

Hypertriglyceridemia-Induced Pancreatitis: A Decade of Experience in a Community-Based Teaching Hospital

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ABSTRACT

INTRODUCTION: Hypertriglyceridemia is the third most common cause of acute pancreatitis. The current evidence on the management of hypertriglyceridemia-induced pancreatitis (HTGP) is mainly derived from case series. It has been suggested that insulin, and plasmapheresis have a role in the management of acute HTGP. We present a retrospective review of patients seen at a community-teaching hospital between 2005 and 2015. Results: Out of the 549 admissions for acute pancreatitis, fourteen patients met our inclusion criteria. The mean age of presentation was 39 ± 8 years and there was a predominance of men (57%). More than two-thirds of the patients were admitted to the intensive care unit. The majority of the patients were treated with insulin drip (n=8), and the rest by subcutaneous insulin (n=3) and insulin drip + plasmapheresis (n=3). In the insulin drip group we noted a gradual decrease of the admission serum triglycerides by $50.6 \pm 16.0\%$ at 24 hours, $65.9 \pm 16.9\%$ at 48 hours, and then $85.2 \pm 7.1\%$ at discharge. Serum triglycerides decreased by 79.8% and 92.6%, at discharge in the subcutaneous insulin and insulin + plasmapheresis cohorts, respectively. The insulin + plasmapheresis cohort stayed in the hospital longer (20.7 ± 3.1 days) compared to the insulin drip (10.3 ± 5.4 days) and subcutaneous insulin (5.7 ± 1.2 days) cohorts.

CONCLUSION: Our study strengthens the evidence for using insulin (infusion or subcutaneous) with or without plasmapheresis in the treatment of hypertriglyceridemia-induced pancreatitis.

KEYWORDS: Hypertriglyceridemia, Acute pancreatitis, Plasmapheresis, insulin therapy

INTRODUCTION

Acute pancreatitis is the leading cause of hospitalization for gastrointestinal diseases in the United States of America.¹ While gallstones and alcohol abuse account for two-thirds of the cases of acute pancreatitis, hypertriglyceridemia is the third most common cause, with an estimated prevalence around (1-4%).² There are no definitive guidelines on the treatment of hypertriglyceridemia-induced pancreatitis (HTGP). Case series have suggested a role for insulin, heparin and plasmapheresis as adjunctive to conventional therapies such as statins and fibrates when treating HTGP.^{3,4}

METHODS

We reviewed records on all patients older than or equal to 18 years of age admitted with the primary diagnosis of acute pancreatitis between 2005 and 2015. This data was obtained from our hospital's electronic and paper-based medical records using the relevant ICD 9 codes. We screened patient with the secondary diagnosis of "Hypertriglyceridemia." Data was collected regarding demographics, clinical presentation, diagnostic method, treatment modalities, length of hospital stay, complications and in-hospital mortality. We compared the rapidity of correction of serum triglyceride levels with the various treatment modalities. For patients with multiple admissions, each was treated as a separate data entry. This study was given an exempt status by the local Institutional Review Board.

Only patients with admission serum triglyceride of $>1000\text{mg/dL}$ were included. Based on the Atlanta classification for acute pancreatitis, the diagnosis of pancreatitis required fulfillment of two out of three criteria (abdominal pain, radiographic evidence or serum lipase at two-thirds the upper limit of normal.⁵ Descriptive statistics were generated for all variables (means and standard deviations for continuous variables; counts and percentages for categorical variables). Due to the small sample size, exact chi-square p-values were calculated when examining differences in categorical variables by treatment group. A number of the continuous variables exhibited non-normal, highly skewed distributions. For this reason, the non-parametric Kruskal-Wallis test was used to examine differences in the continuous variables by treatment group. IBM SPSS version 21 (Armonk, NY) was used to conduct all analyses. A p-value ≤ 0.05 was used to designate a statistically significant result for all analyses.

RESULTS

A total of 549 cases of acute pancreatitis were identified. Three percent (n=18) of these admissions had a secondary admission diagnosis of hypertriglyceridemia. Four of these cases were excluded due to unavailability of serum triglyceride levels at discharge. In the 14 encounters involving a total of 10 patients, all patients received subcutaneous heparin and oral anti lipid agents (fibrate, niacin or statin) during the admission. The majority were treated with an insulin drip (n=8) and the rest by subcutaneous insulin (n=3) or insulin

drip+plasmapheresis (n=3) as shown in **Figure 1**.

The mean age of presentation was 39±8 years (insulin drip: 40±6, subcutaneous insulin: 35±16 and insulin+plasmapheresis:41±1). Fifty seven percent were men while seventy one percent were admitted to the intensive care unit. Every patient presented with abdominal pain while computed tomography confirmed pancreatitis in 71% of the encounters (n=10). The lipase level was three times above the upper limit of normal in 86 % (n=12) of the overall cohort. The most common presenting comorbidity was diabetes mellitus (50%). The mean lipase levels on admission was 452±348, p=0.46 [552.5 ±373.5mg/dL (insulin drip), 261.7±245.9mg/dL (subcutaneous insulin) and 375.3±369.1 mg/dL (insulin+ plasmapheresis)].The overall mean admission triglyceride was 5753± 4056 mg/dL, p=0.90 (insulin drip: 5307 ±4932.3 mg/dL, subcutaneous insulin: 6123±1431 mg/dL and insulin+plasmapheresis: 6575±4214 mg/dL).

The serum triglycerides decreased by 50.6 ±16.0 % within 24 hours (from 5307±4932.3 mg/dL to 2139.9± 1702.5 mg/dL) for the patients admitted on insulin drip. **Figure 2** depicts this trend where the triglyceride decreased through 48 hours (65.9±16.9%) and at the time of discharge (85.2± 7.1%). Interestingly, at the time of discharge the triglyceride had decreased by 79.8% (p=0.02) for subcutaneous insulin and by 92.6±5.6% for insulin+ plasmapheresis. **Figure 3** shows a comparison of the percentage decreases of all three treatment modalities.

There was no death associated with any of the treatment cohorts. The patients treated with insulin+plasmapheresis stayed longer in the hospital (20.7±3.1 days) compared to those on insulin drip (10.3±5.4 days) and subcutaneous insulin (5.7± 1.2 days). None of the patients on subcutaneous insulin had any complication. Half (n=4) of the patients treated with insulin drip had complications, which included small bowel obstruction, spontaneous bacterial peritonitis, and respiratory failure requiring intubation. Two out of the three patients treated with insulin+plasmapheresis had complications. One had respiratory failure requiring intubation and also developed acute tubular nephritis requiring dialysis. The other developed acute respiratory distress syndrome, acute kidney disease and while the intubated patient developed ventilator acquired pneumonia.

Figure 1. Schematic diagram of study design showing the inclusion and exclusion criteria.

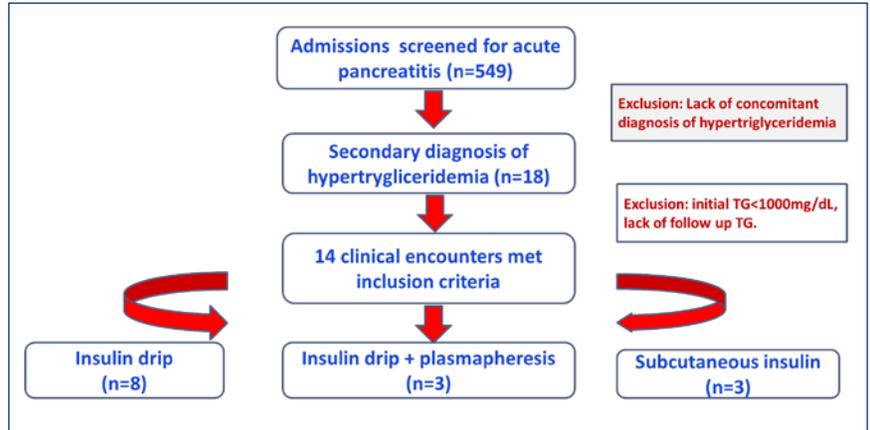


Figure 2. Graph shows the trend of serum triglyceride with intravenous insulin infusion over three days and at time of discharge.

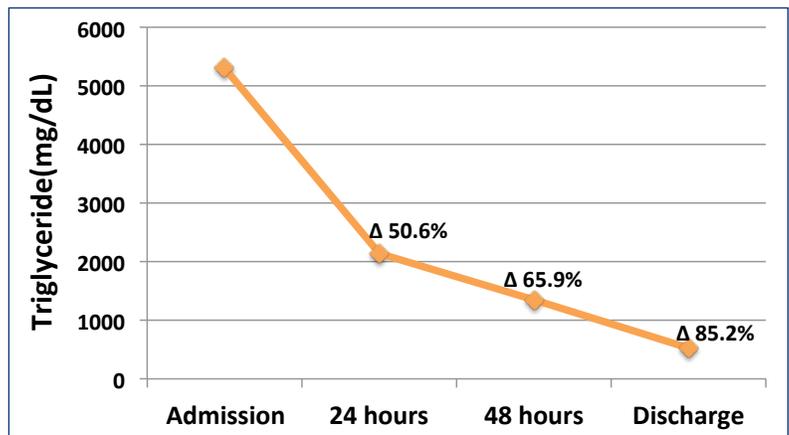
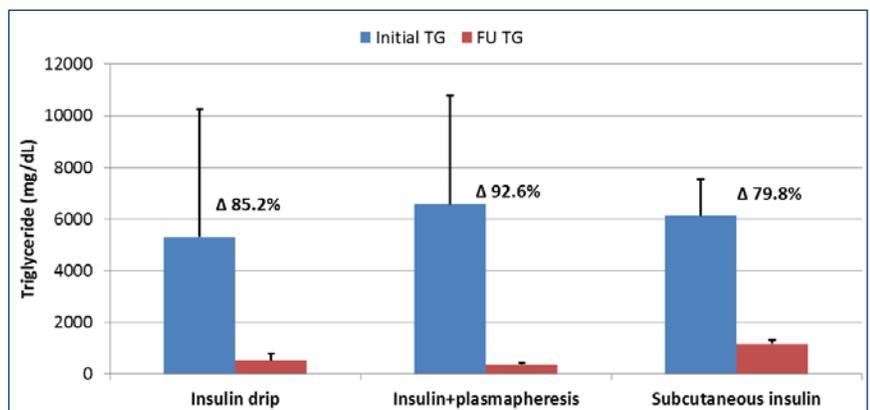


Figure 3. Graph compares admission and discharge serum triglycerides for all three treatment modalities (intravenous insulin infusion, subcutaneous insulin, and insulin+plasmapheresis). The difference is presented as a percentage decrease.



DISCUSSION

HTGP is not an uncommon presentation. Unfortunately there are no guidelines that address its management. The conventional treatment of acute pancreatitis includes restricted oral intake, aggressive intravenous fluid resuscitation, and adequate pain control which were offered to our patients. The primary goal in HTGP is to lower the triglycerides level since this is proven to expedite clinical improvement.

The risk of pancreatitis increases with triglycerides greater than 1000 mg/dL.⁶ Several mechanisms have been postulated for HTGP, all leading down the common pathway of ischemic injury to acinar cells. Excess triglycerides are hydrolyzed by pancreatic lipase resulting in the formation of excess free fatty acids, which cause acinar cell injury and capillary leakage in pancreatic vascular beds.^{7, 8} The resultant ischemia produces an acidic environment which perpetuates a vicious cycle of subsequent ischemia and necrosis. Likewise, excess chylomicrons cause ischemic injury because the resulting hyperviscous plasma causes sluggish flow through the pancreatic beds.⁹

Anti-lipidemic agents are co-adjuvant therapy in HTGP. Fibrates can lower triglycerides by 40-60% and are frequently used for primary hypertriglyceridemia. Fibrates activate lipoprotein lipase which causes triglyceride-rich lipoprotein lipolysis. They also decrease hepatic fatty acid through hepatic β -oxidation, thus reducing triglyceride production.¹⁰ Insulin has been suggested as a therapy for HTGP even in patients without diabetes. Insulin promotes storage of fatty acids, and acts as a potent activator of lipoprotein lipase, which hydrolyzes the circulating triglycerides and aids in their removal from plasma.¹¹

Thuzar et al compared the treatment of HTGP using insulin drip with fasting, insulin drip alone and subcutaneous insulin.¹² At 24 hours, insulin drip and fasting reduced the triglycerides by 87%, while insulin drip alone reduced triglycerides by 40%. In our study a higher reduction (50%) was seen within 24 hours after initiation of the insulin drip. In their review only one patient had been treated with subcutaneous insulin and this had resulted in a 23% reduction of triglycerides while we showed that a 79% reduction could be achieved during the course of hospital stay. No trial has compared insulin drip and subcutaneous drip; however it is suspected that intravenous insulin has a better pharmacokinetics and absorption profile in acutely sick patients.

Plasmapheresis actively removes triglycerides and also supplements the patient with lipoprotein lipase and apolipoprotein which activate three-acyl-glycerols cleavage and clearance. Ramirez-Bueno et al demonstrated 81% reduction in serum triglyceride with plasmapheresis.¹³ We achieved a higher reduction in triglycerides (92%) likely due to the fact that our patients received plasmapheresis in addition to intravenous insulin. Due to limited evidence and conflicting reports, plasmapheresis for as treatment for HTGP is classified as Grade 2C (absence of morbidity and mortality

benefit) by the American Society for Apheresis.¹⁴ Our findings reinforce the role of plasmapheresis in hypertriglyceridemia-induced pancreatitis.

The observed complications in those who received insulin and or plasmapheresis may have reflected the severity of disease on presentation, as opposed to a causal relationship, which likely influenced the choice of more aggressive treatment modalities. This also highlights the fact that acute pancreatitis is not a benign condition as there is a risk of systemic inflammatory response, and also the breakdown of triglycerides into toxic free fatty acids could cause lipotoxicity.

The small sample size and the retrospective design of this study make it difficult to translate the results to a large population size however these findings indicate the need for controlled trials to further understand this clinical entity. Another limitation is the fact that a fasting triglyceride was not measured. In the setting of acute pancreatitis, triglycerides could be falsely elevated.

CONCLUSION

Severe hypertriglyceridemia is associated with acute pancreatitis. Our study strengthens the evidence for using insulin (infusion or subcutaneous) with or without plasmapheresis in the treatment of hypertriglyceridemia-induced pancreatitis. Prospective randomized control trials need to be done to validate these promising therapies.

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