Effects of different triglyceride-lowering therapies in patients with hypertriglyceridemia-induced acute pancreatitis

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Abstract. The aim of the present study was to investigate the effects of various triglyceride (TG)-lowering therapies on hypertriglyceridemia-induced acute pancreatitis (HTGAP). A total of 132 patients with HTGAP were retrospectively divided into an insulin intensive therapy (IIT), a plasma exchange (PE) and a non-intensive insulin therapy (NIIT) group according to the TG-lowering therapies they had received. The clinical and biochemical data of the subjects were analyzed. The baseline data, including sex, age, TG, amylase, severe acute pancreatitis and systemic inflammatory response syndrome were not significantly different among the three groups (P>0.05). The 24-h TG clearance rate (χ^2=7.74, P=0.021), onset to treatment time (χ^2=14.50, P<0.001) and the time required to reach the target TG level (χ^2=6.12, P=0.047) were different in these three groups, but no significant differences were observed between the IIT and NIIT groups (P>0.05). The incidence of therapy-associated complications in the PE group (30.23%) was higher than that in the IIT (2.17%) and NIIT (4.65%) groups. The difference in the incidence of therapy-associated complications was significant among the three groups (P<0.001), but no significant difference was present between the IIT and NIIT groups (P>0.05). In the PE group, the length of stay was increased compared with that in the IIT and NIIT groups (χ^2=7.05, P<0.05), while there was no significant difference between the IIT and NIIT groups (P>0.05). The present study suggested that NIIT at presentation had a similar therapeutic efficacy to that of IIT to improve the prognosis of HTGAP, and NIIT and IIT were associated with fewer complications than PE treatment. NIIT may favorably perform in patients presenting early after symptom onset and may be considered for clinical application.

Introduction

Acute pancreatitis (AP), which manifests as abdominal pain and elevated pancreatic enzymes, occurs due to premature activation of pancreatic enzymes in the pancreas (1). Hypertriglyceridemia (HTG), gallstones and alcohol consumption have been associated with the pathogenesis of AP (2). Changes in lifestyle and diet have contributed to the increased incidence of HTG-induced AP (HTGAP) in recent decades (3). A previous study published in 2016 revealed that HTGAP accounted for 2-5% of AP cases in the US (2). The morbidity rate of severe pancreatitis was estimated to be 12-38% among patients with HTGAP (4). HTGAP poses a serious threat to human health, as it features a young age at onset, serious complications and poor prognosis (5). HTGAP is caused by the release of excessive free fatty acids and lysolecithin from lipoprotein substrates in pancreatic cells, which damage the acinar cells and the microvascular membranes when albumin exceeds the carrying capacity of the pancreas. This results in systemic inflammatory response syndrome (SIRS) (6), pancreatic cell damage (7) and possibly multiple organ dysfunction syndromes (8). A previous study demonstrated that elevated serum triglyceride (TG) is associated with the severity of pancreatitis, and that the progression of HTGAP may be prevented if serum TG levels drop to <5.56 mmol/l (9). Therefore, controlling the serum TG levels in patients with pancreatitis may mitigate the progression of the disease.

In addition to fasting, analgesia, enteral nutrition, fluid replacement and antibiotics, studies have reported that intensive insulin therapy (IIT) (10,11) and plasma exchange (PE) (9,12,13) may be effective methods for reducing serum TG levels (11). Insulin has an important role in enhancing lipoprotein lipase (LPL) activity and lowering serum TG levels. However, other studies revealed that the clinical applications

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of IIT were limited by neurological complications caused by severe hypoglycemia and did not significantly improve the prognosis of critically ill patients (11,14,15). At present, non-intensive insulin therapy (NIIT) is widely used as a therapeutic strategy for patients with HTGAP in China, and is able to reduce the risk of severe hypoglycemia and associated complications. PE is a procedure that removes plasma from the blood and replaces it with new plasma. PE rapidly removes TG and inflammatory mediators from the blood, and is widely used in the treatment of HTGAP. However, previous studies have revealed that PE is associated with complications, including allergy, infection, unstable circulation and abnormal blood coagulation. In addition, PE has a relatively high treatment cost and is highly dependent on blood products (9,16). To the best of our knowledge, no previous study has systematically compared IIT, PE and NIIT.

Therefore, the aim of the present study was to compare the efficacy of the aforementioned TG-lowering therapies to improve the prognosis of patients with HTGAP, as well as their associated complications.

Patients and methods

Patients. The present study retrospectively screened 132 patients with HTGAP admitted to the Departments of Emergency, Gastroenterology and International Medicine and the Medical Intensive Care Unit of Peking Union Medical College Hospital (PUMCH; Beijing, China) and the Department of Emergency of The Second Hospital of Hebei Medical University (Shijiazhuang, China) between January 2013 and August 2018. The inclusion criteria were as follows: i) Confirmed diagnosis of HTGAP; ii) serum TG level ≥11.3 mmol/l; iii) no relevant treatment prior to admission; and iv) age ≥18 years. The exclusion criteria were as follows: i) Biliary, alcoholic, toxic, immune, idiopathic or chronic pancreatitis, or pancreatic tumors; ii) chronic diseases, including malignant tumors, chronic organ failure and nephrotic syndrome; iii) incomplete clinical data; iv) patients receiving TG-lowering agents, including heparin and oral TG-lowering drugs; and vi) insulin allergy. A number of baseline clinical indicators, including age, sex, serum amylase level and the presence of severe AP (SAP) or SIRS were noted.

Diagnostic criteria. The diagnostic criteria for patients were based on the 2012 classification of the International Association of Pancreatology (IAP) (17), according to which patients must exhibit two of the following three characteristics to be diagnosed with AP: i) Abdominal pain consistent with AP; ii) activity of serum amylase and/or lipase at least 3 times higher than the upper limit of normal; and iii) abdominal imaging consistent with changes in AP. HTG was defined as fasting serum TG >11.3 mmol/l or serum TG levels 5.65-11.3 mmol/l and visible chylomicrons in the blood. Patients were diagnosed with HTGAP according to the aforementioned criteria, after excluding biliary diseases, as well as the effects of alcohol, drugs and other factors.

TG-lowering interventions. Following hospital admission, the patients received routine treatment, including fasting, pain management, gastrointestinal decompression, fluid resuscitation, nutritional support and antibiotics, and were put on a TG-lowering regimen. The TG-lowering strategies used were as follows: i) For IIT, patients were treated with a continuous intravenous infusion of 0.1-0.3 U/kg/h insulin and 10% glucose to prevent hypoglycemia. ii) For NIIT, patients continuously received an intravenous injection of insulin and 5 or 10% glucose, at a ratio of 1:4 or 1:6. iii) For PE, a double-lumen venous catheter was inserted into patients without vascular puncture contraindications, and PE was performed using a Gambro AK10 dialysis machine with a PF 2000 N fiber plasma filter. Patients received the first PE procedure within 24 h of admission, then treated PE every other day. During each treatment, 1.5-2.0 plasma volumes were replaced with 5% albumin solution and fresh frozen plasma. Citrate anticoagulation was used during the procedure. The blood glucose levels were maintained at 6.7-11.1 mmol/l in all patients receiving insulin and serum TG levels were monitored every 4 h.

Outcome. Therapeutic indicators, including the 24-h TG clearance rate, onset to treatment time (OTT), time required to reach the target TG levels and the length of stay (LOS), as well as outcome indicators, including mortality, local complications, requirement for surgery and therapy-associated complications (hypokalemia, hypoglycemia, pipeline congestion, shiver, skin rash and deep vein thrombosis), were monitored. Serum TG levels ≤5.65 mmol/l served as the treatment endpoint in the three groups.

Statistical analysis. Statistical analyses were performed using SPSS software (version 24.0; IBM Corp.). Continuous data were expressed as the mean ± standard deviation or median and interquartile range, and the significance of differences between groups was assessed using analysis of variance or the Kruskal-Wallis test followed by Bonferroni's post-hoc test. Categorical data were presented as n or n (%) and comparisons were performed using the χ^2 or Fisher's test. P<0.05 was considered to indicate a statistically significant difference.

Results

Patient characteristics. A flow chart illustrating the patient selection process for the present study is provided in Fig. 1. A total of 132 patients with HTGAP were included in the present study and divided into following three groups: i) The IIT group (n=46), ii) the PE group (n=43) and the NIIT group (n=43). The mean age of patients in the IIT group was 39.00±11.01 years including 30 males and 16 females. In the PE group, the average age was 35.72±8.95 years, and the number of male and female patients was 29 and 14, respectively. There were 31 male and 12 female patients in the NIIT group with the mean age of 37.49±9.66 years. Clinical parameters, including sex, age, serum TG and amylase levels, SAP and SIRS, were not significantly different between the three groups (P>0.05; Table I).

Effects of the TG-lowering therapies. As presented in Table II, the 24-h TG clearance rate (χ^2=7.74, P=0.021), OTT (χ^2=14.50, P<0.001) and the time required to reach the target TG level (χ^2=6.12, P=0.047) were significantly different among the three groups. The 24-h TG clearance rate in patients in the NIIT group was significantly lower than that in the PE group (P<0.05). However, there were no significant differences
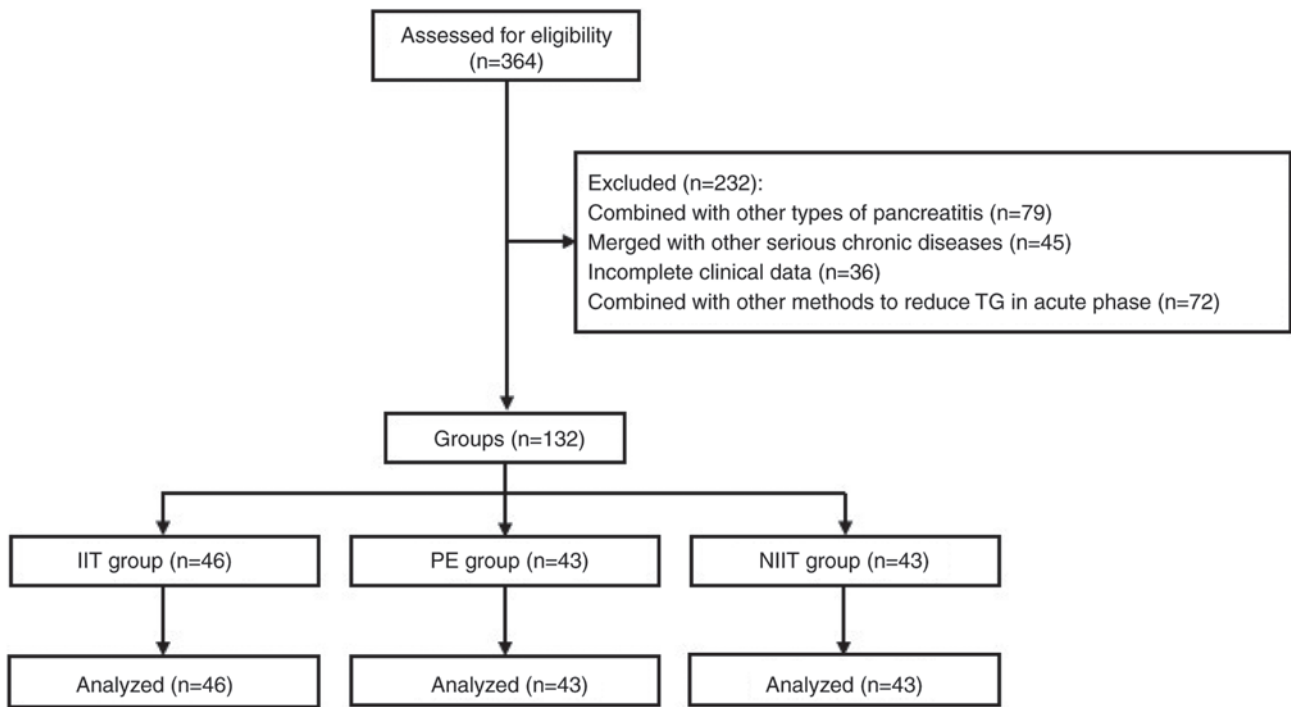
Figure 1. Flow diagram of the selection process of subjects for the present study. TG, triglyceride; IIT, insulin intensive therapy; PE, plasma exchange; NIIT, non-intensive insulin therapy.

between the IIT and NIIT groups or the IIT and PE groups with this regard (P>0.05). The time required to reach the target TG level in patients in the NIIT group was longer than that in the PE group (P<0.05), while there were no such differences between the IIT and NIIT groups or the IIT and PE groups (P>0.05). The OTT of the patients in the PE group was obviously increased compared with that in the IIT and NIIT groups (P<0.05); however, no statistically significant difference in the OTT was observed between the IIT and NIIT groups (P>0.05). After the TG-lowering therapies, the 24-h amylase levels were not significantly different among the three groups (P>0.05).

Complications in the treatment groups. There were no statistically significant differences in mortality, local complications, requirement for surgery, SIR and cure rate among the three treatment groups (P>0.05). The incidence of therapy-associated complications in the PE group (30.23%) was significantly higher than that in the IIT (2.17%) and NIIT (4.65%) groups, while there was no overall difference in the incidence of complications between the IIT and NIIT groups (P>0.05). The incidence of skin rash in the PE group was higher than that in the IIT and NIIT groups (P<0.05), while no obvious difference regarding skin rash was present between the IIT and NIIT groups (P>0.05). The LOS in the PE group was increased compared with that in the IIT and NIIT groups (χ^2=7.05, P<0.05); however, there was no significant difference in the LOS between the IIT and NIIT groups (P>0.05; Table III).

Discussion

AP is one of the most common gastrointestinal diseases that require hospitalization, with >270,000 cases reported annually in the US (18). The clinical characteristics of AP are easily distinguished from other relatively mild and self-limiting illnesses and may lead to persistent or multisystem organ failure. Enhanced serum TG levels are a risk factor for AP and HTG is observed in up to 10% of patients with AP (7). Compared with other causes of AP, HTGAP is associated with an increased incidence of complications (7,19). It has been demonstrated that serum TG, which is hydrolyzed by pancreatic lipase into toxic free fatty acids, is associated with the occurrence and development of HTGAP (9) and serum TG levels in patients with pancreatitis have been reported to be as high as 21% (11.3-22.6 mmol/l) (4,20). Therefore, rapid reduction of serum TG levels during the early onset of the disease and the maintenance of serum TG at levels <5.65 mmol/l may prevent the progression of HTGAP (9). In current clinical practice, insulin and/or PE are commonly used as TG-lowering therapies for HTGAP (21,22); however, to the best of our knowledge, there are currently no uniform, standardized and comprehensive therapeutic guidelines for patients with HTGAP.

LPL is widely expressed in muscle and capillary endothelial cells in adipose tissue, and serves an important role in fat metabolism by catalyzing the breakdown of chylomicrons and low-density lipoproteins into glycerol and free fatty acids (23). Previous studies have demonstrated that insulin reduces chylomicron levels in the blood by enhancing the activity of LPL and inhibits hormone-sensitive lipase in lipocytes to decrease the breakdown of lipocytes and the production of TG (11). Furthermore, insulin promotes the degradation of chylomicrons and decreases the serum levels of TG, which is beneficial in patients with poorly controlled diabetes or diabetic ketoacidosis (24-26). A previous study reported that continuous intravenous infusion of insulin reduced serum TG levels by 40% within 24 h (27), which is similar to the results obtained in the present study. While insulin therapy

Table I. Characteristics of patients under different treatments.

Variable	PE (n=43)	IIT (n=46)	NIIT (n=43)	χ^2/F	P-value
Male gender	29 (67.44)	30 (65.22)	31 (72.09)	0.50	0.779
Age (years)	35.72±8.95	39.00±11.01	37.49±9.66	1.49	0.229
TG (mmol/l)	23.10 (16.62-47.11)	28.22 (23.58-38.90)	26.22 (18.84-40.45)	0.23	0.893
Amylase (U/l)	569.0 (338.0-1104.0)	495.50 (209.0-784.0)	737.0 (292.0-1145.0)	4.47	0.107
SAP	18 (41.86)	20 (43.48)	17 (39.53)	0.14	0.931
SIRS	33 (76.74)	36 (78.26)	32 (62.79)	0.19	0.912

Values are expressed as n (%), mean ± standard deviation or median (interquartile range). TG, triglyceride; IIT, insulin intensive therapy; PE, plasma exchange; NIIT, non-intensive insulin therapy; SAP, severe acute pancreatitis; SIRS, systemic inflammatory response syndrome.

Table II. Comparison of the effects of TG-lowering therapies between different treatment groups.

Variable	PE (n=43)	IIT (n=46)	NIIT (n=43)	χ^2/H	P-value
24-h TG clearance rate (%)	0.71 (0.62-0.84)	0.68 (0.56-0.79)	0.62 (0.47-0.76)[a]	7.74	0.021
24-h amylase levels (U/l)	243.0 (130.0-458.0)	231.50 (86.50-350.75)	492.0 (208.50-912.50)	0.93	0.628
OTT (h)	41.0 (28.0-61.00)	31.0 (25.0-39.0)[a]	26.0 (17.0-36.0)[a]	14.50	<0.001
Time required to reach target TG levels (h)	44.0 (21.0-68.0)	49.0 (32.0-120.0)	72.0 (33.0-120.0)[a]	6.12	0.047

[a]P<0.05 vs. PE group. Values are expressed as the median (interquartile range). PE, plasma exchange; IIT, intensive insulin therapy; NIIT, non-intensive insulin therapy; TG, triglyceride; OTT, onset to treatment time.

Table III. Comparison of clinical outcomes between different treatment groups.

Variable	PE[a] (n=43)	IIT (n=46)	NIIT (n=43)	χ^{2b}	P-value
Mortality	3 (6.98)	3 (6.52)	2 (4.65)	-	1.0
Local complications	20 (46.51)	19 (41.30)	13 (30.23)	2.50	0.287
Requirement for surgery	4 (9.30)	6 (13.04)	7 (16.28)	0.93	0.627
Therapy-associated complications					
None	30	45	41	-	<0.001
Hypokalemia	0	1	0	-	0.351
Hypoglycemia	0	0	2	-	0.210
Pipeline congestion	1	0	0	-	0.326
Shiver	2	0	0	-	0.104
Skin rash	9	0	0	-	<0.001
Deep vein thrombosis	1	0	0	-	0.325
LOS (days)	22.0 (14.0-30.0)	16.50 (12.00-27.0)	14.0 (7.0-22.0)[c]	7.05	0.030
SIRS	15 (29.40)	19 (37.30)	17 (37.30)	0.41	0.815
Cure	32 (74.42)	34 (73.91)	31 (74.42)	0.07	0.967

[a]A total of 2 cases had pipeline congestion + skin rash; 1 case had shiver + skin rash. [b]Fisher's test was used if no value is provided. [c]P<0.05 vs. PE group. Values are expressed as n, n (%) or median (interquartile range). PE, plasma exchange; IIT, intensive insulin therapy; NIIT, non-intensive insulin therapy; LOS, length of stay; SIRS, systemic inflammatory response syndrome.

is widely utilized in early HTGAP due to its ease of use, fewer complications and cost-effectiveness compared with PE treatment, excessive insulin administration may lead to neurological complications caused by severe hypoglycemia and does not significantly improve the prognosis of critically ill patients (28).

Betteridge et al (29) first described the use of PE for the treatment of HTGAP. PE reduces serum TG levels, eliminates excess proteases and supplements protease inhibitors. Several studies have demonstrated that PE decreases TG serum levels by 70-89% (13,30). The results obtained in the present study further demonstrated the efficacy of PE in significantly decreasing TG serum levels. In addition to effectively removing TG from the plasma of patients with HTGAP, PE eliminates pro-inflammatory cytokines, including interleukin-1 and tumor necrosis factor-α (31), and decreases neutrophil extracellular traps. However, previous studies have revealed that PE therapy is limited due to the demand for vascular puncture and indwelling intravenous catheters, and is associated with allergy, infection, unstable circulation and abnormal blood coagulation in patients with HTGAP. Furthermore, PE has a relatively high treatment cost and is highly dependent on blood products (17,32). In 2016, the American Society for Apheresis suggested that HTGAP should only be regarded as a Class III indication for PE (33).

The present study demonstrated that the OTT of patients in the IIT and NIIT groups was decreased compared with that in the PE group. PE treatment requires additional time to prepare the equipment and materials, perform the vascular puncture and to measure coagulation function. In the present study, the LOS in the NIIT group was not significantly longer than that in the PE group, as NIIT induced fewer complications to shorten the inpatient time for HTGAP patients. The complications in the IIT group were similar to those in the NIIT group and significantly less than those in the PE group. The 24-h TG clearance rate in the PE group was 71%, which was higher compared with that in the NIIT group. Furthermore, the incidence of therapy-associated complications in the PE group was higher compared with that in the other two groups. As a type of blood purification treatment, PE sifts out the majority of non-cellular components from the blood. A large-pore filter rapidly and effectively removes TG and their metabolites from the plasma of patients with HTGAP and reduces the levels of pancreatic enzymes. However, repeated PE treatments are not feasible due to the risk of complications, increased demand for blood products and treatment cost (17). In the present study, no significant differences in the OTT, the 24-h TG clearance rate and the incidence of therapy-associated complications were obtained between the IIT and NIIT groups.

To the best of our knowledge, the present study was the first to compare the efficacy of IIT, NIIT and PE in patients with HTGAP. The results demonstrated that patients in the NIIT and IIT groups exhibited a similar OTT, 24-h TG clearance rate, incidence of therapy-associated complications and LOS. Furthermore, patients in the NIIT and IIT groups had fewer complications compared with patients in the PE group. The present study had a retrospective design. A limitation was that only data of patients from northern China were analyzed, as data of patients from southern China were not available. As there may be differences in lipid metabolism between northern and southern populations in China (34), a randomized controlled trial is required to further verify these results.

In conclusion, the present study analyzed the effects of three TG-lowering therapies on the prognosis of patients with HTGAP. Parameters including the OTT, 24-h TG clearance rate, incidence of therapy-associated complications and LOS were compared. Patients who received NIIT and IIT had a similar prognosis and exhibited fewer complications compared with patients treated with PE. NIIT and IIT may perform favorably if administered shortly after symptom onset. To ensure appropriate use of resources and limit medical costs, NIIT may be used to treat patients with HTGAP requiring further clinical assessment.

Acknowledgements

Not applicable.

Availability of data and materials

All data generated or analyzed during the present study are included in this published article.

Authors' contributions

JX, XY and SY conceptualized and developed the study design. DY, XL, KJ, YF and DL aquired, analyzed and interpreted the data. SY and DL discussed the results and wrote the manuscript. LZ, XS and JY provided comments, suggested appropriate modifications and made corrections to the study. SY, JX and XY revised the manuscript. All authors read and approved the final manuscript.

Ethical approval and consent to participate

This study was approved by the institutional review boards of PUMCH (approval no. S-K554) and the Second Hospital of Hebei Medical University (approval no. 2018-P042).

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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