Effectiveness of insulin infusion therapy for hypertriglyceridemia-induced acute pancreatitis

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Abstract

Background: Hypertriglyceridemia (HTG) is an increasingly recognized cause of acute pancreatitis (AP) in Vietnam. Despite its clinical relevance, there are currently no universally accepted guidelines for the use of insulin in the management of HTG-induced acute pancreatitis (HTG-AP). Furthermore, existing evidence on the efficacy and safety of insulin therapy in this setting remains limited. **Objective**: This study aimed to assess treatment outcomes and safety of insulin infusion therapy in mild and moderately severe HTG-AP. **Methods**: Observational study of therapeutic effectiveness, 93 patients with mild and moderately severe HTG-AP treated at the Department of Gastroenterology, Cho Ray Hospital from August 2023 to June 2024 were enrolled. **Results**: Mean value of TG levels decreased rapidly from 4348.4 mg/dL at admission to 1227.3 mg/dL after 48 hours and 747.5 mg/dL after 72 hours of insulin infusion therapy ($p<0.05$). The rates of achieving TG < 500 mg/dL after 48 hours and 72 hours were 34.4% and 52.7%, respectively. Pain relief rates were 28.0% after 48 hours and 63.4% after 72 hours. Mean time to achieve pain relief and fasting was 3.2 days; the average length of hospital stay was 6.2 days. All patients fully recovered and were discharged with no mortality or severe adverse events. Patients with TG > 2000 mg/dL had longer TG reduction time (3.4 vs 2.0 days) and hospitalization (7.1 vs 5.9 days; $p<0.05$). Mild hypokalemia was observed in most patients (95.7%). **Conclusion**: Insulin infusion therapy appeared a safe and effective treatment in patients with mild and moderately-severe HTG-AP.

Keywords: *acute pancreatitis, hypertriglyceridemia, insulin.*

1. INTRODUCTION

Hypertriglyceridemia is the third most common cause of acute pancreatitis [1], determined when serum TG levels exceed 11.3 mmol/L (1000 mg/dL) [2]. Many studies have found that increased TG accounts for 7 - 20% of all AP cases. Hypertriglyceridemia-induced acute pancreatitis (HTG-AP) has a higher rates of complications and mortality compared to other causes of AP [3-5]. In addition to the general treatment regimen for AP, reducing TG levels is also an important goal to prevent progressive pancreatic damage [6]. Plasma exchange is the first-line option in the treatment of HTG-AP, but it is not always available in many medical settings [7-8].

Insulin infusion therapy is considered a suitable alternative due to its ability to rapidly reduce blood TG levels and its ease of application. Many studies [9-13], though based on limited data, have shown its effectiveness and potential role in improving disease outcomes [13-14].

Therefore, we conducted this study to assess the treatment results and some unwanted effects of insulin infusion therapy in patients with mild to moderately- severe HTG-AP.

2. RESEARCH SUBJECTS AND METHODS

Observational study of therapeutic effectiveness of 93 patients with mild to moderately-severe HTG-AP at the Department of Gastroenterology, Cho Ray Hospital from August 2023 to June 2024.

2.1. Criteria for disease selection

Patients ≥ 18 years old who met at least 2 of the 3 diagnostic criteria for AP (acute abdominal pain; blood amylase and/or lipase increased ≥ 3 times the upper limit of normal; CT/MRI/ultrasound imaging suitable for AP) [7] and:

- Serum TG levels > 1000 mg/dL at admission [2].
- Suffering from mild to moderately severe AP according to Atlanta 2012 classification.
- Excluding other causes of AP: alcohol, choledocholithiasis (by taking a medical history and performing CT/ MRI/abdominal ultrasound / endoscopic ultrasound imaging.
- Agreed to participate in the study.

2.2. Exclusion criteria

- Chronic pancreatitis/acute exacerbation of chronic pancreatitis
- Having autoimmune diseases, malignant diseases or end-stage chronic diseases.
- Severe AP according to the Atlanta 2012 criteria.

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2.3. Research methods

Research design

Observational study.

Procedure

- Patients who met the selection criteria and did not have the exclusion criteria were selected for the study. Clinical examination, blood test and diagnostic imaginge were performed.

- The types of acute pancreatitis in this study include mild and moderately severe forms, severity classification of AP was based on Atlanta 2012 consensus [7].

- Treatment of HTG- AP, based on protocol of Cho Ray Hospital, was continuous insulin infusion at a rate of 0.1 - 0.3 IU/kg/hour [15-16].

+ Clinical monitoring, including capillary blood sugar every 1 - 2 hours, serum TG every 12 hours and serum potassium every 12 hours.

+ Maintaining capillary blood sugar within the range of 150 - 200 mg/dL, infusing glucose 5% when capillary blood sugar drops < 150 mg/dL.

+ Insulin dose was adjusted depending on the patient's insulin sensitivity.

+ Stopping insulin infusion when TG was <500 mg/dL and switched to oral lipid-lowering medication.

Research variables

- Serum TG concentration at admission and at 48 hours and 72 hours after insulin infusion.

- Time to reach TG <500 mg/dL

- Duration of abdominal pain relief and fasting and for hospitalization.

- Treatment outcomes: recover and discharged, discharged with hospice care, and died

- Undesirable effects: hypokalemia, hypoglycemia, edema.

2.4. Data processing

Analyzing data by SPSS 22.0 software. The t-test was used for quantitative variables with normal distribution, and the Mann–Whitney U test was applied for non-normally distributed quantitative variables, determining χ^2 for qualitative variables. The difference is statistically significant when $p<0.05$.

3. RESEARCH RESULTS

3.1. General characteristics

Table 1. General characteristics of the study subjects

General characteristics		Result
Gender (n, %)	Male	66 (71.0)
	Female	27 (29.0)
Age (mean ± SD)		40.9 ± 7.8
BMI (kg/m^2, mean ± SD)		24.8 ± 3.0
History (n, %)	Hypertension	14 (15.0)
	Stopped drinking alcohol	15 (16.1)
	Hypertriglyceridemia	20 (21.5)
	The gallbladder had been removed	1 (1.1)
	AP	46 (49.5)
	Diabetes mellitus	32 (34.4)
	Using thiazide, sulfonamide	1 (1.1)
	Other chronic diseases	7 (7.5)
Elevated TG levels (n, %) [17]	Severe (1000-2000 mg /dL)	24 (25.8)
	Very severe (>2000 mg /dL)	69 (74.2)
Type of pancreatitis (n, %)	Edematous	64 (68.8)
	Necrotic	29 (31.2)
Severity classification of AP (n, %)	Mild	67 (72.0)
	Moderately- severe	26 (28.0)
BISAP score (Mean ± SD)		0.8 ± 0.7
CTSI score (Mean ± SD)		4.7 ± 2.1

The majority of the study population was male (71%), with a mean age of 40.9 ± 7.8, and a history of AP in 49.5%, diabetes in 34.4%, and hypertriglyceridemia in 21.5%. The majority of patients had very severe TG elevation (74.2%). Edematous AP accounted for 68.8%, and most of the cases had mild AP (72%). The mean BISAP and CTSI scores were 0.8 ± 0.7 and 4.7 ± 2.1, respectively.

3.2. Therapeutic effects of insulin therapy

3.2.1. Effectiveness in reducing triglyceride levels

Table 2. The effectiveness of insulin infusion therapy in reducing triglyceride levels

Time	Mean TG concentration (mg /dL)			
	Severe n=24	Very severe n=69	Total n=93	p
Hour 0	1367.8	5385.1	4348.4	<0.001
Hour 12	950.1	3833.4	3089.3	<0.001
Hour 24	675.0	2560.0	2073.6	<0.001
Hour 36	654.1	1846.4	1619.3	<0.001
Hour 48	607.9	1339.9	1227.3	0.002
Hour 60	687.5	1060.5	1023.2	0.324
Hour 72	491.3	864.7	820.8	0.136
Hour 84	549.8	771.4	747.5	0.171
Time to reach TG < 500 mg /dL (days)				
Mean	2.0	3.4	3.0	<0.001
Number of patients achieving TG < 500 mg/dL (n=93, %)				
Hour 48			32 (34.3%)	
Hour 72			49 (52.7%)	

Comparison of the effectiveness of insulin infusion in reducing TG between groups with severe and very severe TG elevation showed a statistically significant difference in TG reduction from hour 0 to hour 48. After 48 hours, no statistically significant difference was observed. Time to reach TG levels <500 mg/dL was considerably longer in the group with very severe TG elevation compared to the group with severe TG elevation (3.4 vs 2.0 days, p<0.001). The rates of patients achieving TG < 500 mg /dL at hour 48 and hour 72 were 34.4% and 52.7%, respectively.

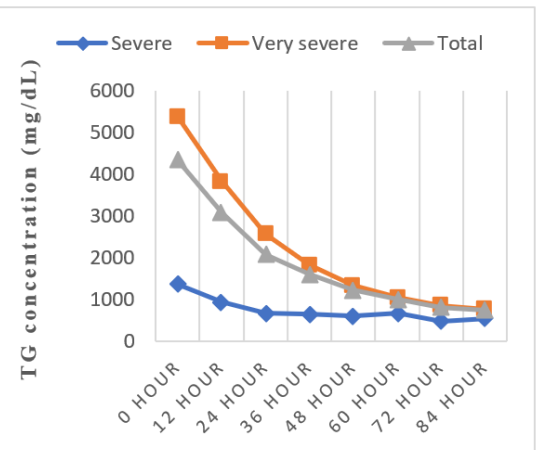

Figure 1. TG concentrations changing over time in severe and very severe TG elevation groups with insulin infusion.

Serum TG decreased faster in severe TG elevation group.

3.2.2. Clinical effectiveness of insulin therapy

Table 3. Clinical effectiveness of insulin infusion therapy

Clinical outcomes	Elevation of TG at admission			
	Severe n=24	Very severe n=69	Total n=93	p
Clinical responses (days, X ± SD)				
Abdominal pain	3.2 ± 1.2	3.4 ± 1.4	3.2 ± 1.2	0.8
Fasting	3.2 ± 1.1	3.3 ± 1.3	3.2 ± 1.2	0.6
Length of stay (LOS)	5.9 ± 2.4	7.1 ± 3.2	6.2 ± 2.7	0.04
Treatment outcomes (n, %)				
Recovered and discharged			93 (100)	
Discharged with hospice care			0 (0)	
Death			0 (0)	

In regard of abdominal pain relief and fasting, there was no statistically significant difference in clinical outcomes between severe and very severe TG elevation at admission. The mean durations of abdominal pain relief and of fasting in the study population were both 3.2 days. LOS was 6.2 days in the study population. 100% of patients recovered and discharged from the hospital. LOS of the very severe TG elevation group (7.1 ± 3.2) was statistically longer than the severe TG elevation group (5.9 ± 2.4) ($p<0.04$).

3.2.3. Adverse effects of insulin therapy

Table 4. Adverse effects of insulin therapy

Unexpected effects		n	%
Local/ systemic allergies		0	0
Hypoglycemia		0	0
Hypokalemia	Mild	89	95.7
	Moderate	1	1.1
	Severe	0	0

Insulin therapy was well tolerated, and no serious complications occurred. Most patients had mild hypokalemia (95.7%).

4. DISCUSSION

In our study, the proportion of males who had HTG-AP was much higher than females (71.0% compared to 29.0%) with a mean age of 40.9 years. This might be related to risk factors that increase TG in this age group such as high-fat diets, lack of exercise, and alcohol use (especially in male) [18].

Nearly 50% of patients had a history of AP, 34.4% had diabetes and 21.5% had previously elevated blood sugar level, which might reflect the high risk of AP recurrence in these patients. [19-20]

The mean BMI which was 24.8 ± 3.0 kg/m² indicating the majority of study population falling into the overweight category (BMI 23 - 24.9 kg/m^2) [21]. This has also been documented by numerous domestic and international studies, with the mean BMI of patients with AP caused by elevated TG reported to range from 24 - 34 kg/m^2 [9].

74.2% of patients had very severe TG elevation (>2000 mg/dL) and 25.8% had severe TG elevation (1000 - 2000 mg/dL) at admission. Interstitial edematous pancreatitis predominated (68.8%) while accounted for 3 - 12%, the majority of patients had mild AP (72%) and 28.0% had moderately- severe AP. The mean BISAP and CTSI scores were 0.8 ± 0.7 and 4.7 ± 2.1, respectively. We did not find a statistically significant difference in CTSI, BISAP scores and AP severity between 2 groups of severe and very severe TG increase at admission ($p>0.05$). This hinted that the degree of hypertriglyceridemia, within the limits of the study, might not directly related to the degree of pancreatic damage.

Therapeutic effectiveness of insulin therapy

After infusing insulin, serum TG decreased rapidly from the average concentration 4348.4 mg/dL at admission to 1227.3 mg/dL after 48 hours and reached to 747.5 mg/dL after 72 hours. The marked decrease in TG during the intertrial period might

demonstrate the effectiveness of insulin in activating lipoprotein lipase [9, 22], promoting chylomicron fractionation, and rapidly reducing TG levels.

It required an average of 3.0 days to reach the target TG level of under 500 mg/dL. Notably, the group with severe TG elevation (1000 - 2000 mg/dL) reached the target (2.0 days) faster than the group with very severe TG elevation (>2000 mg/dL) (3.4 days) ($p<0.001$). This is consistent with pathophysiology of AP, where an increase in TG concentration leads to a corresponding rise in the amount of excess chylomicrons. In a result, it takes longer to completely dissolve [23]. The percentages of patients achieving TG <500 mg /dL after 48 and 72 hours of treatment were 34.4% and 52.7%, respectively. Coskun and Gubensek, in a study on 12 patients with HTG-AP, showed a significant TG reducing effect of intravenous insulin therapy from 1140.75 mg /dL at admission to <500 mg/dL after 3 days of treatment [10-11]. Notably, the TG concentration difference between the severe and very severe TG elevation groups in this study was only statistically significant up to 48 hours ($p < 0.05$). After that, there is no difference observed. These data emphasizes the effectiveness of insulin therapy in reducing blood TG concentrations, regardless of the initial level of TG elevation on patients with mild to moderately - severe HTG-AP.

Research shows that insulin infusion therapy might effectively improves clinical symptoms in patients with HTG-AP. All patients had no abdominal pain and tolerated oral diets well before being discharged. Similarly to Araz and Vo Chi Tuyen [12], [24] , abdominal pain resolution rates after 48 hours and 72 hours were 28.09% and 63.4%, respectively. The mean time to relieve abdominal pain and fasting was both 3.2 days, the mean LOS was 6.2 days. LOS of the very severe hypertriglyceridemia group was significantly longer than that of the severe hypertriglyceridemia group (7.1 days vs. 5.9 days, $p = 0.048$). This could be explained by the need for more time to reduce blood TG to <500 mg/dL as discussed above. The study did not find any difference in the rates of local complications such as organ failure between the two groups of TG elevation, so we do not think that the difference in LOS between these groups might be related to these variables.

100% of patients recovered and were discharged from the hospital without any serious complications. None of them needed invasive interventions such as plasma exchange or dialysis during hospitalization. This might emphasize the effectiveness of insulin therapy in the context of limited equipment conditions, especially at lower-level medical facilities.

Adverse effects of insulin therapy

Our study showed that insulin therapy is well tolerated in patients with HTG-AP with no cases of allergic reactions or hypoglycemia recorded; Hypokalemia was the most common adverse effect (95.7%), but most of cases were mild [only 1 case (1.1%)] of moderate hypokalemia. Many authors also note that the rate of insulin-related hypoglycemia in the treatment of HTG-AP is very low with no cases recorded in Coskun's study. White commented that 9.4% of patients had hypoglycemia on the first day of insulin therapy, but this no longer occurred from the 2nd day of treatment [10, 25]. These are very positive results which highlight the effectiveness of close monitoring and timely adjustment changes in blood glucose levels during treatment.

Limitations of the research

One limitation in our study is the lack of a control group (eg, plasma exchange group). Besides, the study only assessed the mild and moderately severe HTG-AP groups, excluding severe AP patients. Further studies with larger sample sizes and longer follow-up periods would be needed to comprehensively evaluate the effectiveness and safety of this approach.

5. CONCLUSIONS

Intravenous insulin therapy appeared a safe and effective treatment for patients with mild to moderately severe HTG-AP. The main adverse effect is mild hypokalemia with no serious complications occurred. More prospective studies with larger sample sizes and control group are needed to fully evaluate the effectiveness and safety of this therapy.

Author contributions

Thi Minh Tam Vu and Van Huy Tran designed this study, collected the data, wrote and edited this study. Thi Minh Tam Vu and Phuoc Nguyen Ma performed the formal analyses. Van Huy Tran and Tan Phat Ho co - supervised this study

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