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# Effect of Low Molecular Weight Heparin in Treatment of Acute Pancreatitis

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**ABSTRACT**

Acute pancreatitis is a common and serious condition with a mortality rate of 20-40% and high morbidity due to systemic complications. Despite various causes, the final result is the premature activation and retention of proteolytic enzymes along with disturbance in pancreatic micro circulation aggravating the severity. Standard treatment includes fluid management, nutritional care, gastrointestinal decompression and antibiotics when needed. Low molecular weight heparin can reduce the release of cytokine and inflammatory mediators, improving pancreatic micro circulation and thereby reducing the severity of pancreatitis. The aim is to study the Effect of LMWH in treatment of acute pancreatitis. Our study involved 130 patients divided into two groups: GROUP A (Control Group) received conventional treatment for acute pancreatitis (n=65) and GROUP B (Observation Group) received conventional treatment plus LMWH [1mg/kg] (n=65). Results showed that out of 130 patients, 125 recovered and 5 died, all from the control group. There was no significant difference in APACHE II scores between the groups at admission. After 7 days of treatment, the APACHE II scores were significantly lower in the observation group (those treated with heparin) compared to the control group. Additionally, the mean hospital stay was significantly shorter in the observation group. LMWH can significantly enhance the effectiveness of conventional acute pancreatitis treatment, markedly reducing its mortality.

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**Key Words**

Acute pancreatitis, low molecular weight of heparin (LMWH)

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## INTRODUCTION

Acute pancreatitis is a prevalent and potentially fatal gastrointestinal condition[1]. The incidence of acute pancreatitis has been reported to be increasing globally[2]. While most patients experience a mild and self-limiting course, 10-20%[3] develop a rapidly progressing inflammatory response that leads to extended hospital stays and significant morbidity and mortality. Acute pancreatitis is a disease of many etiologies and the mechanism thought to be the abnormal pancreatic enzyme activation inside acinar cells, leading to auto digestion of normal pancreatic parenchyma. In response to this, acinar cells release Pro inflammatory cytokines such as tumor necrosis factor Alpha (TNFa) and Interleukin (IL)-1, IL 2 and IL 6 and anti-inflammatory mediators such as IL 10 and IL1 receptor antagonist. These mediators do not initiate pancreatic injury but instead amplify the response both locally and systemically. Consequently, neutrophils and macrophage are recruited into the pancreatic tissue, leading to the release of more TNFa, IL1, IL6, reactive oxygen metabolites, prostaglandin, platelet-activating factor and leukotrienes. This local inflammatory response further worsens pancreatitis, increasing permeability and damaging the micro circulation of the pancreas. In severe cases this causes local hemorrhage and pancreatic necrosis. This inflammatory cascade is self-limiting in about 80-90%[3] of patients-mild pancreatitis. However, in the remaining patients, a vicious cycle of recurring pancreatic injury and ongoing local and systemic inflammatory responses persists leading to severe acute pancreatitis characterized by pancreatic necrosis, a severe systemic inflammatory response and often multi organ failure. Active neutrophils mediate acute lung injury and induce adult respiratory distress syndrome, which is frequently seen in patients with severe pancreatitis with mortality rates ranging from 10-50%[3]. This persistent inflammatory response is responsible for the mortality observed in the early stages of pancreatitis and mortality after 2 weeks (late phase) is often caused by septic complications[3]. Low molecular weight heparin (LMWH) has antithrombin activity and inhibits the inflammatory cascade by reducing the release of cytokines and inflammatory mediators. Additionally, heparin administration down regulates TNF-a-induced leukocyte rolling[4], blocks the adhesion of leukocytes to the endothelium by inhibiting the interactions between expressed adhesion molecules and endothelial cells[5], reducing the activation of placeless[6]. Additionally, LMWH reduces micro thrombi formation and enhances micro circulation[7]. Experimental and clinical studies have demonstrated that heparin treatment inhibits the development of ischemia/repercussion-induced acute pancreatitis[8]. Recent clinical research indicates that pre-procedural heparin administration significantly reduces the occurrence of endoscopic retrograde cholangio pancreatography (ERCP)-related pancreatitis[9], improves the course of hyper triglyceridemia-induced acute pancreatitis[10] and may improve the prognosis in severe acute pancreatitis[7,10].

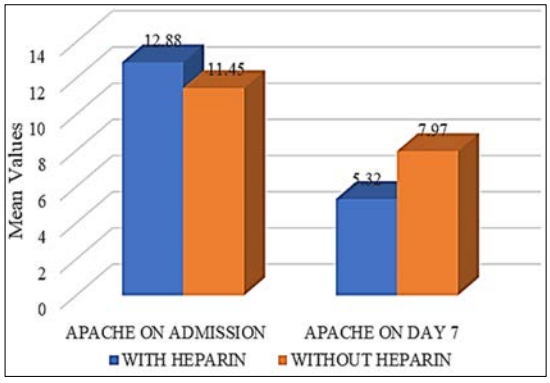
**Aims and Objectives:** The aim is to study the effect of low molecular weight heparin (LMWH) in treatment of acute pancreatitis.

## MATERIALS AND METHODS

This is a randomized prospective comparative and clinical study conducted in a tertiary care centre from January 2021 to June 2022. All those patients admitted in the department of general surgery from 18 years to 80 years with Abdominal pain characteristic of acute pancreatitis (duration < 72 hours) and Serum amylase and/or lipase ≥3 times the upper limit of normal were included in the study and Patients (1) sensitive to LMWH, (2) Pregnant and Breast feeding women, (3) Coagulation disorders Undergoing hematolysis were excluded from the study. After taking informed consent from the patients and the relatives, the particulars of the patient and history were collected by direct interview of the patient and the relatives accompanying the patient. A thorough clinical examination was done in all the patients and the diagnosis is noted. A total of 130 patients were divided into two groups of 65 each, using an odd-even method. Group A received conventional treatment, including management of shock, water and electrolyte balance, fasting, gastrointestinal decompression, administration of pancreatic enzyme inhibitor (octreotide), antibiotics (cephalosporins and metronidazole) and symptomatic treatment. Group B received conventional therapy along with subcutaneous LMWH at a dose of 1 mg per kg, administered twice daily for 7 days. The APACHE II scores were recorded on admission and one week after treatment. The age distribution in the study was as follows: 6 patients were under 20 years, 22 were between 21-30 years, 37 were between 31-40 years, 42 were in the 41-50 years range and 23 patients were over 50 years. The mean age was 40.28 years in Group A and 40.89 years in Group B. Males accounted for 83.8% of the study population, while females made up 16.2%. The groups were well-matched, with no statistically significant differences in sex or age between them ($p>0.05$).

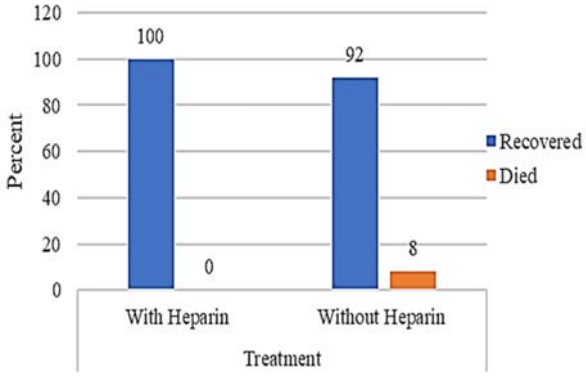
## RESULTS AND DISCUSSIONS

During the study, the mean APACHE II scores at admission were 12.58 for Group A and 12.88 for Group B, with no statistically significant difference ($P= 0.792$). However, after seven days of treatment, the mean APACHE II score in Group B (patients treated with Heparin) decreased significantly to 5.32, compared to 7.97 in Group A ($P=0.001$). (Graph 1).



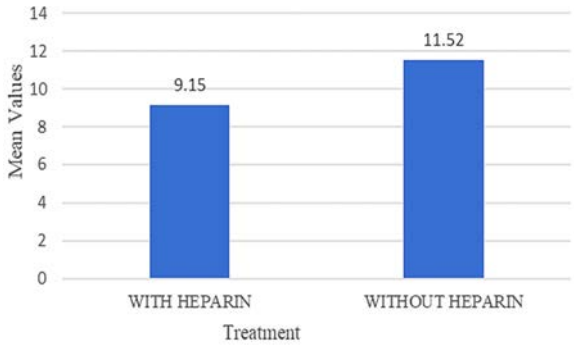

Graph 1: Comparison of Apache II Scores among Groups

Among the 130 patients, 125 recovered while 5 died, all from Group A (patients not treated with Heparin), making the difference in recovery rates between the two groups statistically significant ($p<0.05$). (Graph 2).




Graph 2: Final Outcome Among Groups

The mean duration of hospital stay was significantly shorter in patients treated with Heparin (9.15 days) compared to those without Heparin (11.52 days), with statistical significance ($p<0.05$). (Graph 3).




Graph 3: Mean Duration of Hospital Stay among Groups

Acute pancreatitis represents a prevalent abdominal pathology characterized by diverse degrees of severity. Mild acute pancreatitis has an uneventful course with spontaneous recovery within a week. Conversely, moderately severe acute pancreatitis (MSAP) and severe acute pancreatitis may entail a spectrum of both local and systemic complications. Severe acute pancreatitis (SAP) is notably grave, often culminating in mortality rates ranging between 10-50%. The exact pathogenesis of pancreatitis remains debatable, but it is closely related to the dysfunction of balance between pro-inflammatory and anti-inflammatory responses. There will be premature activation of pancreatic proteases within the pancreas. Pro inflammatory cytokines are produced and released with excessive leukocyte activation, stimulating the inflammatory cascade associated with microvascular disturbance and hemorrhagic necrosis. Ischemia repercussion injury and micro thrombosis are intricately linked to disturbance in pancreatic micro circulation, triggering escalated cytokine release that can elicit local manifestations and systemic complications, ultimately precipitating multiple organ failure (MOF). In patients suffering from severe acute pancreatitis (SAP), MOF emerges as the primary contributor to mortality as seen in our study. The pancreas is vulnerable to ischemic injury. Furthermore, mounting evidence implicates both pancreatic and systemic microvascular disruptions in pancreatitis pathogenesis, characterized by vasoconstrictor, shunting, insufficient perfusion and heightened blood viscosity and coagulation. These processes constitute pivotal pathological mechanisms underlying the progression of severe acute pancreatitis (SAP). Therefore, ameliorating disturbances in pancreatic and systemic microvasculature is crucial for impeding the pathological and clinical progression of pancreatitis. Our study has demonstrated a reduction in micro thrombus formation, resulting in improvement in micro circulation decreasing the mortality. In our study of 130 patients, 125 recovered while 5 died, all from the control group. The recovery rate differed significantly between the groups ($p<0.05$). Mortality causes included acute respiratory distress syndrome in 2 patients and septic shock with multi-organ failure in 3. Admission APACHE II scores were not significantly different ($p>0.05$), but after 7 days, scores in the heparin-treated group were lower than controls ($p<0.05$). Mean hospital stay with heparin treatment was 9.15 days compared to 11.52 days without, showing statistical significance ($p<0.05$). In this study, it was observed that the group treated with LMWH exhibited notable enhancements in clinical outcomes, reduced duration of hospitalization and lower mortality rates compared to the control group. These findings indicate that LMWH also exerted a substantial therapeutic impact on the clinical management of severe acute pancreatitis (SAP). Lu XS, Qiu F, Li JQ[7] conducted a similar study, yielding comparable results wherein the clinical presentation improvement rate

and improvement in laboratory parameters were significantly higher in the LT group compared to the control (C) group (p<0.05-0.01). Moreover, the LT group exhibited notably lower APACHE II scores, complication rates, mortality rates, and mean hospital stay compared to the C group (p<0.05-0.01). Dr. Anilkumar[11] conducted a prospective comparative study that revealed analogous findings. The APACHE II scores and length of hospital stay were notably diminished in the LMWH-treated group, demonstrating statistical significance (P<0.05). These results suggest substantial enhancements in laboratory parameters, improved cure rates and a decreased incidence of complications. A systematic review and meta-analysis of randomized controlled trials, carried out by Q Qiu, GJ Li, L Tang, Y Guo[12], assessed relevant studies published up to March 2019 across five databases (MEDLINE/PubMed, EMBASE, the Cochrane Central Register of Controlled Trials in Cochrane Library, China National Knowledge Infrastructure and the Chinese Journal of Science and Technology of VIP database). The review concluded that LMWH may play a potential role in reducing hospital stays, mortality rates, incidences of multiple organ failure, pancreatic pseudo cysts and operation rates. However, our study is a small, population-based study from a single institution, from among patients admitted during a brief time-frame. Larger, multi-institutional studies with larger sample size and longer time frames are needed to confirm validity and accuracy of our results. Patients were followed up till the time of discharge. Further follow up., to analyze further late complications of acute pancreatitis did not fall under the parameters of our study. Pediatric patients were not included.

## CONCLUSION

LMWH reduces cytokine release and inflammation, improving pancreatic micro circulation. This slows disease progression, lessens severity and complications and shortens hospital stays, making it effective in non-surgical acute pancreatitis treatment.

**Compliance with Ethical Standards:**

**Conflict of Interest:** The authors declare that they have no conflict of interest.

**Human Rights:** All intervention performed in studies involving human participants were in accordance with the ethical standards of the institutional committee.

## REFERENCES


1. Li, C.L., M. Jiang, C.Q. Pan, J. Li and L.G. Xu, 2021. The global, regional, and national burden of acute pancreatitis in 204 countries and territories, 1990–2019. BMC Gastroenterol., Vol. 21 .10.1186/s12876-021-01906-2.
2. Iannuzzi, J.P., J.A. King, J.H. Leong, J. Quan and J.W. Windsor et al., 2022. Global Incidence of Acute Pancreatitis Is Increasing Over Time: A Systematic Review and Meta-Analysis. Gastroenterology, 162: 122-134.
3. Townsend, C.M. and D.C. Sabiston., 2004. Textbook of surgery: the biological basis of modern surgical practice. PA: Elsevier Saunders, Philadelphia,
4. Salas, A., *et al.,* 2000. Heparin attenuates TNF-alpha induced inflammatory response through a CD11b dependent mechanism. Gut, 47: 88-96.
5. Koenig, A., K. Norgard-Sumnicht, R. Linhardt and A. Varki, 1998. Differential interactions of heparin and heparan sulfate glycosaminoglycans with the selectins. Implications for the use of unfractionated and low molecular weight heparins as therapeutic agents.. J. Clin. Invest., 101: 877-879.
6. Evangelista, V., P. Piccardoni, N. Maugeri, G.D. Gaetano and C. Cerletti, 1992. Inhibition by heparin of platelet activation induced by neutrophil-derived cathepsin G. Eur. J. Pharmacol., 216: 401-405.
7. Xin-Sheng, L., Q. Fu, L. Jie-Qin, F. Qin-Qiao and Z. Ri-Guang *et al.,* 2009. Low Molecular Weight Heparin in the Treatment of Severe Acute Pancreatitis: A Multiple Centre Prospective Clinical Study. Asian J. Surg., 32: 89-94.
8. Ceranowicz, P., A. Dembinski, Z. Warzecha, M. Dembinski, J. Cieszkowski and K. Rembisz, et al., 2008. Protective and therapeutic effect of heparin in acute pancreatitis. J Physiol. Pharmacol. , 59: 103-125.
9. Rabenstein, T., S. Roggenbuck, B. Framke, P. Martus and B. Fischer et al., 2002. Complications of endoscopic sphincterotomy: Can heparin prevent acute pancreatitis after ERCP? Gastrointestinal Endoscopy, 55: 476-483.
10. Alagözlü, H., M. Cindoruk, T. Karakan and S. Ünal, 2006. Heparin and Insulin in the Treatment of Hypertriglyceridemia-Induced Severe Acute Pancreatitis. Digestive Dis. Sci., 51: 931-933.
11. MS, D.A.K. and D.S.V. Jain, 2022. A comparative study of low molecular weight heparin in the management of acute pancreatitis VS conventional treatment-a prospective comparative clinical study. Int. J. Surg. Sci., 6: 76-79.
12. Qiu, Q., G.J. Li, L. Tang, Y. Guo and L.Z. Wen et al., 2019. The efficacy of low molecular weight heparin in severe acute pancreatitis: A systematic review and meta-analysis of randomized controlled trials. J. Digestive Dis., 20: 512-522.