulo Medical Journal*, *138*(4), 349–351. https://doi.org/10.1590/1516-3180.2020.0221.r2.22072020

Liu, Y., Lee, J. M., & Lee, C. (2020). The challenges and opportunities of a global health crisis: the management and business implications of COVID-19 from an Asian perspective. *Asian Business and Management*, *19*(3), 277–297. https://doi.org/10.1057/s41291-020-00119-x

Paolisso, P., Bergamaschi, L., D'Angelo, E. C., Donati, F., Giannella, M., Tedeschi, S., Pascale, R., Bartoletti, M., Tesini, G., Biffi, M., Cosmi, B., Pizzi, C., Viale, P., & Galié, N. (2020). Preliminary Experience With Low Molecular Weight Heparin Strategy in COVID-19 Patients. *Frontiers in Pharmacology*, *11*. https://doi.org/10.3389/fphar.2020.01124

Tang, N., Li, D., Wang, X., & Sun, Z. (2020). Abnormal coagulation parameters are associated with poor prognosis in patients with novel coronavirus pneumonia. *Journal of Thrombosis and Haemostasis*, *18*(4), 844–847. https://doi.org/10.1111/jth.14768

Zhang, J., Meng, G., Li, W., Shi, B., Dong, H., Su, Z., Huang, Q., & Gao, P. (2020). Relationship of chest CT score with clinical characteristics of 108 patients hospitalized with COVID-19 in Wuhan, China. *Respiratory Research*, *21*(1). https://doi.org/10.1186/s12931-020-01440-x

Zhang, L., Dong, L., Ming, L., Wei, M., Li, J., Hu, R., & Yang, J. (2020). Severe acute respiratory syndrome coronavirus 2(SARS-CoV-2) infection during late pregnancy: a report of 18 patients from Wuhan, China. *BMC Pregnancy and Childbirth*, *20*(1). https://doi.org/10.1186/s12884-020-03026-3