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

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OBJECTIVE: To study the effect of low molecular weight heparin (LMWH) in the treatment of severe acute pancreatitis (SAP).

METHODS: A total of 265 SAP patients were randomly divided into two groups: firstly, the conventional treatment group (C group, $n = 130$; and secondly the conventional treatment plus the LMWH treatment group (LT group, $n = 135$). The clinical parameters, laboratory parameters and computed tomography (CT) score of pancreatic necrosis (CTSPN) in the two groups were compared.

RESULTS: On admission, all the clinical parameters, laboratory parameters and CTSPN in the two groups were not significantly different ($p > 0.05$). However, after treatment, in LT group, the clinical presentation improvement rate and laboratory parameters improvement were significantly higher than those in C group ($p < 0.05$–0.01), and the acute physiology and chronic health evaluation (APACHE) II score, complication rate, mortality and mean hospital stay in LT group were obviously lower than those in C group ($p < 0.05$–0.01). The CT score in LT group was much lower than that in C group ($p < 0.05$). Two weeks after treatment FBI decreased obviously in C group, but not in LT group, and no haemorrhagic complications occurred.

CONCLUSIONS: LMWH can enhance the effect of conventional treatment for SAP, and can markedly decrease the mortality of SAP. LMWH is a simple, safe, economic and effective method for treatment of SAP. It is can be used in every hospital. [*Asian J Surg* 2009;32(2):89–94]

Key Words: low molecular weight heparin, prospective clinical study, severe acute pancreatitis

Introduction

Severe acute pancreatitis (SAP) is a severe and frequently lethal disorder which occurs suddenly and develops rapidly. SAP is usually accompanied with systemic inflammatory cascades and microcirculatory disturbance. Microcirculatory disturbance is a trigger factor in the development of SAP, and plays a key role in the development of multiple

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organ dysfunction syndrome or multiple organ failure (MODS/MOF), which result in high mortality of SAP. Although the basic research of SAP has shown promising advances, and the therapeutic methods have improved, nowadays the mortality rate of SAP is still as high as 20–40%.[1–3] Therefore searching for a new therapeutic method is still a hot point in the field of pancreatic surgery.

Low molecular weight heparin (LMWH) is known to posses a special anti-thrombin activity which is stronger and safer than unfrationated heparin. LMWH can reduce the release of cytokines and inflammatory mediators, resulting in an improvement of the microcirculation of pancreas. Our experimental study provides evidence that LMWH can decrease TNF-α production in serum, and block the initiation of an inflammatory storm; LMWH decrease ET-1 leading to improvement of microcirculation system; and has anti-thrombus effect to reduce the formation of microthrombosis in pancreas. These findings demonstrate the important therapeutic effect of LMWH in the treatment of SAP.[4]

From August 1998 to February 2004, a prospective multicentre study on the treatment of SAP using conventional therapy plus LMWH was performed in the Xiangya Hospital, Central South University, Changsha; The 163 Central Hospital, Changsha; The Second Affiliated Hospital, Nanhua University, Hengyang; and Central Hospital of Longgang District, Shenzhen, China.

Materials and methods

Patients selection

All the 265 patients with SAP in this series were diagnosed clinically according to the diagnosis criteria of SAP approved by the Chinese Association of Surgery in 1997.[5] Patients that were sensitive to LMWH, pregnant, breast-feeding, had coagulation disorders, or those undergoing haemodialysis, were excluded from this study. The etiology of these patients included biliary diseases in 154 patients (58.1%), alcoholism in 73 (27.5%), excessive eating in 28 (10.6%), and undetermined causes in 10 (3.9%). The diagnosis of SAP is acute pancreatitis (AP) complicated with the following conditions: 1) organ dysfunction and/or pancreatic necrosis, abcesses or pseudocysts; 2) peritonitis and/or Gey-Turer sign, Cullen sign; 3) blood calcium < 1.87 mmol/L (7.5 mg/dL); (4) acute physiology and chronic health evaluation (APACHE) II score ≥ 8; (5) Balthazar computed tomography (CT) score ≥ class II.

The 265 patients were randomly divided into a conventional therapy group (C group) and conventional therapy plus LMWH treatment group (LT group).

Conventional therapy group ($n = 130$)

There were 72 males and 58 females with aged 7–72 years in this group. The median age was 54 years old. On admission, 130 patients (100%) had severe abdominal pain, 105 (80.8%) had nausea and/or vomiting, and 79 (60.8%) had fever. Among the 130 patients, six (4.6%) were accompanied with acute respiratory distress syndrome (ARDS), five (3.8%) with shock, seven (5.3%) with acute renal failure (ARF), three (2.3%) with mild upper gastrointestinal (GI) bleeding, and one with diffuse intravascular clotting (DIC). Six patients (4.6%) had failure of two or more organs. The average APACHE II score in the 130 patients was 11.5 ± 3.4.

The LT group ($n = 135$) included 84 males and 51 females aged 9–75 years (the median age was 56 years old) in this group. On admission, 135 patients (100%) had severe abdominal pain, 113 (83.7%) had nausea and/or vomiting, and 85 (63.0%) had fever. Among the 135 patients, 11 (8.1%) were accompanied with ARDS, five (3.7%) with shock, nine (6.7%) with acute renal failure, three (2.3%) with mild upper gastrointestinal bleeding, and seven (5.2%) patients had failure of two or more organs.

The average APACHE II score in the 135 patients was 11.6 ± 3.6. On admission, the clinical parameters and APACHE II scores between the C group and the LT group were not significantly different ($p > 0.05$).

Treatment protocol

C group

The treatment included management of shock, maintenance of the water and electrolytes balance; fasting gastrointestinal decompression; administration of pancreatic enzymes inhibitor (sandostatin), losec, antibiotics (cephalosporins/metronidazole) and oral manganese sulfate; and symptomatolytic treatment.

LT group

The treatment included following the methods used in the C group, plus administering LMWH at 100 μg/kg per day by subcutaneous injection starting from the admission day and continuing for 7 days. Nesobiliary drainage was not used in the C and LT group.

Operative indications

An operation should be performed when the following are in evidence 1) Patients with clinical presentation of biliary pancreatitis and with no change or had deterioration of symptoms within 24–48 hours after treatment; 2) Patients whose clinical presentations deteriorated rapidly 24–48 hours after treatment; 3) Pancreatic necrosis accompanied with infection or pancreatic abscess formation; 4) Pancreatic pseudocyst formation with a diameter more than 6 cm.

Observation parameters

Clinical parameters

APACHE II scores, clinical presentation improvement rate, operation rate, complication rate, occurrence rate of organ failure, in hospital mortality, curative rate, and mean hospital stay in the two groups were observed and compared.

Laboratory tests

The following parameters on admission, at 1 week, and at 2 weeks after treatment were determined: white blood cells (WBC), haematocrit (HCT), platelets, serum and urine amylase (AMS), coagulation function, blood sugar, serum calcium, hepatic function, renal function and blood gas analysis.

CT scan scores[6]

The CT scores on admission, at 1 week, and at 2 weeks after treatment were compared in the LT group (35 cases treated at Xiangya Hospital) and the C group (30 cases treated at Xiangya Hospital).

Statistical analysis

Data were analysed using the software package SPSS 10 (SPS, Chicago, IL, USA). Results were expressed including standard deviation (SD). The values were compared using Student's t-test. A value of $p < 0.05$ was considered significant.

Results

Symptoms improvement rate

One week and two weeks after treatment, improvement of clinical symptoms occurred in 16 (53.3%) and 23 patients (76.7%) in the LT group respectively, and in eight (26.7%) and 15 patients (50.0%) in the C group respectively ($p < 0.05$ in all groups).

APACHE II scores

APACHE II scores in the LT and C groups were not significantly different on admission (11.6 ± 3.6 *vs.* 11.5 ± 3.4) or 1 week after treatment (10.4 ± 2.9 *vs.* 10.5 ± 2.3) (all values of $p > 0.05$). However 2 weeks after treatment the APACHE II score in the LT group (8.5 ± 1.8) was significantly lower than that in the C group (9.6 ± 2.4) ($p < 0.05$).

CT scores

On admission the CT score in the LT group (5.4 ± 1.9) and the C group (5.0 ± 1.5) was not significantly different ($p > 0.05$), however 1 week and 2 weeks after treatment the CT score in the LT group (3.8 ± 2.2, 2.1 ± 1.0) was significantly lower compared with that of the C group (4.9 ± 2.4, 4.3 ± 2.6) (all values of $p < 0.05$).

Blood and urine AMS

The levels of blood and urine AMS between the two groups were not significantly different on admission ($p > 0.05$). However at 1 week and 2 weeks after treatment the levels of blood and urine AMS in the LT group were significantly lower than those in the C group (all values of $p < 0.05$) (Table 1).

Blood levels for prothrombin time (PT), fibrinogen (FBI), kaolin partial thromboplastine time (KPTT) and platelet (PLT)

On admission and 1 week and 2 weeks after treatment, the blood levels of PT, KPTT and PLT between the two groups were not significantly different (all values of

Table 1. Levers of blood AMS (U/L) and urine AMS (U/L3484) ($x \pm s$)

Group	Time point	Blood AMS	Urine AMS
C group	On admission	3684 ± 895	5723 ± 993
	7 DAT	3163 ± 864	4563 ± 862
	14 DAT	1738 ± 346	2453 ± 473
LT group	On admission	3629 ± 963	5677 ± 981
	7 DAT	11934 ± 326*	3462 ± 656†
	14 DAT	913 ± 281*	1893 ± 295†

Comparing with the time point of on admission of C group, *$p < 0.05$; †$p < 0.001$; AMS = amylase; DAT = days after treatment.

Table 2. Blood levels of PT, PFBI, KPTT and PLT ($x \pm s$)

Group	Time point	PT(sec)	FBI(g/L)	KPTT(sec)	PLT(109/L)
C group	On admission	15.0±1.5	3.5±0.7	35.7±3.9	180±27
	7 DAT	15.0±2.5	3.0±0.6	39.7±5.7	240±32
	14 DAT	15.0±2.5	2.5±0.5*	39.8±5.9	292±37
LT group	On admission	15.0±1.8	3.6±0.9	36.5±4.0	175±19
	7 DAT	15.0±1.9	3.1±0.7	36.5±4.0	230±28
	14 DAT	16.0±1.6	3.0±0.6	39.8±5.6	294±49

Comparing with the time point of on admission of C group, *$p < 0.001$; DAT = days after treatment; PT = prothrombin time; FBI = fibrinogen; KPTT = kaolin partial thromboplastine time; PLT = platelet.

Table 3. MOF occurrence rate

Organ failure	Group	On admission	*p* value	During treatment	*p* value	Successful treatment rate (%)	*p* value
ARDS	C	6 (4.6)	>0.05	46 (35.4)	<0.001	85.6 (45/52)	>0.05
	LT	11 (8.1)		17 (12.6)		82.1 (23/28)	
Shock	C	7 (5.4)	>0.05	0	>0.05	85.7 (6/7)	>0.05
	LT	9 (6.7)		0		88.8 (8/9)	
ARF	C	7 (5.4)	>0.05	0	>0.05	100 (9/9)	>0.05
	LT	9 (6.7)		0		100 (7/7)	
PE[8]	C	0	>0.05	13 (10.0)	<0.01	53.8 (7/13)	>0.05
	LT	0		3 (2.2)		66.7 (2/3)	
GI bleeding	C	3 (2.2)	>0.05	6 (4.6)	>0.05	100 (9/9)	>0.05
	LT	3 (2.3)		5 (3.7)		100 (8/8)	
DIC	C	1 (8.0)	>0.05	0	>0.05	0	>0.05
	LT	0		0		0	
MODS/MOF	C	6 (4.6)	>0.05	28 (21.5)	<0.01	32.8 (13/34)	<0.05
	LT	7 (5.2)		12 (8.9)		68.4 (13/19)	

ARDS = acute respiratory distress syndrome; ARF = acute renal failure; PE = pancreatic encephalopathy; GI bleeding = gastrointestinal bleeding; DIC = diffuse intravascular clotting; MODS/MOF = multiple organ dysfunction syndrome/multiple organ failure.

$p > 0.05$). Two weeks after treatment, the level of blood FBI in the C group decreased significantly, but in the LT group, the blood FBI had no significant change (Table 2). No coagulation disturbance occurred in either of the two groups.

MODS/MOF

During the process of treatment, in the C group ARDS occurred in 46 patients (35.4%), pancreatic encephalopathy in (PE)[7] 13 (10.0%) and GI bleeding in six (4.6%). Among those patients, 28 patients (21.5%) had failure of two or more organs.

In the LT group, ARDS occurred in 17 patients (12.6%), pancreatic encephalopathy in three (2.2%) and GI bleeding in five (3.7%). Among those patients, 12 patients (8.9%) had failure of two or more organs.

Organ failure,[8] especially ARDS, occurred more often in the C group and the successful treatment rate in the C group was lower than that of the LT group (Table 3).

Other complications and the successful treatment rate

During the process of treatment, the occurrence rate of pancreatic pseudocysts, peripancreatic abscesses, pancreatic fistulas and intestinal fistulas in the LT group and the

C group was not significantly different (all values of $p > 0.05$). The successful treatment rate of such complications in the LT group and the C group was also not significantly different (all values of $p > 0.05$).

Operation rate

During the process of treatment, in the C group, 15 cases were converted to undergo operations including necrotic pancreatic tissue debridement plus abdominal irrigation and drainage (PDAID) in eight cases (26.7%). In the LT group, six (20.0%) were converted to undergo operation, including PDAID in one case (3.3%) (all values of $p < 0.05$).

Curative rate and mortality

The curative rate in the C group (69.4%, 90/130) was significantly lower than that in the LT group (89.6%, 121/135) ($p < 0.05$). The mortality in the C group (30.6%, 40/130) was significantly higher than that of the LT group (10.4%, 14/135). The deaths of all the patients in the two groups were due to MOF.

Mean hospital stay days

The mean hospital stay in the C group was 43 ± 11 days, and in the LT group it was 30 ± 8 days ($p < 0.01$).

Discussion

Acute pancreatitis is a disease which 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 haemorrhagic necrosis. Ischemia reperfusion injury and tiny thrombus are closely associated with pancreatic microcirculation disturbance,[4] which causes further secretion of cytokines. The released inflammatory mediators can induce local effects and systemic complications[1] which can finally result in MOF.[9] MOF is the main cause of death in patients with SAP. In our series, all the deaths were due to MOF. So attenuation of cytokines and improvement of microcirculation of pancreasis are very important in the treatment of SAP.

The pancreas is divided into lobules supplied by lobar artery. The lobar artery is an end artery and is not divided into branches. Obstruction of the artery will cause sublobular ischemia and necrosis, so the pancreas is susceptible to ischaemic insult. There is also increasing evidence of pancreatic and systemic microvascular disturbances in the pathogenesis of pancreatitis, including vasoconstriction, shunting, inadequate perfusion, and increased blood viscosity and coagulation, which is a key pathological process in the development of SAP. These processes may be caused or exacerbated by ischemia-reperfusion injury and the development of oxygen-derived free radicals.[10,11] So, improvement of pancreatic and systemic microvascular disturbance is very important in blocking the pathological and clinical process of the development of pancreatitis. Our 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-α and IL-6. IL-6 is induced by IL-1, and seems to correlate with the severity of the SAP, reduce the formation of microthrombosis resulting in improvement of the microcirculation of the pancreas, lung, kidney and brain, and decrease the mortality in SAP.[3] These studies suggested that LMWH had an obvious effect on the treatment of SAP in humans and rats. In this clinical study, we 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 obviously lower than those of the C group. These results suggest that LMWH also had a significant effect on the treatment of SAP clinically.

Leizorovicz et al[12] 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 appears to have a higher benefit to risk ratio than unfractionated heparin in the treatment of venous thrombosis. In our study, 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. Thus, some clinicians may even prefer to use LMWH, since it is easier to administer and does not require adjustment of the dose by laboratory analysis.

In conclusion, the addition of LMWH in the treatment of SAP is a safe, simple, economic and effective method, which can be widely used.

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