Low molecular weight heparin treatment of acute moderate and severe pancreatitis: A randomized, controlled, open-label study

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ABSTRACT

Background/Aims: *Acute pancreatitis (AP) runs a moderately severe and severe course in 20%-30% of cases. The purpose of the present study was to determine the effect of low molecular weight heparin (LMWH) for the prevention of pancreatic necrosis (PN) in moderately severe and severe AP (MSAP).*

Materials and Methods: *A total of 100 patients with MSAP were randomized to receive either standard care (SC) or SC plus LMWH. LMWH was administered at 1 mg/kg via subcutaneous injection twice a day between days 1 and 7. The revised Atlanta criteria were used in the diagnosis of MSAP. Patients with a Harmless AP Score of ≥1 and a Balthazar computed tomography (CT) score of D and E were included in the study.*

Results: *The mean age±SD of the patients (46 male and 54 female) was 52±19 years (range, 17-100). There were 50 patients in each group. On admission, clinical and laboratory parameters and Balthazar CT scores were similar between the groups. Initially, PN was present in one patient in the LMWH group and two in the SC group. Over the course, PN developed in 3 (6.1%) patients in the LMWH group and 11 (22.9%) in the SC group ($p<0.05$). Local and systemic complications were significantly lower in the LMWH group ($p<0.05$). No hemorrhagic complication occurred. Mortality was not significantly different between the groups ($p=0.056$).*

Conclusion: *Low molecular weight heparin treatment is safe and provides better prognosis in MSAP.*

Keywords: *Severe acute pancreatitis, moderately severe acute pancreatitis, low molecular weight heparin, pancreatic necrosis, complication*

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). Infected necrosis and persistent organ failure have poor prognosis. The beginning and progression of AP is accompanied with systemic inflammatory cascade activation and a pancreatic microcirculatory disturbance that plays an important role in the pathogenesis of necrosis affecting not only the pancreas but also the kidneys, lungs, liver, and intestine in the course of severe AP (SAP) (1).

The exact pathogenesis of pancreatitis remains debatable, but it is probably closely related to the dysfunction of balance between proinflammatory and anti-inflammatory responses. 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). Inflammatory substances, such as endothelin-1 (ET-1), nitric oxide, and other free radicals, damage the vascular endothelium, leading to microcirculatory disturbance and organ dysfunction (5). Anti-inflammatory cytokines, such as IL-10, cause immunosuppression, and its excess levels may increase the rate of infectious complications in the later stages of severe disease (6).

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The reported mortality rate in SAP is 7%-15% (7,8). The risk is higher in patients with persistent organ failure and infected necrosis. PN in itself is a severe complication and an important cause of death in AP; mortality rate can reach up to 10%-23%(4). Therefore, prevention of PN or controlling its severity is the most important measure to decrease mortality in AP; however, we lack the effective means for this purpose.

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 (9), blocks the adhesion of leukocytes to the endothelium by inhibiting the interactions between expressed adhesion molecules and endothelial cells (10), and reduces the activation of platelets (11) In addition, LMWH reduces the formation of microthrombi and improves microcirculation (12,13). Some experimental and clinical studies showed that treatment with heparin inhibits the development of ischemia/reperfusion-induced AP (14), ameliorates the severity of taurocholate-induced pancreatitis (15), and decreases the incidence of pancreatic encephalopathy (PE) (16). Recent clinical studies have shown that pre-procedural heparin administration significantly reduces endoscopic retrograde cholangiopancreatography (ERCP)-related pancreatitis (17). It improves the course of hypertriglyceridemia-induced AP (18) and may improve the prognosis in SAP (13,19).

The purpose of our study was to determine the efficacy of LMWH in the prevention of PN in MSAP in a randomized, controlled and open-label fashion.

MATERIAL AND METHODS

This was a single-center, prospective, randomized controlled study conducted in patients who were admitted to the emergency department with a diagnosis of AP over a period of 16 months. We included patients whose symptoms started within 24 h.

Study population

In the study period, a total of 322 patients were admitted with a diagnosis of AP. 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 more than three times the upper limit of normal, and 3. characteristic findings of AP in imaging (20). All patients had both 1 and 2.

Moderately severe and severe acute pancreatitis was defined according to the revised Atlanta criteria. Moderately severe AP is characterized by local complications (peripancreatic fluid collections and pancreatic and peripancreatic necrosis) and/or transient organ failure (<48 h). Severe AP is characterized by persistent organ failure (>48 h). Harmless AP Score (rebound tenderness on abdominal examination and abnormal hematocrit and creatinine levels, one point each) was calculated (21), and computed tomography (CT) results were classified according to the Balthazar and Modified CT Severity Index (MCTSI) (22).

Exclusion criteria included the presence of chronic pancreatitis, hypersensitivity to LMWH or radiocontrast agents, pregnant or breast feeding, coagulation disturbances, and severe comorbidities (Charlson Comorbidity Index (CCI) score ≥5) (23).

According to power analysis based on the prediction of 30% necrosis in MSAP and estimated reduction of risk of 10% with LMWH, we calculated that 100 patients would be adequate to detect a significant difference between the groups. Therefore, we stopped enrollment after we reached this number.

Study design

Patients were randomized according to a computer generated randomization and assigned to either the SC or the LMWH group by the pharmacist of the department blinded to the study. Randomization was balanced with every four patients enrolled and stratified by center.

Treatment protocol

Patients in the SC group received intravenous (IV) fluids, analgesics, and antibiotics in case it was needed. Patients in the LMWH group received that of the SC, in addition to enoxaparin sodium 1 mg/kg twice daily (the recommended dosage in deep vein thrombosis and pulmonary embolism), from admission until day 7 (inclusive) by subcutaneous injection. Patients were closely monitored in the hospital.

Clinical parameters and study endpoints

The primary outcome measure was the development of PN according to contrast-enhanced CT examination. The secondary outcome measures were time to tolerate oral intake, development of complications (local complications, such as pseudocyst and walled-off necrosis, as well

as systemic complications, such as renal and pulmonary failure and cardiovascular and gastrointestinal complications), need for endoscopic and surgical interventions, length of hospital stay, and mortality.

Laboratory tests

The following parameters were monitored on admission and during the following 7 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 were performed at the time of hospital admission (in the first 12 h) and on day 7. AP severity was assessed using MCTSI. According to the

Table 1. Demographic data and basal prediction of AP severity by means of a CT scan of study patients

	SC Group (n=50)	LMWH Group (n=50)	p
Mean age±SD (range)	52±20 (17-100)	51±16 (20-85)	NS
Gender F:M, n	26:24	28:22	NS
Diabetes Mellitus, n (%)	9 (%18)	10 (20%)	NS
Charlson comorbidity score	0.56±1.1	0.52±0.9	NS
Etiology, n (%)			
Biliary	31 (62%)	24 (48%)	NS
Post ERCP	3 (6%)	1 (2%)	
Hyperlipidemia	4 (8%)	4 (8%)	
Alcohol	4 (8%)	2 (4%)	
Drug/toxic	2 (4%)	6 (12%)	
Idiophatic	6 (12%)	13 (26%)	
Balthazar, n (%)			
Stage D	20 (40%)	23 (46%)	NS
Stage E	30 (60%)	27 (54%)	
Modified CTSI, n (%)			
Moderate	48 (96%)	49 (98%)	
Severe	2 (4%)	1 (2%)	

SC: Standard care; LMWH: Low molecular weight heparin; ERCP: Endoscopic retrograde cholangiopancreatography; CTSI: Computed tomography severity index; NS: Non-significant

Table 2. Evolution of Computed tomography graded severity from the first 12 hours to the 7th day in groups

	At 12th hours					
	SC group			LWMH group		
Severity	Moderate	Severe	Total	Moderate	Severe	Total
At 7th day	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Mild	8 (16.6%)	0	8 (16%)	23 (46.9%)	0	23 (46%)
Moderate	29 (60.4%)	0	29 (58%)	23 (46.9%)	0	23(46%)
Severe	11 (23%)	2 (100%)	13 (26%)	3 (6.2%)	1 (100%)	4 (8%)
Total	48 (100%)	2 (100%)	50 (100%)	49 (100%)	1 (100%)	50 (100%)

SC: Standard care; LMWH: Low molecular weight heparin

MCTSI, scores between 0 and 2 indicated mild, 4 and 6 moderate, and 8 and 10 severe AP (22). Patients with mild pancreatitis according to the MCTSI in initial CT were excluded from the study.

Table 3. Clinical outcomes of patients who received standard treatment or standard treatment plus LMWH

	SC Group (n=50)	LMWH Group (n=50)	p
Time to oral feeding, mean days (range)	7.1±12.2 (1-73)	2.7±1.5 (1-6)	0.013*
Length of hospital stay, mean days (range) (3-73)	11.8±12.5 (4-16)	7.8±3.4	0.13
CT changes, n (%)			
Regression	8 (16%)	27 (54%)	0.017*
Progression	16 (32%)	3 (6%)	
No change	26 (52%)	20 (40%)	
Endoscopic/surgical necrosectomy, n (%)	2 (4%)	1 (2%)	0.56
Mortality, n (%)	5 (10%)	0 (0%)	0.056

*p<0.05
SC: Standard care; CT: Computed tomography; LMWH: Low molecular weight heparin

Table 4. Local and systemic complications in the groups

	SC Group (n=50)	LMWH Group (n=50)	p
Local complications, n (%)	17 (34%)	7 (14%)	0.019
Pancreatic necrosis	11 (22.9%)	3 (6.1%)	0.017
<30%	7	2	
>30%	4	1	
Pseudocyts	11 (22%)	4 (8%)	
Walled of necrosis	6 (12%)	2 (4%)	
Systemic complications, n (%)	37 (74%)	18 (36%)	0.001
Pleural effusion	33 (66%)	17 (34%)	0.001
Vascular complication	7 (14%)	1 (2%)	
ARDS	8 (16%)	3 (6%)	
Renal insufficiency	8 (16%)	3 (6%)	
Multiorgan failure	5 (10%)	0	
All complications, n (%)	37 (74%)	18 (36%)	0.001

SC: Standard care; LMWH: Low molecular weight heparin; ARDS: Acute respiratory distress syndrome

Ethics statement

All participants provided written consent for participation in the study. Approval for the study was obtained from the local ethics committee. All procedures were in accordance with the ethical standards of the committee on human experimentation of our institution and the Declaration of Helsinki.

Imaging technique and image analysis

Contrast-enhanced helical CT scans (collimation, 4×2.5 mm; slice thickness, 5 mm; range of reconstruction, 5 mm; section 64, Aquilion; Toshiba Medical Systems, Tokyo) were obtained 65 s after the administration of 100 mL Iohexol (Omnipaque 300) at a rate of 3 mL/s. All images were analyzed by a radiologist blinded to the clinical findings of the patients.

Data analysis

The Statistical Package for Social Sciences (SPSS) version 22 software (IBM Corp.; Armonk, NY, USA) was used for statistical analyzes. Quantitative data were expressed as percentages and mean±standard deviation. Normally distributed parameters were compared using Student's t-tests, and non-normally distributed parameters were compared using Mann-Whitney U tests. Qualitative data were compared using chi-square test. A p value <0.05 was considered statistically significant.

RESULTS

A total of 325 patients were screened for inclusion in the study. However, 7 were pregnant, 212 had mild AP, 3 had comorbid conditions (CCI scores ≥5), and 3 did not provide consent for inclusion in the study. Figure 1 shows the process of enrollment and flowchart of randomization. One hundred patients (54% female and 46% male) with MSAP with a mean age of 52±19 (range: 17-100) years were included in the study. The etiology of AP was biliary in 55 patients, hypertriglyceridemia in 8, drug associated in 8, alcohol in 6, and post ERCP in 4. In 19 patients, the etiology remained idiopathic. Balthazar's score was stage D and E in 43 and 57 patients, respectively, at admission. In the stratification of pancreatitis severity as determined by MCTSI, 97 patients were moderate AP, and 3 were severe AP at admission. Table 1 shows the demographic data and basal prediction of AP severity by means of CT scan of study patients. On admission, the clinical parameters and AP severity scores of the SC and the LMWH groups were similar (p>0.05). Endoscopic intervention

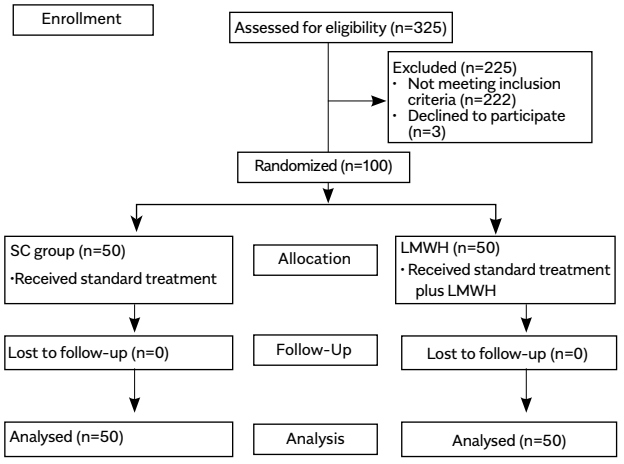

Figure 1. Flow chart for randomisation

was required in 19 patients (11 from the SC and 8 from the LMWH groups).

In the SC group, there were 50 patients, with 24 males aged 17-100 (mean age: 53±21 years) years. According to the MCTSI, 48 (96%) patients had moderate, and 2 (4%) had severe pancreatitis at admission. In the follow-up, 8 (16.6%) patients with moderate AP regressed to mild, 29 (60.4%) had remained moderate, and 11 (23%) progressed to severe AP. Two patients who had severe AP initially remained so (Table 2).

In the LMWH group, there were 50 patients, with 22 males aged 20-85 (mean age±SD: 51±17) years. According to the MCTSI, 49 (98%) patients had moderate, and 1 (2%) patient had severe pancreatitis in the first 12 h. In the course of patients with moderate AP, 23 (46.9%) regressed to mild, 23 (46.9%) remained moderate, and 3 (6.2%) progressed to severe AP. One patient who had severe AP initially remained so (Table 2). In moderate patients, the regression, as well as the progression, rates were significantly better in the LMWH group than in the SC group (p=0.002).

Time to tolerate oral intake was significantly lower in the LMWH group than in the SC group (2.7±1.5 vs. 7.1±12.2 days; p=0.013). There was a trend for shorter hospital stay in the LMWH group, but the difference was not significant (7.8±3.4 vs. 11.8±12.5 days; p=0.13). Mortality was not statistically different between the groups (0 [0%] vs. 5 [10%] for the LMWH and SC groups, respectively; p=0.056 by Fisher's exact test). Overall, compared with the SC group, regression at day 7 CT findings was significantly higher, and progression was significantly lower in the LMWH group (54% vs. 16% regression and 6% vs. 32% progression for the LMWH and SC groups, respectively, p<0.05) (Table 3).

Overall, complications developed in 55 patients (18 in the LMWH and 37 in the SC groups). Local complications were significantly lower in the LMWH group than in the SC group (7 [14%] vs. 17 [34%]; p=0.019). PN was present at the beginning in one patient in the LMWH group and 2 in the SC group. In the study period, PN developed significantly less frequently in the LMWH group (3 [6.1%] vs. 11 [22.9%] for the LMWH and SC groups, respectively; p<0.05). Systemic complications were significantly lower in the LMWH group than in the SC group (18 [36%] vs. 37 [74%]; p=0.001) (Table 4). For the 5 patients who died, all from the SC group, mortality was due to acute respiratory distress syndrome, septic shock, and multiorgan failure secondary to infected necrosis.

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 AP can only be achieved with successful management strategies toward SAP.

Previous clinical and experimental data revealed that the fate of AP is dictated in the early hours of pancreatitis, and impairment of microcirculation is the pivotal derangement leading to necrosis. The presence of a hematocrit value >44% and failing to decrease it with IV fluid boluses is considered to predict severe prognosis. Hemoconcentration may be a cause for the impairment of microcirculation and may play an important role in the transition of edematous to necrotizing pancreatitis. Abundance of several inflammatory cytokines in the microenvironment of the pancreas in the setting of AP is also a precipitating event (24). Proinflammatory cytokines, such as IL-1β, IL-6, and TNF-α, increase during the course of AP and are responsible for the progression of microvascular disturbance. Microcirculatory disturbance is as important as enzymatic and free radical damage in the pathogenesis of AP.

Thrombosis, associated with denudation of endothelial cells, sludge formation, and resultant stasis, in the pancreatic circulation is an event as early as mucoid swelling in the acini in the course of AP. It starts from the periph-

ery and extends toward the center. Fibrin accumulates at the distal part of the thrombus.

Enoxaparin is an LMWH that binds to and accelerates the activity of antithrombin III (ATIII). By activating ATIII, enoxaparin preferentially potentiates the inhibition of coagulation factors Xa and IIa. Factor Xa catalyzes the conversion of prothrombin to thrombin and prevent fibrin clot formation. The heparin-ATIII complex reduces the activity of trypsin and chymotrypsin and inhibits trypsinogen activation (25). The anti-inflammatory properties of heparin are different from its anticoagulant activity (26). Heparin reduces recruitment of inflammatory cells into the site of injury and leucocyte adhesion to vascular endothelial cells (27). LMWH has been shown to downregulate ET-1, TNF-α, and IL-6, leading to the reduction of the formation of microthrombosis, improving microcirculation (28). Furthermore, heparin inhibits pancreatic enzymes and accelerates pancreatic regeneration during the course of the disease (14).

The treatment of AP is mainly supportive and relies on fluid and electrolyte replacement, pain control, nutrition, and antibiotic therapy, if necessary. Since we do not have specific treatment modalities aiming to prevent enzymatic and free radical damage, anticoagulation treatment appears to be the only means to limit acinar cell damage. Furthermore, preserving the patency of microcirculation would limit the extent of enzymatic and free radical damage. Since recanalization follows shrinkage and cicatrization of vessels, reperfusion injury may have a role in the morphogenesis of AP, which is also prevented by anticoagulation treatment.

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 hemorrhage, preserving the patency of microcirculation.

There are experimental and clinical studies on the protective effect of heparin in the treatment of AP. Qiu et al. demonstrated the protective effect of LMWH on PE progression in rats with SAP. They reported that the severity of brain damage significantly decreases in the LMWH group (12). In another study, they showed that LMWH decreases TNF-α and ET-1 and has a positive effect on morphological changes and vascular flow in rats with SAP (5). Lu et al. performed a randomized trial to study the effect of LMWH in the prevention of PE in 256 patients with SAP. The results indicated that LMWH markedly decreases the PE incidence and improves the survival rate in SAP (16). A clinical study conducted by Lu et al. showed that LMWH results in mortality reduction and improves CT score in patients with SAP (13). In a small study (17 cases), Jiao et al. showed that LMWH decreases the white blood cell count and increases the arterial blood partial oxygen pressure of patients with AP (19).

In our study, we selected patients with moderately severe and severe pancreatitis because microcirculatory disturbance is, mostly, pronounced in this subset. However, since we did not encounter any untoward effect of heparin, it may be used in all cases.

As it appears from the present study, early administration of LMWH improved the radiological picture with regression in the majority. Progression occurred in only 3 (6%) patients. In the SC group, the radiological picture worsened in 1/3, and regression occurred in only 8 (16%) patients. Furthermore, most of the clinical parameters were better in the treatment group, with lower rate of admission to the intensive care unit, time to oral feeding, hospital stay, and occurrence of necrosis. Actually, all these parameters are dependent to each other, and clinical course is dictated by the very early course of AP. Prevention of stasis in this phase by LMWH may be a very important measure to prevent ischemia/reperfusion injury, including a free radical induced one. It appears that enzymatic injury is a reparable condition in case there is no significant impairment in microcirculation.

In conclusion, LMWH treatment is safe and provides better prognosis in MSAP. Future multicenter trials on the effectiveness of LMWH should be undertaken in the very early course of AP.

Ethics Committee Approval: Ethics committee approval was received for this study from the Local Institutional Ethical Committee.

Informed Consent: Written informed consent was obtained from all the patients who participated in this study.

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