Role of Low Molecular Weight Heparin in the Management of Acute Pancreatitis – A Prospective Study in a Tertiary Care Hospital, Tirupati

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ABSTRACT

BACKGROUND

Acute pancreatitis (AP) runs a moderately severe and severe course in around 20 % - 30 % of cases. It can progress into severe acute pancreatitis (SAP) and pancreatic necrosis if not appropriately intervened. This study aims to study the effect of low molecular weight heparin in treating acute pancreatitis.

METHODS

This was a prospective hospital-based study. Patients presenting to the emergency ward in our hospital with acute pancreatitis features with a duration of 72 hours or less and fulfilling the inclusion and exclusion criteria were included. They were randomly divided into those receiving standard care alone, and standard care low molecular weight heparin in addition to routine management, and results were calculated using the chi-square test.

RESULTS

The number of patients in the present study was 100. The most common age group affected was 30 - 40 years. Out of 100, 94 were male patients, and 6 were female patients. There is no notable difference in the mean age group between the groups. The recovery percentage is 98 % in patients with low molecular weight heparin. The recovery rate is 86 % in patients without low molecular weight heparin. The mortality rate is 2 % in patients with low molecular weight heparin. The mortality rate is 14 % in patients without low molecular weight heparin. It was found that the low molecular weight heparin usage has brought a significant difference in the patients. Outcome affected with acute pancreatitis had a significant P - value of 0.02.

CONCLUSIONS

The low molecular weight heparin by its property of improving the micro circulations relieves the abdominal pain, prevents the disease's further progression, and hence reduces the duration of hospital stay, morbidity, and mortality associated with the disease and enhances the recovery rate.

KEYWORDS

Acute Pancreatitis, Severe Acute Pancreatitis, Low Molecular Weight Heparin, Microcirculation, Systemic Inflammatory Response

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BACKGROUND

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 %.[1]

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.[2] 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.[3]

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 cells[4] and reduces the activation of platelets.[5] In addition, low molecular weight heparin minimizes the formation of microthrombi and improves microcirculation.[6,7] 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.

In this scenario, our study was intended to determine the efficacy of low molecular weight heparin in preventing acute pancreatitis progression into more severe forms of severe acute pancreatitis, moderately severe acute pancreatitis, and pancreatic necrosis (PN).

METHODS

This hospital-based study was conducted in the Department of General Surgery over one year in S.V.R.R.G.G.H. hospital, Tirupathi. The eligible hundred subjects fulfilling the inclusion and exclusion criteria were randomly divided into two groups using the lottery method. The two groups were those receiving standard care alone and those receiving routine care plus low molecular weight heparin and were studied during their hospital course.

Inclusion Criteria

Patients diagnosed with acute pancreatitis based on the following criteria:

1. Abdominal pain characteristic of acute pancreatitis with a duration < 72 hrs.
2. Serum amylase and lipase ≥ 3 times the upper limit of normal.
3. Radiological findings suggestive of acute pancreatitis.

Exclusion Criteria

1. The presence of chronic pancreatitis and gall stone induced pancreatitis
2. Hypersensitivity to the administration of low molecular weight heparin or radiocontrast agents
3. Computed tomography (CT) findings suggestive of complicated pancreatitis
4. Pregnant or breastfeeding
5. Coagulation disturbances
6. Severe comorbidities (Charlson Comorbidity Index (CCI) score ≥ 5).[8]

The study was conducted in our tertiary care hospital for over one year. Our study patients underwent a general physical examination and clinical examination after obtaining written informed consent: routine hematological, biological, and radiological investigations were done for each patient. The diagnosis was based on the American College of Gastroenterology guideline with the presence of at least two of the following three:

1. Characteristic epigastric pain
2. Serum amylase value of greater than three times the upper limit of standard weight
3. Characteristic findings of acute pancreatitis in imaging.[9]

All patients included in our study had both 1 and 2. Moderately severe and severe acute pancreatitis was defined according to the revised Atlanta criteria. Moderately severe acute pancreatitis is characterized by local complications (peripancreatic fluid collections and pancreatic and peri - pancreatic necrosis) and transient organ failure (<48 h). Severe acute pancreatitis is characterized by persistent organ failure (> 48 h). Harmless acute pancreatitis score (rebound tenderness on abdominal examination and abnormal hematocrit and creatinine levels, one point each) was calculated,[10] and computed tomography results were classified according to the Balthazar and Modified Computed Tomography Severity Index (MCTSI).[11]

Those satisfying the inclusion criteria were randomly assigned into groups and were started on treatment in which one group received conventional therapy, which includes management of shock, fasting, maintenance of water and electrolytes balance, gastrointestinal decompression, administration of pancreatic enzymes inhibitor (octreotide), antibiotics (cephalosporin and metronidazole) and symptomatic treatment. The other group received treatment

with above mentioned conventional treatment plus administering low molecular weight heparin at 100 micrograms/kg per day subcutaneous injection starting from the admission day and continuing for the next seven days.

Statistical Analysis

The results were studied. Data was entered in Microsoft Excel, and analysis was done using statistical package for social sciences (SPSS) version 17. Categorical data was expressed in proportions and continuous variables in means and standard deviations. Chi-square and Fishers exact test were applied wherever necessary. A P - value of < 0.05 was considered statistically significant.

Laboratory Tests

The following parameters were monitored on admission and during the next seven days: hematocrit, white blood cell count, serum amylase and lipase, calcium, creatinine, albumin, transaminases, bilirubin, C-reactive protein, blood glucose level, and international normalized ratio.

CT Scores

Abdominal CT scans of all patients was performed at hospital admission (in the first 12 hrs) and as repeated on the seventh day from the day of admission. Acute pancreatitis severity was assessed using M.C.T.S.I. According to the M.C.T.S.I., scores between 0 and 2 indicated mild, 4 and 6 moderate, and 8 and 10 severe AP forms. According to the M.C.T.S.I. in initial CT patients with moderately severe and severe pancreatitis were excluded from the study.

RESULTS

Age in Years	No of Patients	Percentage
< 30	24	24 %
30 - 40	30	30 %
40 - 50	29	29 %
50 - 60	10	10 %
> 60	7	7 %

Table 1. Distribution of Study Population Based on Age

Treatment	Number of Patients	Mean age Group in Years
Standard care	50	40
Standard care + L.M.W.H.	50	40.4

Table. 2. Mean Age Distribution

Sex	No of Patients	Percentage
Male	94	94 %
Female	6	6 %

Table 3. Distribution of the Study Group Based on Sex

	Treatment	
Gender	With heparin	Without heparin
Male	48	46
Female	2	4

Table 4. Sex Distribution among the Group (Chi Square 0.177 P - Value: 0.6)

Outcome	No of Patients	Percentage
Recovered	92	92 %
Died	8	8 %

Table 5. Distribution Based on the Outcome

	Treatment	
Outcome	With heparin	Without heparin
Recovered	49	43
Died	1	7

Table 6. Distribution among the Groups Based on the Outcome (P Value: 0.05 Fishers Exact Test)

In our study, the most common age group affected is 30- 40 years, and the overall age group was between 25 and 65 years. The mean age distribution of the patients treated with standard care alone is 40. Those treated with routine maintenance and low molecular weight heparin are 40.4. There was not much significant difference between the mean ages of the two groups. In our study among the 100 patients studied 94 patients were males, and six patients were females with a percentage of 94 % and 6 %. In our study, among the 100 patients studied, 92 were recovered, and eight were dead.

In our present study, it was found that among the 100 patients studied, the outcome was better in patients who received low molecular weight heparin in addition to the standard care with a recovery rate of 98 % and mortality rate of 2 %, with low molecular weight heparin. The recovery percentage was 86 %, and the mortality percentage was 14 % in patients who received only routine maintenance. Among the 50 patients treated with heparin, 49 had recovered, which is significant compared with those treated without heparin - a significant P - value was calculated using fishers' exact test.

DISCUSSION

Acute pancreatitis runs a severe course in a minority of patients. However, this subset is responsible for the burden of the disease. Therefore, decreasing the burden of acute pancreatitis can only be achieved with successful management strategies towards the condition. Previous clinical and experimental data revealed that acute pancreatitis fate was dictated in the early hours of pancreatitis, and microcirculation impairment was the pivotal derangement leading to necrosis and further damage. The presence of a hematocrit value of greater than 44 % and failing to decrease it with intravenous fluid boluses was considered to predict a severe prognosis. Hemoconcentration may cause microcirculation impairment and may play an essential role in the transition of edematous to necrotizing pancreatitis. The abundance of several inflammatory cytokines in the pancreas microenvironment in the setting of acute pancreatitis is also considered as one of the precipitating events.

Pro-inflammatory cytokines, such as interleukins- IL-1β, IL-6, and TNF-α increase during acute pancreatitis and are responsible for the progression of microvascular disturbance. The microcirculatory disruption is as essential as enzymatic and free radical damage in the pathogenesis of acute pancreatitis. Thrombosis, associated with denudation of endothelial cells, sludge formation, and resultant stasis, in the pancreatic circulation is an event occurring as early as mucoid swelling within the acini in the course of AP. These described changes in the pancreatic

tissue usually start from the gland's peripheral part and extend toward the gland's center part. In addition to the microthrombi formation, there will be an accumulation of fibrin at the distal portion of the thrombus.

Enoxaparin is low molecular weight heparin that binds to antithrombin III and accelerates antithrombin III activity (A.T.I.I.I.). By activating antithrombin III, Enoxaparin preferentially potentiates the inhibition of coagulation factors Xa and IIa. Factor Xa is involved in catalyzing prothrombin's conversion to thrombin and prevents the formation of fibrin clot. The heparin - antithrombin III complex reduces the activity of trypsin and chymotrypsin. It inhibits trypsinogen activation, thereby preventing the progression of the disease.

The anti-inflammatory properties of heparin are different from its anticoagulant activity. Heparin reduces inflammatory cells into the cells' recruitment of injury and leukocyte adhesion to vascular endothelial cells. Low molecular weight heparin has been shown to down-regulate endothelin–1(ET-1), TNF-α, and IL-6, leading to the reduction of micro thrombosis formation, improving microcirculation. Furthermore, heparin inhibits pancreatic enzymes and accelerates pancreatic regeneration during the disease.

However, hemorrhage into the parenchyma resulting from microcirculatory paresis is inevitable, ranging from minimal to massive in the form of diapedesis. Enoxaparin may paradoxically prevent bleeding, preserving the patency of microcirculation. Some experimental and clinical studies have already shown that treatment with heparin inhibits the development of ischemia/reperfusion-induced acute pancreatitis, lessens the severity of taurocholate-induced acute pancreatitis, and decreases the incidence of pancreatic encephalopathy (PE). Recent clinical studies have shown that pre-procedural heparin administration significantly reduces endoscopic retrograde cholangitis pancreatography (ERCP) related pancreatitis. It improves the course of hypertriglyceridemia-induced acute pancreatitis and may improve severe acute pancreatitis prognosis.[12] There are experimental and clinical studies on the protective effect of heparin in the treatment of acute pancreatitis.

Qiu et al. demonstrated the protective effect of low molecular weight heparin on pancreatic encephalopathy progression in rats with severe acute pancreatitis. They reported that the severity of brain damage significantly decreases in the low molecular weight heparin group.[11] Another study showed that low molecular weight heparin decreases TNF-α and ET-1 and has a positive effect on morphological changes and vascular flow in rats with severe acute pancreatitis.[4]

Lu et al. performed a randomized trial to study the effect of low molecular weight heparin in preventing pancreatic encephalopathy in 256 patients with severe acute pancreatitis. The results indicated that low molecular weight heparin markedly decreases the pancreatic encephalopathy incidence and improves the survival rate in severe acute pancreatitis. L.M.W.H. results in mortality reduction and improves CT score in patients with SAP.[13]

In a small study (17 cases), Jiao et al. showed that L.M.W.H. decreases the white blood cell count and increases the arterial blood partial oxygen pressure of patients with AP. Apart from the management of acute pancreatitis, L.M.W.H. can also be employed in the direction of severe acute pancreatitis, as shown in the studies conducted by Xin-Sheng. Their study stated that L.M.W.H. could enhance the effect of conventional treatment for SAP and markedly decrease SAP mortality. L.M.W.H. is a simple, safe, economical, and effective method for the treatment of SAP. It can be used in every hospital.

In a similar study conducted by Aravind et al. The results have shown that the decrease in APACHE-II scores in the group treated with low molecular weight heparin was more extensive than that in the group treated with conventional treatment without using low molecular weight heparin and lower values than those in the group without low molecular weight heparin ($P < 0.05 – 0.01$). The authors had found a significant benefit in terms of mean hospital stay, morbidity, and mortality rate in the L.M.W.H. group.

L.M.W.H. can enhance the effect of conventional treatment for acute pancreatitis and can markedly decrease the mortality of acute pancreatitis. L.M.W.H. is a safe, economical, and effective method for the treatment of acute pancreatitis.

Ai-Hua Han et al. has conducted a study to assess the clinical efficacy of ulinastatin (U.T.I) combined with low-molecular-weight heparin in children with acute pancreatitis. In their research, they have included a total of 560 patients with severe acute pancreatitis. They divided the patients into control (280 patients) who received treatment with ulinastatin plus conventional treatment) and observational groups (280 patients) who received therapy with L.M.W.H. plus ulinastatin + traditional medicine).

They have assessed the clinical parameters, laboratory test indices, computed tomography score of pancreatic necrosis (CTSPN) and acute physiology and chronic health evaluation (APACHE II) score in both groups. They have found no significant differences clinically and in laboratory parameters at the time of admission CTSPN between the two groups (all $P > 0.05$), or APACHE II scores. After two weeks of treatment, urine amylase, serum amylase, prothrombin time, partial thromboplastin time, fibrinogen and platelet count among the study group were 913 ± 281 U/L, 1893 ± 295 U/L, 16 ± 1.60 s, three ± 0.60 g/L, 39.80 ± 5.60 s, and 294 ± 49 × 109/L, considerably, all of which were similar or found to be superior to the control group (1738 ± 346 U/L, 15 ± 1.50 S, 2453 ± 473 U/L, 39.80 ± 5.90, 2.50 ± 0.50, and 192 ± 37 × 109/L)). Scores like APACHE II and CTSPN after two weeks following the treatment among the observation group were 8.50 ± 1.80 and 2.10 ± 1, considerably, and were superior compared to the control group (9.60 ± 2.40 and 4.30 ± 2.60, respectively; $P < 0.05$).

They also observed that the incidence of complications, the average duration of the hospital stay, and the mortality rate within the group treated with low molecular weight heparin were lower than those treated without low molecular weight heparin ($P > 0.05$). The cure rate with in the observation group was at a higher level than that in the control group. They have concluded that L.M.W.H. combined with U.T.I. enhances the efficacy of conventional treatment

and reduces mortality. It is a potentially effective treatment strategy for severe acute pancreatitis in children.

There are some experimental as well as clinical studies showing beneficial effects of heparin administration in acute pancreatitis. Experimental studies were performed using two edematous critical pancreatitis models, acute pancreatitis induced by using cerulein and severe lethal taurocholate or bile-induced forms of acute pancreatitis. In cerulein-induced pancreatitis in rats, Dobosz et al. had shown that pre-treatment using heparin prevents the development of pancreatic damage, decreases the pancreatitis-induced rise in serum level of pro-inflammatory interleukin-6, and improves blood flow along with the visceral organs and skeletal muscle. But in their study, they did not examine the influence of heparin on various established markers in acute pancreatitis severity like plasma levels of lipase or amylase. Another drawback is the short time of observation. They have terminated the experiment 5 hour after the first injection of cerulein.

For this reason, their statement is limited to the initial period of acute pancreatitis. In bile-induced forms of severe acute pancreatitis in dogs, Gabryelewicz et al. found that pre-treatment with heparin reduces pancreatic damage and serum amylase activity and increases animals survival rate similar effects were observed by Qiu et al. They have shown that low molecular weight heparin, administered four hour after applying taurocholate, reduces serum level of amylase, TNF-α, and endothelin-1 improves pancreatic morphology and pancreatic circulation and increases the survival rate of rats with taurocholate induced pancreatitis. In both the studies, the examination of the severity of acute pancreatitis was performed 24 hours after initiation of acute pancreatitis, showing the effect of heparin administration only on the initial phase of this disease.

CONCLUSIONS

Findings from our study found that the use of L.M.W.H. in treating acute pancreatitis, which acts by improving microcirculation, is an effective drug in the non-surgical treatment of acute pancreatitis. There was a considerable improvement in laboratory values, higher cure rate, and lower complications, such as necrosis, abscess, sepsis, organ failure, etc., in patients treated with L.M.W.H. Thus, L.M.W.H. can effectively relieve acute pancreatitis-related inflammation and reduce the incidence of complications. In conclusion, initiation of L.M.W.H. treatment in the early course of acute pancreatitis is safe and provides a better prognosis in AP.

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