ISSN: 2581 – 3633
PubMed - National Library of Medicine - ID: 101745081

International Journal of Medical Science and Advanced Clinical Research (IJMACR)

Available Online at:www.ijmacr.com

Volume – 6, Issue – 4, August - 2023, Page No. : 01 - 11

A prospective clinical study of use of low molecular weight heparin in the treatment of acute pancreatitis

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How to citation this article: Dr. Zubin Adiraja Abubacker, Dr. Shivashankar Bhat, "A prospective clinical study of use of low molecular weight heparin in the treatment of acute pancreatitis", IJMACR- August - 2023, Volume – 6, Issue - 4, P. No. 01 – 11.

Type of Publication: Original Research Article

Conflicts of Interest: Nil

Abstract

Acute Pancreatitis results in edema and eventually necrosis of the pancreas, it releases cytokines and this study focuses on the use of the Anti-inflammatory property of the Low molecular weight Heparin in the treatment pf the same. Tozlu et al stated that it prevents the release of inflammatory mediators such as TNF alpha, IL-1, etc, and microcirculatory level and improves patient outcome and general condition. In this study, we have used response to treatment using various parameters such as age-wise comparisons of outcome, duration of stay in the hospital, and incidence of complications of acute pancreatitis. We have compared the use of Low molecular weight heparin in the treatment of Acute Pancreatitis of various Etiology and its outcome using scoring systems for acute pancreatitis, APACHE-2.

Introduction

There are several etiopathogeneses for acute pancreatitis. Each Etiology appears to have some effect on the pancreatic acinar cell, causing early activation and retention of strong proteolytic enzymes. Macrophages, neutrophils, and endothelial cells are stimulated in the early stages of pancreatitis1,3. Acute pancreatitis causes the production of proinflammatory cytokines and an increase in inflammation factors, which have been linked to the development of pancreatitis-related microvascular disruption and haemorrhagic necrosis. Disturbance of pancreatic microcirculation is directly related to ischemia, reperfusion damage, and microthrombosis2.It is an inflammatory condition that is clinically characterized by abdominal pain and laboratory tests show elevated levels of pancreatic enzymes in blood namely amylase and lipase1,2.An initial pancreatic

injury is hypothesised to trigger the early activation of pancreatic enzymes, especially the trypsin from acinar cells. Tryspin can release amylase and lipase into the serum when it is improperly activated, which results in pancreatic irritation and autodigestion4,5. When trypsin is released in large amounts, additional pro-inflammatory cytokines including tumor necrosis factor and proteolytic enzymes are also released into the blood stream, which can lead to pancreatic necrosis, systemic inflammatory response syndrome, septic shock, and multiorgan failure6,8,10. Numerous severity levels have been offered since it is crucial to determine the illness severity earlier in order to maximise treatment, avoid organ failure, and local consequences1,5.Multiple organ failure is triggered by microcirculation disruption, which is a key element in the process. The hot topic in the field of pancreatic surgery is the hunt for a brand-new form of treatment due to the high death rate. This experimental investigation shows that LMWH can prevent the start of an inflammatory surge, improving the microcirculation system, and can prevent the development of micro thrombosis in the pancreas by acting as an anti-thrombin5,7. These results support the critical therapeutic advantage of LMWH in the management of acute pancreatitis1.The anti-thrombin activity of low molecular weight heparin (LMWH), which is more effective than unfractionated heparin, is well recognised1,3,7. The pancreatic microcirculation can be improved by LMWH by reducing the release of inflammatory mediators.

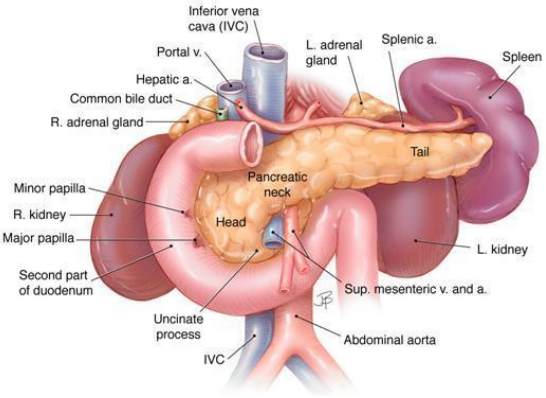

Figure 1

Pathophysiology of Acute Pancreatitis

The probable mechanism in pancreatitis is assumed to be premature activation of enzymes produced from the pancreas before it's secreted out of the pancreas causing autodigestion of the pancreas. Injury to acinar cells impairs the secretion of zymogens or causes damage to ductal epithelium causing a delay in enzymatic secretion52,55.Autodigestion in healthy individuals is prevented as the protease precursors are packaged in zymogen granules and also due to the presence of protease inhibitors like PSTI (pancreatic secretory trypsin inhibitor) or SPINK1 which inactivates trypsin6,7. Other trypsin inhibitors include mesotryspin, chymotrypsin c, and enzyme y which are found in acinar cells and pancreatic secretions. Also, low calcium levels within the acinar cells promote the inactivation of spontaneously activated trypsin11,13. Any loss in one of these mechanisms can lead to the activation of zymogens and autodigestion. The cellular injury causes the release of bradykinin peptides, vasoactive substances, and histamine causing vasodilation, increased vascular permeability, and edema leading to pancreatic edema, haemorrhage, and necrosis19,20. Inflammation leads to the release of inflammatory mediators into the circulation causing systemic complications like hemodynamic instability, acute kidney injury, pleural

effusion, acute respiratory distress syndrome, bacteremia, and disseminated intravascular coagulation21,33.Gallstone pancreatitis is triggered by the passage of gallstones to the common bile duct. Higher risk is seen in people with small gallstones and a wide cystic duct12.The pathogenic factors behind alcoholic pancreatitis is varied including diet, malnutrition, direct toxicity of alcohol, concomitant tobacco smoking, hypersecretion, duct obstruction or reflux and hyperlipidaemia15,17.Patients with hereditary pancreatitis have cationic trypsinogen gene mutation and tend to suffer from acute pancreatitis in their teenage and develop chronic pancreatitis in the next 10-20 years and are at a higher risk to develop pancreatic cancer later on their lives15,17. Other gene mutations include SPINK1 (pancreatic secretory trypsin inhibitor, CFTR and MCP-1 (monocyte chemotactic protein-1) Drugs can cause pancreatitis either as a result of a hypersensitivity reaction or as a result of the production of toxic metabolites. Smoking was previously considered a risk factor because of its connection to alcohol. However, at least three sizable investigations have indicated that smoking is a distinct risk factor for acute pancreatitis through as yet unknown mechanisms. Serum triglyceride concentrations above 1000 mg/dL can precipitate attacks of acute pancreatitis, although the pathogenesis of inflammation in this setting is unclear. Hypertriglyceridemia may account for 1.3 to 3.8 percent of cases of acute pancreatitis.

Symptoms

1. Abdominal pain: Cardinal symptom. Epigastric/ diffuse, radiating to back, severe, constant, relieved on leaning forwards with not much use from usual doses of painkillers.
2. Repeated vomiting and retching.

Local complications: Usually develop after the first week.

Acute fluid collection

Acute necrotic collections (ANCs): non-encapsulated heterogeneous non-liquefied material in the first four weeks.

1. Sterile pancreatic necrosis- acute necrotic collection
2. Infected pancreatic necrosis
3. Pancreatic abscess – infection of acute necrotic collection or the walled off necrosis. after 4 weeks; it is an encapsulated heterogeneous, non-liquefied substance.
4. Pseudocyst – can lead to pain/ rupture/hemorrhage/ infection/ obstruction of stomach/ duodenum/ colon. Pancreatic pseudocysts are common sequelae of acute pancreatitis or chronic pancreatitis, and the most common cystic lesion of the pancreas. They are important both in terms of management and differentiation from other cystic processes or masses in this region[45,48].
5. Walled off necrosis
6. Pancreatic ascites – disruption of main pancreatic duct/ leaking pseudocyst
7. Pleural effusion
8. Portal/ splenic vein thrombosis
9. Pseudoaneurysm

Lab Investigations

The diagnosis of AP is generally based on clinical features that are confirmed by laboratory and imaging tests[32.]. The release of pancreatic enzymes into the bloodstream is a defining feature of AP. Although amylase and lipase make up a small portion of all pancreatic enzymes, they are the easiest and quickest to measure[17,21]. In general, the elevation of serum amylase in AP is greater than threefold that of normal values.

Ultrasonography

Transabdominal ultrasonography is widely accessible, reasonably priced, and generally safe. Unfortunately, underlying intestinal gas and overhanging fat planes, which tend to be accentuated in the severely inflamed pancreas due to ileus and peripancreatic edema, limit pancreatic imaging by ultrasound[15,16]." As a result, the sensitivity and specificity of this method for the diagnosis of AP are low. In the early stages of AP, "transabdominal ultrasound is still useful for checking for gallbladder stones or sludge, calculating how much choledocholithiasis has dilated the common bile duct, and looking for other probable causes of intense abdominal pain[10,11].

Computed Tomography Scan

The computed tomography (CT) scan is invaluable in the diagnosis and management of AP, especially when performed with spiral or multidetector technology. Nonetheless, not every case of AP necessitates a CT scan[33,80]."

CT is strongly recommended if the initial diagnosis is uncertain or for prognostic purposes in critically ill patients, as discussed in the risk stratification section[11,17]."

The role of CT is to document the correct findings that confirm the diagnosis of AP as well as to rule out other intraabdominal disasters that can mimic AP (e.g., a perforated viscus)[17,19].

CT scan findings that support the diagnosis of AP include:

Diffuse or segmental pancreas enlargement. Pancreatic contour irregularity with the annihilation of the peripancreatic fat planes.

Areas of low density within the pancreas. Fluid accumulates in the pancreas or in the lesser sac or pararenal spaces outside the gland.

Scoring Systems In Acute Pancreatitis In This Study:

Apache-II/ Acute Physiology And Chronic Health Enquiry

The original score was first developed by American intensivist Willian knaus in 1981. It was revised in 1985 to form APACHE- II[13,19].

APACHE-II uses 12 physiological variables and generates a score from 0 to 71.

Though APACHE-III (1991), APACHE-IV (2006-current) has been developed, APACHE-II is still the most commonly used scoring system in intensive care units especially for acute pancreatitis since it has higher sensitivity to predict pancreatic necrosis and organ failure in the first 48 hours of initial presentation[21,27].

It is assessed in two sections- one to assess the severity of the illness and another to assess the medical comorbities of the patient.

The poorer values achieved in the first 24 hours of admission are considered for the scoring.

Higher the score, higher the risk of hospital death[16]. It has 73% sensitivity and 84% specificity.

Materials and Data

Source of data: The study will be conducted in the Department of General Surgery in A.J. Institute of Medical Sciences and Research Centre, Mangalore among patients who have acute pancreatitis, who meet the inclusion criteria and consent to be a part of the study.

Inclusion criteria

1. Abdominal pain characteristic of acute pancreatitis (duration <72hrs)

2. Serum Amylase and/or Lipase >or =3 times above normal value.
3. Feature suggestive of acute pancreatitis on radiological investigation (USG/CT)

Exclusion Criteria

1. Sensitive to LMWH
2. Pregnant
3. Breast feeding
4. Coagulation disorder
5. Undergoing hemodialysis

Methodology: A comparison between the outcome of patient with/ without use of low molecular weight heparin.

Group A patients: They will undergo conventional therapy that includes management of shock, maintenance of water and electrolytes balance, fasting, gastrointestinal decompression, administration of pancreatic enzymes inhibitor (Sandostatin), antibiotics (cephalosporin and metronidazole), and oral manganese sulfate and symptomatic treatment.

Group B patients: The treatment included following the methods used in GROUP A patients, plus administering LMWH at 100 microgram/kg per day subcutaneous injection starting from the admission day and continuing for 7 days.

Statistical Analysis: Baseline data will be represented by tables and diagrams. The data will be represented by percentages and mean. Standard deviation will be used to describe qualitative data.

Z test will be used to test the significance difference in the outcomes such as mean duration of stay, lab parameters like serum amylase, serum lipase and total count between the groups.

$(Chi)^2$ test will be used to test the significant difference in the outcomes such as recovery and complications between the groups.

Results and Discussion

Comparison between groups: In our study, 36 patients (30 males, 6 women) were in the observation group, while 36 patients were in the control group (28 men, 8 women). General data differences between the groups, such as sex and age, were not statistically significant ($p > 0.05$). The groups were comparable as a result.

Changes In Apache Scores After Treatment

The APACHE II scores at admission were not significantly different between the groups. After 7 days of treatment, the APACHE II scores in the observation group were significantly lower than those in the control group.

Discussion

Despite recent advances in study into the pathophysiology and processes of severe acute pancreatitis, the underlying reason for the high fatality rate is still unknown. When pancreatitis first develops Endothelial cells, neutrophils, and macrophages are stimulated. Acute pancreatitis causes the production of proinflammatory cytokines and an increase in inflammatory factors, which have been linked to the advancement of pancreatitis-related microvascular disruption and hemorrhagic necrosis. Disturbance of pancreatic microcirculation is intimately related with ischemia, reperfusion damage, and small thrombosis. When used as an anticoagulant, LMWH can successfully reduce thrombin and blood coagulation factor Xa activity, limit platelet aggregation, and enhance microcirculation. By reducing the expression of pro-inflammatory, inflammatory, and adhesive factors, LMWH can also lessen inflammation. In this

investigation, the therapeutic benefits of lmwh addition alone in Acute pancreatitis treatment was compared to standard practice. The results indicated that LMWH was safe and effective for treating severe acute pancreatitis, with evident improvements in laboratory indicators, a much greater cure rate, and a lower incidence of complications in the observation group than in the control group. Additionally, the outcomes demonstrated that the APACHE-II score drop in the observation group was greater than that in the control group and lower than that in the C group (p 0.05-0.01). Our study's findings are comparable to another research conducted abroad. The increase in APACHE-II scores is seen in the early stages (0–48 h), and it accelerates from 24–48 h. After discharge, an APACHE-II score that keeps rising typically suggests illness. Patients under the age of 18 were excluded from the study.

Method of collection of data

Study Design - A hospital based observational study.

Period of study – DECEMBER 2020 TO MAY 2022

Place of study: A. J. Institute of Medical Science and research Centre, Mangalore

Sample size –Based on the study conducted by Tozlu M IN 2019 (1) in order to detect a difference of 3.9 days (approx. 4 days) assuming 95% confidence interval, 80% power and pooled standard deviation of 6 days, the sample size estimated for the study is 36 individuals in each group hence a total of 72 individuals who meet the inclusion criteria will be considered for the study.

$$n = \frac{[Z_{1-\alpha/2} + Z_{1-\beta}]^2 \times 2(\text{standard deviation})^2}{(\text{mean difference})^2}$$

Sampling Technique: Convenience sampling will be adopted to select the individuals for the study Approval from the institutional research review and ethical board was obtained for the study. Patients and their attenders were explained about the study and informed consent was taken if they were willing to take part in the study.

All patients who were admitted in department of general surgery and general medicine with features suggestive of acute pancreatitis who were brought to hospital within 48 hours of onset of symptoms were included in the study. The patients were followed up till discharge from the hospital. Patients with typical epigastric pain, vomiting, S. amylase more than thrice the normal limit, elevated serum amylase and/ or sonological features suggestive of acute pancreatitis were included in the study.

		Heparin						
		Yes		No		Total		
		Count	Column N %	Count	Column N %	Count	Column N %	Chi square test p value
AGE	30 and below	7	19.4%	12	33.3%	19	26.4%	0,247, NS
	31 – 40	8	22.2%	11	30.6%	19	26.4%	
	41 – 50	12	33.3%	9	25.0%	21	29.2%	
	51 – 60	9	25.0%	4	11.1%	13	18.1%	
	Total	36	100.0%	36	100.0%	72	100.0%	

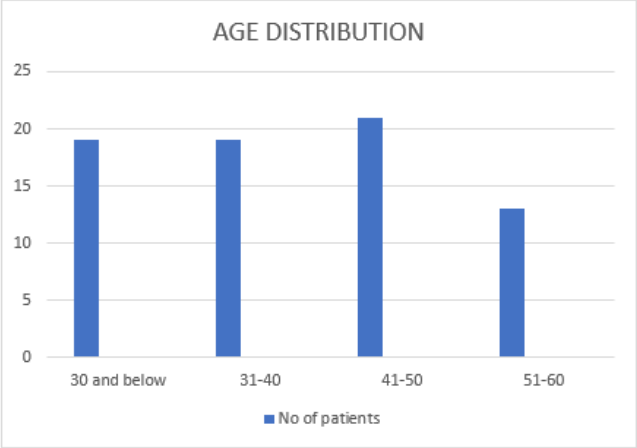

Figure 2: Age Distribution Among Groups

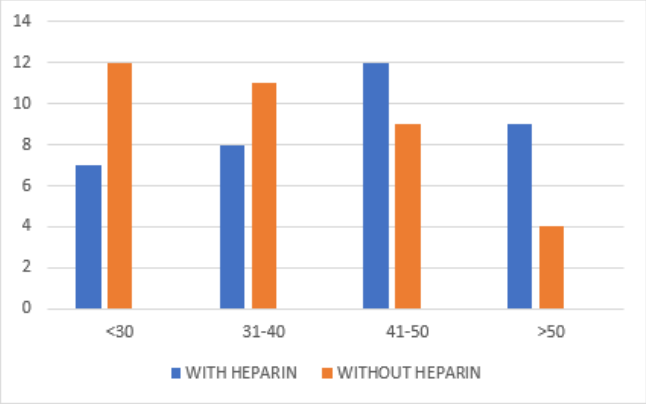

Figure 3: Changes In Apache Scores After Treatment

The APACHE II scores at admission were not significantly different between the groups. After 7 days of treatment, the APACHE II scores in the observation group were significantly lower than those in the control group.

Table 2

Heparin		N	Mean	Std. Deviation	Mean difference	S.D of difference	Change (%)	Comparison Adm to day 7	comparison of change between Heparin Yes vs No
Yes	Apache On Ad	36	13.33	5.727	7.92	3.89	59.38	0.000, HS	0.000, HS
	Apache On Day 7	36	5.42	3.706					
No	Apache On Ad	36	11.17	5.685	3.00	3.28	26.87	0.000, HS	
	Apache On Day 7	36	8.17	4.526					

Changes In Duration of Hospital Stay

Table 3

Heparin		N	Mean	Std. Deviation	T test p value
Days in hospital	Yes	36	9.22	2.674	0.000, hs
	No	36	12.69	4.774	

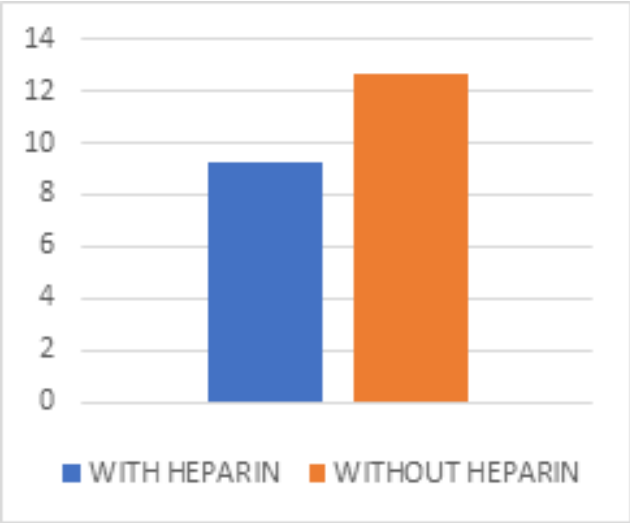

Figure 4

Conclusion

Results of Our Study It has been discovered that the non-surgical treatment of acute pancreatitis using LMWH, a medication that improves microcirculation, is beneficial. According to our study, the APACHE II Scores significantly decreased in the group receiving LMWH treatment, indicating a significant improvement in laboratory results, a higher cure rate, and fewer complications. include necrosis, abscess, sepsis, and organ failure, among others. Therefore, LMWH can effectively reduce inflammation associated with acute pancreatitis and lower the likelihood of complications.

By delaying disease development, lowering intensity and complication rates, cutting the length of hospital stays, and increasing cure rates, LMWH can quickly relieve abdominal pain.

List of abbreviations

Abbreviation	Expansion
ICU	Intensive care unit
MODS	Multiorgan Dysfunctionsyndrome
SIRS	Systemic inflammatory response syndrome
CRP	C-Reactive protein
ERCP	Endoscopic Retrograde Cholangio Pancreatography
ARDS	Acute respiratory distress syndrome
APACHE	Acute physiology and chronic health Evaluation
BISAP	Bedside index for severity of acute pancreatitis
CSI	CT severity index
TPN	Total parenteral nutrition
AP	Acute pancreatitis
LDH	Lactate dehydrogenase
AST	Aspartate transaminase
BUN	Blood urea nitrogen
AUC	Area under curve

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