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Low Molecular Weight Heparin in the Treatment of Severe Acute Pancreatitis: A Prospective Clinical Study

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ABSTRACT

Acute pancreatitis is a disease that has many aetiologies. Each aetiology seems to affect the pancreatic acinar cell in some way that results in premature activation and retention of potent proteolytic enzymes. Severe acute pancreatitis (SAP) is frequently a lethal disorder. Its mortality rate reaches up to 25-40%. SAP is usually complicated with systemic inflammatory cascades and microcirculatory disturbance-related morbidity due to infected pre pancreatic necrosis. Our objective was to study the effect of low molecular weight heparin (LMWH) in the treatment of severe acute pancreatitis (SAP). A total of 60 severe acute pancreatitis patients admitted to the hospital (MSRMTH) from September 2010 to October 2018 were included in the study. Necessary data was collected. 30 patients were grouped as control (A) and 30 patients as a test (LT). A group treated as conventional method and an LT group were given LMWH with conventional treatment. And comparison was done between the two groups. Patients satisfying the inclusion criteria were enrolled after taking informed consent and were assigned into 2 groups 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 (Sandostatin), 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. The mean age of presentation was 39-45 years. 50% of the patients were aged between 30 and 50 years in both groups. The male population was around 80% in each study group. Improvement in the clinical symptoms in both the controls and cases were equal to 96.7%. LMWH is a simple, safe, economic and effective method for the treatment of SAP. It can be used in every hospital. Renal complications were more common among the cases as compared to complications related to sepsis among the control group. However, it was statistically not significant. The incidence of organ failure was slightly more but not statistically significant amongst the cases. However, larger human trials need to be conducted to evaluate the beneficial use.

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Key Words

Low molecular weight heparin, Severe Acute Pancreatitis, Pancreatitis

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INTRODUCTION

Severe acute pancreatitis (SAP) is severe and frequently a lethal disorder. Its mortality rate reaches up to 25-40%[1,2]. SAP is usually complicated with systemic inflammatory cascades and microcirculatory disturbance-related morbidity due to infected pre pancreatic necrosis. Microcirculation disturbance is a trigger factor and plays an important role in the development of multi-organ failure[3,4]. Due to the high mortality rate, search for newer modalities of treatment is a hot point in the field of pancreatic surgery. LMWH is known to reduce the release of cytokines and inflammatory mediators and result in the improvement of microcirculation of the pancreas. LMWH decreases ET-1 leading to improvement of microcirculation system and anti-thrombus effect to reduce the formation of microthrombi in the pancreas[5].

Aims and Objectives: To study the effect of low molecular weight heparin (LMWH) in the treatment of severe acute pancreatitis (SAP). The efficiency of LMWH in improving the outcome in patients with severe acute pancreatitis.

MATERIALS AND METHODS

This is a randomized, prospective, comparative clinical study conducted in the Department of General Surgery of M. S. Ramaiah Hospitals, Bangalore from October 2010 to March 2018.

Inclusion Criteria:

- Organ dysfunction and pancreatic necrosis, abscess or pseudocyst
- Blood calcium <1.87 mmol/L (7.5mg/dL)
- Acute physiology and chronic health evaluation (APACHE) II score = 8
- Balthazar computed tomography (CT) score = class II

Exclusion Criteria:

- Sensitive to LMWH
- Pregnant
- Breastfeeding
- Coagulation disorders
- Undergoing haemodialysis

Sample Size Estimation:[6] Proportion Known populations

$n = [(z^2\ pq) + ME^2]/[ME^2 + z^2\ pq/N]$

Proportion Unknown population

$n = [(z^2\ pq) + ME^2]/(ME^2)$

ME: is the margin of error, a measure of precision and Z is 1.96 as a critical value at 95% CI

N: population size

n: Sample size

σ: Standard deviation

z: Critical value based on Normal distribution at 95% Confidence Interval.

Patients satisfying the inclusion criteria were enrolled after taking informed consent and were assigned into 2 groups (30 patients in each group) by random number table. Group A patients underwent conventional therapy including management of shock, maintenance of water and electrolyte balance, fasting, gastrointestinal decompression, administration of pancreatic enzymes inhibitor (Sandostatin), 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.

Descriptive and inferential statistical analysis was carried out in the present study. Results on continuous measurements were presented on Mean ±SD (Min-Max) and results on categorical measurements were presented in Number (%). Significance was assessed at a 5% level of significance[7,8]. Chi-square test, Fisher Exact test and students t-test were used. A $p<0.05$ was considered significant. Data were entered into MS Excel and analysed with SAS 9.2, SPSS 15.0, Stata 10.1, MedCalc 9.0.1, Systat 12.0 and R environment ver.2.11.1.

RESULTS AND DISCUSSIONS

Improvement in the clinical symptoms in both the controls and cases was equal (96.7 %). Renal complications were more common among the cases as compared to complications related to sepsis among the control group. However, it was statistically not significant. The incidence of organ failure was slightly more but not statistically significant amongst the cases. The mortality rate was equal to 3.3% in either group and 29 patients in each group were cured of the illness post-treatment. The mean hospital stay was comparable in both groups and was 9-10 days. On comparing the laboratory parameters in the two groups at 3 timings, i.e., at admission, after 1 and 2 weeks, the results were similar for the hematocrit, platelet count, random blood sugar, serum amylase, serum calcium, serum potassium, serum chloride, serum creatinine, liver function test and arterial blood gas analysis. However, there was a significant improvement in the total leucocyte count on 1 and 2 weeks of follow up, the prothrombin and partial thromboplastin time was significantly less on 1 week of follow up. Serum sodium had normalized earlier in the LMWH group. Blood urea nitrogen was lower in the conventional therapy group by 2nd week. The necrosis score, Balthazar grade and CT severity scores swere

Table 1: Demographic Distribution and Age distribution of patients studied and Gender distribution of patients studied

	Cases		Controls	
Age in Years	**No**	**Percentage**	**No**	**Percentage**
18-30	10	33.3	4	13.3
31-40	14	46.7	8	26.7
41-50	1	3.3	6	20.0
51-60	3	10.0	3	10.0
>61	2	6.7	9	30.0
Total	30	100.0	30	100.0
Mean ± SD	39.20±11.48		44.70±14.77	
Gender				
Male	24	80.0	24	80.0
Female	6	20.0	6	20.0
Total	30	100.0	30	100.0

Samples are age-matched with p = 0.113 and Samples are gender-matched with p = 1.000

Table 2: Comparison of complications in two groups of patients studied

	Cases (n = 30)		Controls (n = 30)	
Complications	**No**	**percentage**	**No**	**percentage**
ARDS	1	3.3	1	3.3
ARDS, ARF	1	3.3	0	0.0
ARF	3	10.0	2	6.7
CRF	1	3.3	0	0.0
CRF, cholecystitis	1	3.3	1	3.3
Pancreatic abscess	1	3.3	1	3.3
Pleural effusion	2	6.7	2	6.7
Pneumonia	0	0.0	1	3.3
Pneumonia, liver failure	1	3.3	0	0.0
Sepsis	0	0.0	1	3.3
Sepsis, ARF	0	0.0	1	3.3

The mean age of presentation was 39-45 years. 50 % of the patients were aged between 30 and 50 years in both groups.
The incidence of complications is statistically similar in two groups with p=1.000

Table 3: Comparison of any organ failure in two groups of patients studied

	Cases (n = 30)		Controls (n = 30)	
Any Organ Failure	**No**	**percentage**	**No**	**percentage**
Renal	8	26.7	6	20.0
Respiratory	1	3.3	1	3.3
Hepatic	1	3.3	0	0.0
MODS	1	3.3	0	0.0
SIRS	0	0.0	1	3.3

Incidence of organ failure is statistically similar in two groups with p=0.580

Table 4: (A) Comparison of outcomes of treatment and Comparison of improved clinical symptoms in two groups of patients studied.

	Cases (n = 30)		Controls (n = 30)	
Improved Clinical Symptoms	**No**	**percentage**	**No**	**percentage**
No	1	3.3	1	3.3
Yes	29	96.7	29	96.7
Total	30	100.0	30	100.0

Clinical symptoms are statistically similar in two groups with P=1.000

(B) Comparison of hospitality mortality in two groups of patients studied

	Cases		Controls	
In Hospitality Mortality	**No**	**percentage**	**No**	**percentage**
No	29	96.7	29	96.7
Yes	1	3.3	1	3.3
Total	30	100.0	30	100.0

In-hospital mortality is statistically similar in two groups with p=1.000

(C) Comparison of cured of illness in two groups of patients studied

	Cases		Controls	
Cured of Illness	**No**	**percentage**	**No**	**percentage**
Yes	29	96.7	29	96.7
No	1	3.3	1	3.3
Total	30	100.0	30	100.0

Cured of illness is statistically similar in two groups with p = 1.000

(D) Comparison of in-hospital stay (days) in two groups of patients studied

	Cases		Controls	
Hospital Stay (Days)	**No**	**percentage**	**No**	**percentage**
<5 days	10	33.3	2	6.7
5-10 days	10	33.3	17	56.7
10-15 days	8	26.7	7	23.3
>15 days	2	6.7	4	13.3
Total	30	100.0	30	100.0
Mean ± SD	8.83±4.01		9.93±4.38	

Mean hospital stay is statistically similar in two groups with p = 0.315

Table 5: Comparison of variables in two groups of patients studied.

Variables	Group	At admission	Follow up after 1 week	Follow up after 2 weeks
PT	Cases	15.71 ± 2.69	15.7 ± 2.21	15.7 ± 2.21
	Controls	17.11 ± 2.27	17.2 ± 2.25	15.7 ± 2.21
	P value	0.034*	0.013*	1.000
APTT	Cases	26.38 ± 3.18	25.92 ± 2.35	25.92 ± 2.35
	Controls	30.2 ± 4.09	28.33 ± 4.28	25.92 ± 2.35
	P value	<0.001**	0.010*	1.000
INR	Cases	0.95 ± 0.24	0.92 ± 0.25	0.84 ± 0.26
	Controls	1.01 ± 0.24	0.94 ± 0.24	0.92 ± 0.25
	P value	0.353	0.702	0.253

Table 6: Comparison of Balthazar grade score, necrosis score and CT severity score in the two groups of patients studied.

Variables	Group	At admission	Follow up after 1 week	Follow up after 2 weeks
Balthazar grade score	Cases	1.97±1.47	1.79±1.21	1.79±1.21
	Controls	2.13±1.25	1.93±1.49	1.79±1.21
	P value	0.639	0.699	1.000
Necrosis score	Cases	0.73±1.31	0.62±1.18	0.62±1.18
	Controls	1.1±1.35	0.62±1.18	0.62±1.18
	P value	0.290	1.000	1.000
CT severity score	Cases	2.7±2.51	2.41±2.15	2.41±2.15
	Controls	3.2±2.28	2.55±2.41	2.41±2.15
	P value	0.422	0.819	1.000

comparable and statistically similar in both groups at admission, 1st and 2nd week of follow up.

Acute pancreatitis is a disease that has many etiologies. Each etiology seems to affect the pancreatic acinar cells in some way that results in premature activation and retention of potent proteolytic enzymes. In the early stages of pancreatitis, macrophages, neutrophils and endothelial cells are activated. Proinflammatory cytokines are released and inflammation factors are elevated during acute pancreatitis and have been implicated in the progression of pancreatitis associated microvascular disturbance and hemorrhagic necrosis[9,10]. Ischemia-reperfusion injury and tiny thrombus are closely associated with pancreatic microcirculation disturbance, which causes further secretion of cytokines. The released inflammatory mediators can induce local effects and systemic complications which can finally result in MOF. MOF is the main cause of death in patients with SAP. So attenuation of cytokines and improvement of microcirculation of pancreas is very important in the treatment of SAP. Due to the high mortality rate, searching for a newer modality of treatment is a hot point in the field of pancreatic surgery[11,12]. The main modality of management includes establishing the diagnosis, estimating its severity, addressing the major symptoms (i.e., pain, nausea, vomiting and hypovolemia), i.e., taking care of nutrition, aggressive fluid-electrolyte balance and pain management and limiting its progression. Most patients require narcotic medications. Meperidine and its analogues are probably preferable to morphine for pain management. The role of prophylactic antibiotics is controversial[13,14]. Treatments of limited or unproven value are peritoneal dialysis, nasogastric decompression, other attempts to reduce gastrointestinal or pancreatic secretion (i.e., H2 blockers, proton pump inhibitors, antacids, atropine, somatostatin, glucagon, calcitonin). The use of anti-inflammatory agents (i.e., steroids, prostaglandins and indomethacin) has not been helpful, although recent experimental studies have suggested that specific inhibition of cyclooxygenase-2 might be beneficial.

Many attempts to treat pancreatitis with agents designed to inhibit activated proteolytic enzymes (e.g., aprotinin, gabexate mesilate), hypothermia, thoracic duct drainage, plasmapheresis, procainamide, isoproterenol, heparin, dextran, vasopressin and anti-platelet-activating factor (PAF) have been supported by experimental animal studies, particularly when the treatment is begun before the onset of pancreatitis, human clinical trials have failed to show a beneficial effect on the course of patients with established pancreatitis and at present, none of these treatments is commonly employed. LMWH is known to reduce the release the cytokines and inflammatory mediators and result in the improvement of microcirculation of the pancreas. LMWH decreases ET-1 leading to improvement of microcirculation system and anti-thrombus effect to reduce the formation of microthrombi in the pancreas. This trial was hence conducted to study the effect of LMWH in the treatment of SAP by improving the microcirculation[15,16].

Demographic Characteristics: The mean age of presentation was 39-45 years. 50 % of the patients were aged between 30 and 50 years in both groups which were like other studies. The male population was around 80 % in each study group which was comparable to other studies.

Outcome Parameters: Experimental and clinical studies showed that LMWH therapy can ameliorate the damage of the pancreas, lungs, kidneys and brain in SAP, prevent SAP-mediated organ damage by down-regulating the level of serum ET-I and

suppressing the activity of NF-KB to down-regulate the levels of TNF-a and IL-6. IL-6 is induced by IL-1 and seems to correlate with the severity of the SAP, reduce the formation of micro thrombosis resulting in improvement of the microcirculation of the pancreas, lung, kidney and brain and decrease the mortality in SAP. These studies suggested that LMWH had an obvious effect on the treatment of SAP in humans and rats. In these clinical studies, it was found that in the LT group the clinical presentation improvement rate was significantly higher than that in the C group and the complications, operation rate, mortality and mean hospital stays were lower than those of the C group. These results suggested that LMWH also had a significant effect on the treatment of SAP clinically. Leizorovicz *et al*. did a study to compare the effect and safety of LMWH and unfractionated heparin in the initial treatment of deep venous thrombosis. The results indicated that LMWH appeared to have a higher benefit to risk ratio than unfractionated heparin in the treatment of venous thrombosis. In the study done by Lu Xin-Sheng *et al*. the coagulation function of all the patients in the LT group had no statistical difference before and after LMWH treatment and no bleeding complications occurred[17].

CONCLUSIONS

LMWH is a simple, safe, economic and effective method for the treatment of SAP. It can be used in every hospital. LMWH neither showed any marked enhancement in the effect of conventional treatment for SAP, nor there was a decrease in the mortality of SAP. Improvement in the clinical symptoms, mortality rate and number of patients cured of the illness in both the controls and cases were equal.

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