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A comparative study of low molecular weight heparin in the management of acute pancreatitis VS conventional treatment- a prospective comparitive clinical study

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Abstract
Acute pancreatitis is serious disorder in any kind of severity with a mortality up to 20-40% and with a high magnitude of morbidity due to other kinds of systemic complications and despite of the various aetiologies, the final outcome is premature activation and retention of proteolytic enzymes. The main triggering factor and the etiological factor in development of Severe Acute Pancreatitis leading to multiple organ failure is the disturbance in microcirculation of the pancreas. The standard treatment for pancreatitis that is given is fluid management, nutritional care, gastrointestinal decompression, antibiotics (when indicated) The need for introducing Low molecular weight heparin (LMWH) in the treatment line of acute pancreatitis is that LMWH can reduce the release of cytokines and inflammatory mediators, resulting in an improvement of the microcirculation of pancreas thereby minimising the severity of pancreatic necrosis.

Keywords: Acute pancreatitis, Low molecular weight heparin (LMWH), APACHE II score

Introduction
Acute pancreatitis (AP) is a common disease with varying severity. Mild AP has an uneventful course with spontaneous recovery in <1 week. Moderately severe and severe AP (MSAP) is associated with local and systemic complications, notably, necrosis (sterile or infected) and organ failure (transient or persistent) [1] After premature activation of pancreatic proteases and extravasation of these activated digestive enzymes into the pancreas and peripancreatic tissues, cytokines and other inflammatory mediators are produced and released with excessive leukocyte activation. They stimulate the inflammatory cascade, leading to systemic inflammatory response syndrome [2] Proinflammatory cytokines, such as tumor necrosis factor (TNF)-α and interleukin (IL)-1β, IL-6, and IL-8, increase the capillary permeability with fluid loss, aggravating pancreatic injury.[2] TNF-α damages the acinar cells and is probably responsible for pancreatic necrosis (PN) and damage to other organs, such as lungs, liver, intestine, and spleen [3, 4]. The reported mortality rate in SAP is 7%–15% [5, 6]. The risk is higher in patients with persistent organ failure and infected necrosis. Pancreatic necrosis (PN) in itself is a severe complication and an important cause of death in AP where the mortality rate can reach up to 10%–23% [4]. Low molecular weight heparin (LMWH) has antithrombin activity and inhibits the inflammatory cascade by reducing the release of cytokines and inflammatory mediators. Moreover, heparin administration downregulates TNF-α-induced leukocyte rolling [7], blocks the adhesion of leukocytes to the endothelium by inhibiting the interactions between expressed adhesion molecules and endothelial cells [8], and reduces the activation of platelets [9] in addition, LMWH reduces the formation of microthrombi and improves microcirculation [10].

Materials and Methods
- **Study Design:** Prospective comparative clinical study
- **Study Duration**: 18 months
- **Sampling technique**: Purposive sample.
- **Sample size** - calculated using the following formula: S = Z 2 pq/d 2

Where z is the standard deviation which is 1.96 at 95% confidence interval.
p is the prevalence of the Acute pancreatitis in JSS hospital, which was found to be 3.1% as per

a pilot study through Hospital statistics.
q is (1-p)
d is clinically expected variation of 5%.
S= 46.1 rounded off to 50.
Hence sample size will be 50 individuals in each group of the study.

- **Study setting and Method of collection of data:**
- Patient who satisfy the inclusion criteria will be taken up in the study. Prior informed consent will be taken from the patients and relatives before enrolling them into the study. Patients will be assigned to 2 groups A and B.
- Group A patients will undergo conventional therapy that is management of shock, fluid and electrolytes management, fasting, gastrointestinal decompression, antibiotics (carbapenems and metronidazole) and symptomatic treatment.
- Group B patients will undergo the treatment given to Group A patients plus administering LMWH 1 mg/kg twice daily from admission until day 7 (inclusive) by subcutaneous injection.
- The APACHE II scores on admission and at 1 week after treatment will be determined.
- **Study Population and source of data:** All consecutive cases coming to surgical department in JSS HOSPITAL

- **Subject Eligibility**

a. Inclusion Criteria- Patients diagnosed with acute pancreatitis based on 2 out of 3criteria
1. Patient presenting with Abdominal pain characteristic of Acute pancreatitis of duration
less than 72 hours
2. serum amylase and/or lipase ≥ 3 times the upper limit of normal
3. Characteristic finding of Acute Pancreatitis on abdominal CT scan

b. Exclusion Criteria- Patients
1. Sensitive to LMWH
2. Pregnant
3. Breast feeding
4. Coagulation disorders
5. Patients undergoing to haemodialysis

Data Analysis
The analysis has been done by Descriptive and inferential methods.
The descriptive methods include mean, standard deviation, frequency and percentage.
The inferential analysis includes chi-square test, repeated measure anova, T-Test paired samples, T-test independent samples.
The statistical data will be analysed using SPSS software.

Results
- The mean age in Low molecular weight heparin group was 40.48 ± 8.96 and mean age in conventional group was 38.64 ± 11.79.
- 86% were male and 14% were female in low molecular weight heparin and conventional group
- In low molecular weight heparin group, 4% had score of 0-5, 46% had score of 6-10, 16% had score of 11-15, 28% had score of 16-20 and 6% had score of >21.
- In conventional group, 12% had score of 0-5, 26% had score of 6-10, 30% had score of 11-15, 20% had score of 16-20 and 12% had score of >21.
- In low molecular weight heparin group, 60% had score of 0-5, 28% had score of 6-10, 8% had score of 11-15, 4% had score of 16-20
- In conventional group, 26% had score of 0-5, 34% had score of 6-10, 32% had score of 11-15, 8% had score of 16-20
- The mean duration of hospital stay in days in Low molecular weight in heparin group was 9.0 ± 2.65 and in conventional group was 12.52 ± 5.21. There was a statistically significant difference observed with relation to duration of stay between the groups as the p value calculated to be <0.05.
- In Low molecular weight heparin group, 100% have recovered. 94% in convention group had recovered and 6% died due to complications
- In the present study, in low molecular weight heparin group mean APACHE Score at admission was 12.38 ± 5.52 and in conventional group was 13.24 ± 6.39. this was not statistically significant as p value calculated to be >0.05.
- In low molecular weight heparin group mean APACHE Score at day 7 was 5.46 ± 3.91 and in conventional group was 8.58 ± 4.81. This was statistically significant as p value calculated to be <0.05.
- APACHE Score at admission shows a cut off of >23 had 100% sensitivity and 96.9% specificity in predicting the outcome.
- APACHE Score at 7 days shows a cut off of >11 had 66.7% sensitivity and 85.6% specificity in predicting the outcome.

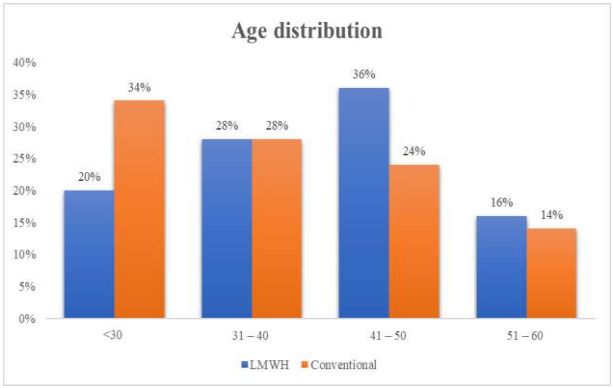

Fig 1: Age distribution

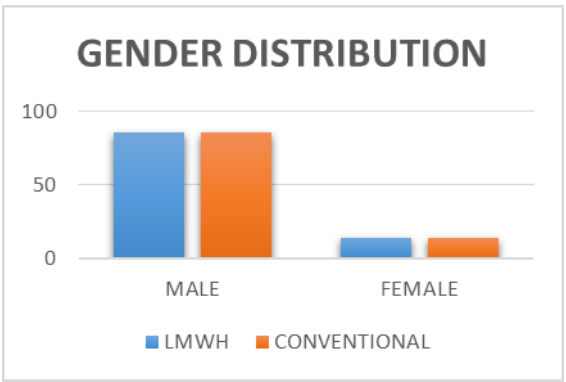

Fig 2: Gender distribution

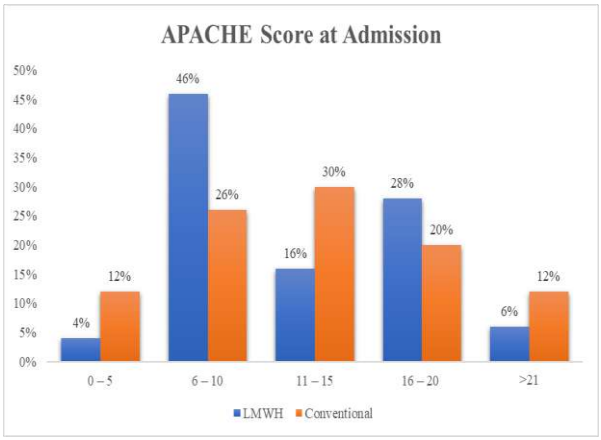

Fig 3: Apache II score at admission

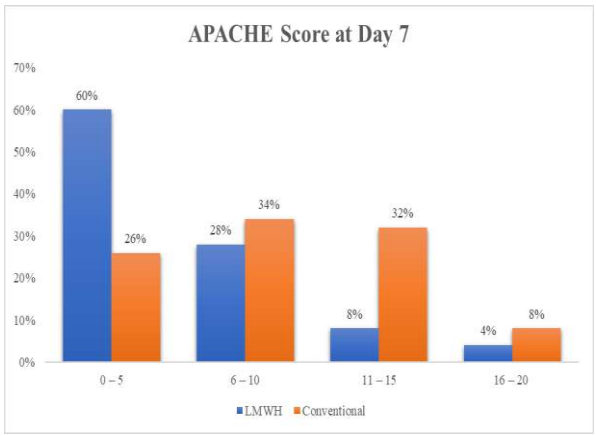

Fig 4: Apache II score at Day 7

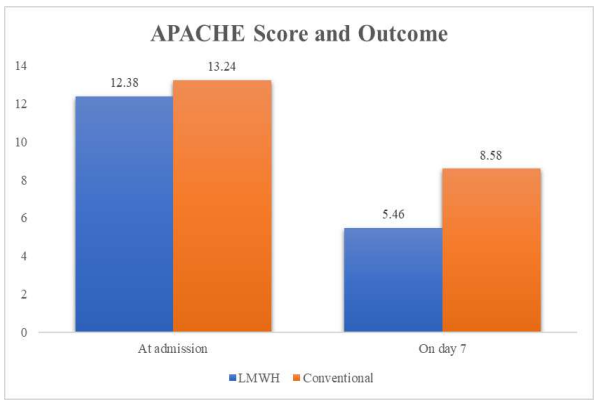

Fig 5: Apache II scores on day 1 and day 7

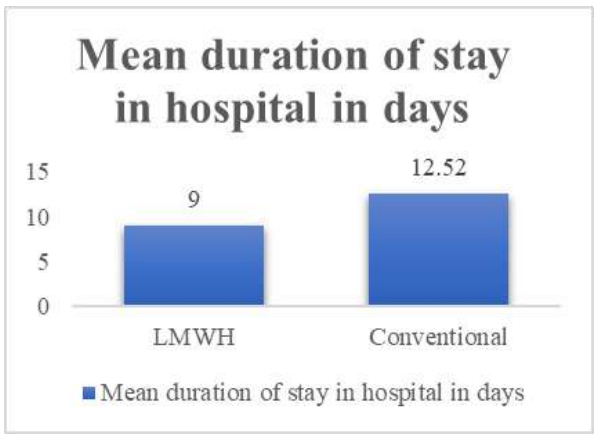

Fig 6: Mean duration of stay in hospital (in days)

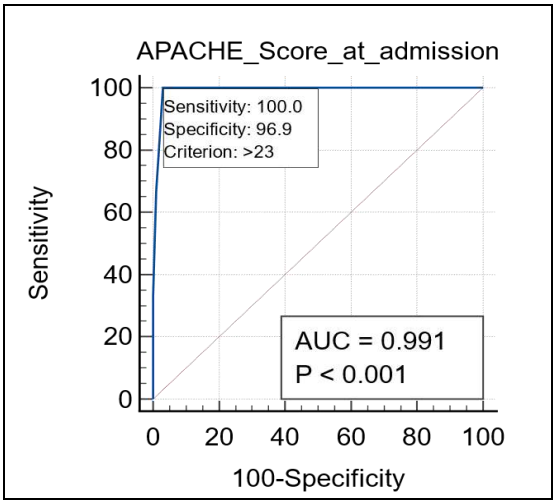

Fig 7: ROC curve of APACHE II score on admission

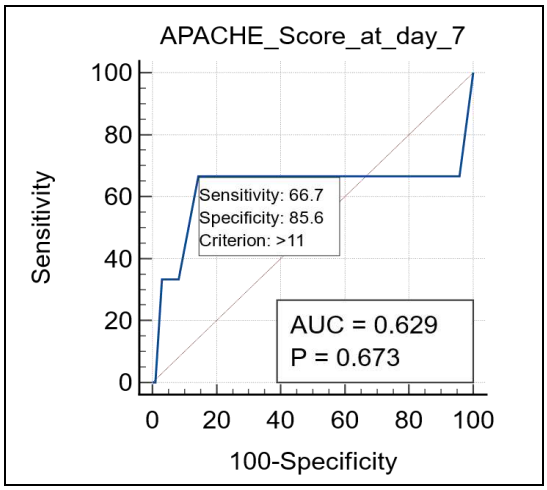

Fig 8: ROC curve of APACHE II score on day 7

Discussion

Acute pancreatitis is a common abdominal condition with varying severity. Mild acute pancreatitis has an uneventful course with spontaneous recovery in < 1 week. Moderately severe acute pancreatitis (MSAP) and severe acute pancreatitis can be complicated with various local and systemic complications. Severe acute pancreatitis (SAP) is severe and frequently a lethal disorder. Its mortality rate reaches up to 25 to 40 % [11].

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 and extravasation of these activated digestive enzymes into the pancreas. Peripancreatic tissues, cytokines, and other inflammatory mediators are produced and released with excessive leukocyte activation. They stimulate the inflammatory cascade, leading to systemic inflammatory response syndrome [12].

Infected necrosis and persistent organ failure carry a poor prognosis. Pathogenesis of necrosis affects the pancreas and also lungs, liver, and intestine in the course of severe acute pancreatitis [13].

Low molecular weight heparin (LMWH) possesses a unique anti-thrombin activity, healthier and safer than unfractionated heparin. Low molecular weight heparin also inhibits the inflammatory cascade by reducing the release of cytokines and inflammatory mediators.

Moreover, heparin administration down-regulates tumor necrosis factor-alpha (TNF-α-) induced leukocyte rolling, blocks the adhesion of leukocytes to the endothelium by inhibiting the interactions between expressed adhesion molecules and endothelial cells4 and reduces the activation of platelets [14].
In addition, low molecular weight heparin minimizes the formation of micro thrombi and improves microcirculation [15]. These findings can be helpful in the essential therapeutic effect of low molecular weight heparin in treating acute pancreatitis. Therefore, low molecular weight heparin by its anti-thrombus effect and by blocking the initiation of an inflammatory storm leads to improvement in the microcirculation system and reduces the formation of micro thrombosis in the pancreas leading to a better outcome of the patients suffering from acute pancreatitis.

Conclusion
As per the study, the APACHE II Scores were found to be reduced considerably in the group treated with LMWH, suggesting that there was a considerable improvement in laboratory values, better cure rate and lower incidence of complications. LMWH is shown to improve the microcirculation of the pancreatic parenchyma by preventing the formation of micro thrombi in the vasculature and down regulating the inflammatory cascade set by pancreatitis. As compared to unfractionated heparin, LMWH is found to be relatively safe to administer in the treatment regimen owing to its lesser side effects and with no need to monitor the coagulation profile in the patients. Thus, the use of LMWH can be considered in relieving acute pancreatitis related inflammation and in reducing the incidence of complications. LMWH can slow down the progression of disease, lessen the severity and complications, shorten the length of hospital stay and increase the cure rate.

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