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Study of role of low molecular weight heparin in conjunction with conventional therapy in severe acute pancreatitis

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ABSTRACT

Background: Acute pancreatitis is a disease which has many etiologies. Each etiology seems to affect the pancreatic acinar cell in some way that results in premature activation and retention of potent proteolytic enzymes. Low molecular weight heparin (LMWH) is known to reduce the release the cytokines and inflammatory mediators and result in the improvement of microcirculation of pancreas. **Aims and Objectives:** The aim of the study was to determine the efficacy of LMWH therapy in patients with severe acute pancreatitis (SAP). **Materials and Methods:** Our research comprised of 100 patients who were randomly assigned to one of two groups: Conventional treatment for SAP (n = 50) or conventional therapy + LMWH (n = 50). All the data were statistically analyzed in SPSS software 15.0. **Results:** In both groups, the death rate was 2%, and 49 patients in each group were cured of their disease after therapy. The minimum hospital stay in the heparin group is 5 days, while the highest hospital stay is 17 days. In the conventional group, the minimum hospital stay is 4 days, and the maximum hospital stay is 21 days. **Conclusion:** For the treatment of SAP, LMWH is a straightforward, safe, effective, and cost- efficient technique. It is suitable for usage in any hospital. There was no significant improvement in the impact of traditional SAP therapy with LMWH, nor was there any reduction in SAP mortality. Renal problems were more prevalent among the patients than sepsis-related complications among the conventional group. It was, however, statistically insignificant.

Key words: Acute pancreatitis; Low molecular weight of heparin; Proteolytic enzymes

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INTRODUCTION

Acute pancreatitis is a disease that has many etiologies. Each etiology appears to impact the pancreatic acinar cell in some way, causing powerful proteolytic enzymes to be activated and retained prematurely.[1,2] Macrophages, neutrophils, and endothelial cells are active in the early stages of pancreatitis. Inflammation factors are re-elevated and pre-inflammatory cytokines are produced. It has been linked to the advancement of pancreatitis-related microvascular disruption and hemorrhagic necrosis during acute pancreatitis. Ischemia, reperfusion damage, and small thrombosis are the factors in pancreatic microcirculation disruption.[3]

A lot has been learned about the natural history and pathophysiology of acute pancreatitis in the past few years. Acute pancreatitis can range in severity from a minor transient type to a severe necrotizing condition. Around 80% of acute pancreatitis episodes are minor and self-limiting, and they go away on their own after 11–13 days. Patients with mild pancreatitis respond well to medical treatment and only require analgesics and IV fluid resuscitation. Severe pancreatitis, on the other hand, is defined as pancreatitis that results in organ failure and/or local complications such as necrosis, abscess formation, or pseudocysts.[4,5]

In most cases, severe pancreatitis progresses in two stages. For the first 2 weeks after the onset of symptoms, the

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Systemic Inflammatory Response Syndrome (SIRS) is evident. The development of SIRS-related pulmonary, cardiovascular, and renal failure is thought to be influenced by pro-inflammatory mediators. Pancreatic necrosis, on the other hand, manifests itself fully within the first 4 days after the onset of symptoms. Despite the fact that SIRS can be found in the early stages of acute pancreatitis without considerable pancreatic necrosis, computed tomography (CT) scans show pancreatic necrosis in the majority of patients with severe early organ failure.[6,7] Low molecular weight heparin (LMWH) is heparin salts with a molecular weight of <8000 Da on average and at least 60% of all chains with a molecular weight <8000 Da. These are made in a variety of ways by fractionating or depolymerizing polymeric heparin.[8,9] Severe acute pancreatitis (SAP) is a life-threatening condition. It has a mortality rate of up to 25–40%.[6,7] SAP is usually exacerbated by systemic inflammatory cascades and microcirculatory disturbance-related morbidity as a result of infected pre pancreatic necrosis.

Multi-organ failure is triggered by microcirculation disruption, which plays a significant role in the progression of the disease.[10,11] The research for a newer method of treatment is a hot topic in the field of pancreatic surgery due to the high death rate. LMWH has been shown to lower the release of cytokines and inflammatory mediators, resulting in improved pancreatic microcirculation.[12,13] LMWH reduces ET-1, which improves microcirculation and has an anti-thrombus effect, preventing microthrombi from forming in the pancreas.[6,14]

Aims and objectives

The aim of the study was to determine the efficacy of LMWH therapy in patients with SAP.

MATERIALS AND METHODS

This is a randomized, prospective, comparative, and clinical study conducted in the Department of General Surgery, Sri Venkateswara Ramnarayan Ruia Government General Hospital (SVRRGGH), Tirupati from September 2020 to December 2021. All patients in the Department of General Surgery, SVRRGGH - Tirupati, were screened for study based on the following inclusion and exclusion criteria.

Inclusion criteria

The following criteria were included in the study:

- SAP with organ dysfunction and/or pancreatic necrosis.
- Blood calcium <1.87 mMol/L (7.5 mg/dL).
- Acute physiology and chronic health evaluation score (APACHE) II =8.
- Balthazar CT score=Class II.
- Subjects who give written and informed consent.

Exclusion criteria

The following criteria were excluded from the study:

- Sensitive to LMWH.
- Pregnant women.
- Lactating mother.
- Children <12 years of age.
- Coagulation disorders.
- Undergoing hemodialysis.

Patients satisfying the inclusion criteria were enrolled after taking informed consent and 100 patients were assigned into two groups, 50 patients in each group by random number table. Group A patients underwent conventional therapy, including management of shock, maintenance of water and electrolytes balance, fasting, gastrointestinal decompression, administration of pancreatic enzymes inhibitor (octreotide), antibiotics (cephalosporins and metronidazole), and oral magnesium sulfate and symptomatic treatment. Group B patients received conventional therapy plus 100 mcg/kg/day of subcutaneous LMWH from the admission day and continued for 7 days.

Statistical software

The data were analyzed using SPSS 15.0 statistical software, graphs, tables, and other illustrations were created using Microsoft Word and Excel.

RESULTS

A comparative and case–control study with 50 cases and 50 controls is undertaken to study the effect of LMWH in the treatment of SAP.

In our study, we enrolled 100 patients in two divided groups. Thrity-two patients in the age group of 18–30 followed by 25 patients in 31–40 years, 20 patients in >60 years, 14 patients in 41–50 years, and only nine patients in 51–60 years of age group (Table 1).

Out of the 100 patients, 50 patients were in conventional group and 50 patients were in heparin group. Mostly male

Table 1: Comparison of age categories among the heparin and conventional groups

Age group (years)	Conventional	Heparin	Total
18–30	7	25	32
31–40	11	14	25
41–50	10	4	14
51–60	4	5	9
>60	18	2	20
Total	50	50	100

patients were enrolled. Eighty-three were male and 17 were female (Table 2).

In our study, 40 complications were observed out of which 17 patients were in conventional group and 23 were in heparin group. Incidence of complications is statistically similar in two groups with P=1.00 (Table 3).

In our study, we observed organ failure in 37 patients out which 14 patients were in conventional group and 23 were in heparin group. Incidence of organ failure is statistically similar in two groups with P=0.062 (Table 4).

Cured of illness is statistically similar in two groups with P=1.00 (Table 5).

In heparin group, minimum hospital stay is 5 days, maximum hospital stay is 17 days. In conventional group, minimum hospital stay is 4 days, maximum hospital stay is 21 days. Heparin group has less hospital stay comparatively. However, it is insignificant with P=0.187 (Table 6).

The table below shows the comparison of complete blood count parameters at admission, 1st week and 2nd week of admission in both the group (Table 7).

The table below shows the comparison of serum amylase and serum calcium at the time of admission, 1st week and 2nd week of admission in both the groups (Table 8).

The table below shows the comparison of liver function test at admission, 1st week and 2nd week of admission in both the groups (Table 9).

Table 2: Comparison of gender groups among the heparin and conventional groups

Gender	Conventional	Heparin	Total
Female	9	8	17
Male	41	42	83
Total	50	50	100

Table 3: Distribution of study population based on complications among the groups

Complications	Conventional	Heparin	Total	P value
No	33	27	60	0.221
Yes	17	23	40	

Table 4: Distribution of study population based on any organ failure among the groups

Organ failure	Conventional	Heparin	Total	P value
No	36	27	63	0.062
Yes	14	23	37	
Total	50	50	100	

The table below shows the comparison of renal parameters at admission, 1st week and 2nd week of admission in both the groups (Table 10).

The table below shows the comparison of serum electrolytes at admission, 1st week and 2nd week of admission in both the groups (Table 11).

There was no statistical significance in arterial blood gas (ABG) levels (Table 12).

In our study, comparison of Balthazar, Necrosis, and CT severity scores is showed no statistically significant differences (Table 13).

DISCUSSION

Acute pancreatitis may be caused by a variety of factors. Each etiology seems to have an effect on the pancreatic acinar cells, resulting in the premature activation and retention of powerful proteolytic enzymes.

Macrophages, neutrophils, and endothelial cells are stimulated in the early stages of pancreatitis. During acute pancreatitis, proinflammatory cytokines and inflammation factors are generated, which have been linked to the advancement of pancreatitis-related microvascular disruption and hemorrhagic necrosis. Ischemia reperfusion damage and small thrombus are linked to a disruption in pancreatic microcirculation, which leads to increased cytokine release. The inflammatory mediators that are generated may cause local and systemic consequences, which can lead to Multiple Organ Failure (MOF). In the majority of SAP patients, MOF is the cause of mortality. As a result, reducing cytokines and improving pancreatic microcirculation are critical in the therapy of SAP. The quest for innovative treatment modalities is a significant topic in the area of pancreatic surgery due to the high death rate.

Table 5: Distribution of study population based on cured illness among the groups

Illness cured	Conventional	Heparin	Total	P value
Expired	1	1	2	1.00
Yes	49	49	98	
Total	50	50	100	

Table 6: Comparison of hospital stay in days in both the groups

Hospital stay (days)	Conventional	Heparin	Total
<5 days	1	0	1
5–10 days	24	31	55
11–15 days	13	17	30
>15 days	12	2	14
Total	50	50	100

Table 7: Comparison of CBC parameters at admission, 1st week and 2nd week of admission in both the groups

Variables	Group	At admission	Follow-up after 1 week	Follow-up after 2 weeks
Total count	Heparin	17191.70±3668.34	14283.27±3510.27	12067.55±2787.05
	Conventional	15758.30±2965.25	15691.47±2906.57	13631.43±3142.82
	P value	0.03*	0.03*	0.01*
PCV	Heparin	44.82±5.20	46.47±2.93	47.58±5.66
	Conventional	42.85±5.72	45.53±5.87	42.84±5.61
	P value	0.08	0.31	0.001**
Platelet count	Heparin	2.06±0.63	2.1288±0.58	2.0735±0.59
	Conventional	2.10±0.57	2.1384±0.59	2.1369±0.55
	P value	0.75	0.93	0.58

CBC: Complete blood count, PVC: Packed cell volume
(*Significant p<0.05)

Table 8: Comparison of serum amylase, and calcium at admission, 1st week and 2nd week of admission in both the groups

Variables	Group	At admission	Follow-up after 1 week	Follow-up after 2 weeks
S. amylase	Heparin	1116.68±891.19	964.24±716.032	678.02±458.30
	Conventional	1316.60±1138.39	1325.53±1148.422	1011.94±874.74
	P value	0.33	0.06	0.02*
S. calcium	Heparin	8.81±1.22	8.99±0.83	9.18±0.71
	Conventional	8.99±1.17	8.98±1.18	9.11±0.82
	P value	0.45	0.96	0.66

S. amylase: Serum amylase, S. calcium: Serum calcium
(*Significant p<0.05)

Table 9: Comparison of LFT at admission, 1st week and 2nd week of admission in both the groups

Variables	Group	At admission	Follow-up after 1 week	Follow-up after 2 weeks
Total bilirubin	Conventional	1.17±0.58	1.07±0.58	1.05±0.50
	Heparin	1.11±0.63	1.01±0.50	1.01±0.50
	P value	0.63	0.60	0.73
Direct bilirubin	Conventional	0.47±0.44	0.39±0.43	0.37±0.34
	Heparin	0.37±0.44	0.34±0.32	0.34±0.32
	P value	0.28	0.54	0.65
S. albumin	Conventional	3.56±0.68	3.85±0.71	3.79±0.75
	Heparin	3.89±0.69	3.74±0.72	3.81±0.45
	P value	0.01*	0.43	0.87
AST/SGOT	Conventional	176.3±204.99	156.09±191.04	131.19±142.55
	Heparin	151.61±166.66	131.79±132.27	131.79±132.27
	P value	0.51	0.46	0.98
ALT/SGPT	Conventional	85.18±69.37	78.56±62.74	70.04±58.24
	Heparin	84.01±59.67	72.34±55.30	72.35±55.30
	p Value	0.92	0.60	0.84
ALP	Conventional	124.26±88.21	123.39±66.58	112.45±53.72
	Heparin	125.20±74.11	107.39±48.20	107.39±48.20
	p Value	0.94	0.17	0.62

LFT: Liver function test, S. amylase: Serum amylase, AST: Aspartate transaminase, ALT: Alanine transaminase, ALP: Alkaline phosphatase, SGOT: Serum glutamic-oxaloacetic transaminase
(*Significant p<0.05)

Establishing the diagnosis, evaluating the severity, treating the principal symptoms (pain, nausea, vomiting, and hypovolemia), that is, nutrition, vigorous fluid-electrolyte balance, and pain management, and restricting its development are the main modalities of therapy. The majority of patients need narcotics. For pain relief, meperidine and its equivalents are probably preferable to morphine. The role of prophylactic antibiotics is debatable. Peritoneal dialysis, nasogastric decompression, and other measures to lower gastrointestinal or pancreatic output are treatments with limited or unproven benefit (i.e., histamine 2 blockers, proton pump inhibitors, antacids, atropine, somatostatin, glucagon, and calcitonin). Anti-inflammatory drugs (e.g., steroids, prostaglandins, and indomethacin) have not helped, but new experimental investigations show that particular inhibition of cyclooxygenase-2 may be useful.

Table 10: Comparison of renal parameters at admission, 1st week and 2nd week of admission in both the groups

Variables	Group	At admission	Follow-up after 1 week	Follow-up after 2 weeks
BUN	Conventional	18.40±8.65	18.22±8.80	15.42±4.96
	Heparin	14.68±5.13	15.42±4.96	12.18±3.19
	P value	0.01*	0.05*	0.001*
Creatinine	Conventional	1.18±0.61	1.21±0.62	1.24±0.52
	Heparin	1.33±0.59	1.41±0.76	1.33±0.59
	P value	0.24	0.14	0.45

BUN: Blood urea nitrogen
(*Significant p<0.05)

Table 11: Comparison of serum electrolytes at admission, 1st week and 2nd week of admission in both the groups

Variables	Group	At admission	Follow-up after 1 week	Follow-up after 2 weeks
Na	Conventional	132.50±4.12	132.45±4.14	137.16±3.92
	Heparin	132.74±4.46	137.80±4.47	137.80±4.47
	P value	0.78	0.001*	0.45
K	Conventional	4.50±0.75	4.51±0.75	4.38±0.37
	Heparin	4.51±0.77	4.33±0.37	5.99±0.40
	P value	0.93	0.12	0.001*
Cl	Conventional	99.04±8.36	98.84±8.42	103.55±6.81
	Heparin	98.70±8.01	102.06±6.36	105.41±11.93
	P value	0.83	0.03*	0.347

(*Significant p<0.05)

Table 12: Comparison of ABG at admission, 1st week and 2nd week of admission in both the groups

ABG	Conventional	Heparin	Total	P value
At admission				
Normal	31	27	58	0.51
Met Acidosis	7	13	20	
Respiratory acidosis	9	9	18	
Respiratory alkalosis	3	1	4	
At 1st week				
Normal	31	32	63	0.46
Respiratory acidosis	9	8	17	
Metabolic acidosis	6	8	14	
Respiratory alkalosis	3	1	4	
AT 2nd weeks				
Normal	34	32	66	0.45
Respiratory acidosis	8	8	16	
Metabolic acidosis	4	8	12	
Respiratory alkalosis	3	1	4	

ABG: Arterial blood gas

Table 13: Comparison of Balthazar, Necrosis, and CT severity scores at admission, 1st week and 2nd week of admission in both the groups

Score	Group	At admission	Follow-up after 1 week	Follow-up after 2 weeks
Balthazar	Conventional	2.02±1.23	1.86±1.44	1.76±1.21
	Heparin	2.04±1.64	1.82±1.23	1.82±1.23
	P value	0.94	0.88	0.80
Necrosis	Conventional	0.94±1.21	0.51±1.06	0.51±1.06
	Heparin	0.62±1.22	0.55±1.13	0.55±1.13
	P value	0.19	0.85	0.85
CT severity	Conventional	2.92±2.10	2.37±2.27	2.27±2.04
	Heparin	2.66±2.64	2.37±2.15	2.37±2.15
	P value	0.58	1.00	0.81

CT: Computed tomography

Many attempts to treat pancreatitis with agents that inhibit activated proteolytic enzymes (e.g., aprotinin and gabexate mesylate), hypothermia, thoracic duct drainage, plasmapheresis, procainamide, isoproterenol, heparin, dextran, vasopressin, and anti-platelet-activating factor have been supported by experimental animal studies, but human clinical trials failed to show favorable effect.

Enoxaparin is an LMWH that binds to antithrombin-III and speeds up its activity (AT-III). Enoxaparin selectively potentiates the inhibition of coagulation factors Xa and IIa through activating AT-III. Factor Xa prevents fibrin clot formation by catalyzing the conversion of prothrombin to thrombin. The heparin-AT-III combination inhibits trypsinogen activation and reduces the activity of trypsin and chymotrypsin.[15] Heparin's anti-inflammatory activities are distinct from its anticoagulant capabilities.[16] Heparin inhibits leukocyte adherence to vascular endothelial cells and lowers the recruitment of inflammatory cells to the site of injury.[17] LMWH has been demonstrated to reduce the production of microthrombosis and improve microcirculation by downregulating ET-1, TNF-, and IL-6.[1]

The purpose of this study was to see how effective LMWH is in treating SAP by improving microcirculation. Our research comprised 100 patients who were randomly assigned to one of two groups: Conventional treatment for SAP (n=50) or conventional therapy +LMWH (n=50).

The average age of the participants was 18–30 years old. In both groups, 32% of the patients were between the ages of 18 and 30, which was comparable to the previous studies. In each research group, the male population was roughly 82%, which was similar to earlier studies.

Experimental and clinical investigations have shown that LMWH medication may reduce the damage to the pancreas, lungs, kidneys, and brain in SAP, as well as prevent SAP-mediated organ damage, by lowering serum ET-I levels and decreasing the activation of NF-KB to lower TNF-α and IL-6 levels. IL-6 is produced by IL-1 and seems to be associated with the severity of SAP. It appears to diminish the development of microthrombosis, improving the microcirculation of the pancreas, lung, kidney, and brain, and lowering SAP mortality. According to these investigations, LMWH had a clear impact on the therapy of SAP in both people and rats. In these clinical tests, it was discovered that the LT group had a much greater clinical improvement rate than the C group, and that the LT group's complications, operation rate, mortality, and mean hospital stays were all significantly lower than the C group's. These findings revealed that LMWH had a clinically meaningful impact on the treatment of SAP. In the first therapy of deep venous thrombosis, Leizorovicz et al.,[18] compared the impact and safety of LMWH with unfractionated heparin. In the treatment of venous thrombosis, the findings showed that LMWH had a greater benefit-to-risk ratio than unfractionated heparin.[19]

The coagulation function of all the patients in the LT group had no significant difference before and after LMWH medication in the research done by Lu Xin-Sheng et al., and no bleeding issues occurred. The improvement in clinical symptoms was 96.7% in both controls and patients. Renal issues were more prevalent among the patients than sepsis-related complications among the controls. It was, however, statistically insignificant. Organ failure was somewhat more common among the patients, although the difference was not statistically significant.[5]

In both groups, the death rate was 2%, and 49 patients in each group were cured of their disease after therapy. The minimum hospital stay in the heparin group is 5 days, while the highest hospital stay is 17 days. In the conventional group, the minimum hospital stay is 4 days and the maximum hospital stay is 21 days. Hospital stay is shorter in the heparin group. The results for hematocrit, platelet count, random blood sugar, serum amylase, serum calcium, serum potassium, serum chloride, serum creatinine, liver function test (LFT), and arterial blood gas (ABG) analysis were similar when comparing the laboratory parameters in the two groups at three time points, namely, at admission, after 1 week, and after 2 weeks.

On 1 and 2 weeks of follow-up, however, there was a considerable improvement in total leucocyte count, and the prothrombin and partial thromboplastin time were significantly reduced. In the LMWH group, serum sodium had normalized earlier. By the 2nd week, the conventional treatment group had a lowered blood urea nitrogen (BUN) level. At admission, 1st and 2nd week of follow-up, the Necrosis score, Balthazar grade, and CT severity score were equivalent and statistically similar in both groups.

Lu et al., studied the effect of LMWH in preventing PE in 256 individuals with SAP in a randomized trial. According to the findings, LMWH reduces the incidence of PE and improves the survival rate in SAP patients.[20] A clinical study conducted by Lu et al., showed that LMWH lowers mortality and improves CT scores in individuals with SAP.[5] Jiao et al., found that LMWH lowers white blood cell count and raises arterial blood partial oxygen pressure in patients with AP in a small study (17 cases).[21]

Limitations of the study

There are no limitations to this study.

CONCLUSIONS

For the treatment of SAP, LMWH is a straightforward, safe, effective, and cost-efficient technique. It is suitable for usage in any hospital. There was no significant improvement in the impact of traditional SAP therapy with LMWH, nor was there any reduction in SAP mortality.

Both the controls and the cases had similar improvements in clinical symptoms, death rates, and the number of patients who were cured of their condition.

Renal problems were more prevalent among the patients than sepsis-related complications among the conventional group. It was, however, statistically insignificant.

In both groups, the average length of stay in the hospital was 9–10 days. The heparin group spends less time in the hospital. However, it is statistically insignificant. The results for hematocrit, platelet count, random blood sugar, serum amylase, serum calcium, serum potassium, serum chloride, serum creatinine, LFT, and arterial blood gas analysis were similar when comparing the laboratory parameters in the two groups at three time points, namely, at admission, after 1 week, and after 2 weeks.

On 1 and 2 weeks of follow-up, however, there was a considerable improvement in total leucocyte count, and the prothrombin and partial thromboplastin times were much shorter. In the LMWH group, serum sodium had returned to normal in earlier time. By the 2nd week, the conventional treatment group had a reduced BUN level. At admission, 1st and 2nd week of follow-up, the Necrosis score, Balthazar grade, and CT severity score were equivalent and statistically similar in both groups. However, additional human studies are needed to determine if LMWH is effective in SAP.

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