

Treatment of Hypertriglyceridemia with Aggressive Continuous Intravenous Insulin

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ABSTRACT – Purpose: Severe hypertriglyceridemia requiring hospitalization for intravenous insulin to lower triglycerides and prevent complications of pancreatitis is becoming an increasing problem with little consensus treatment evidence. This is the largest case series to date to evaluate this under-studied area of literature. The objective of this study was to determine the average time to triglyceride lowering less than 500 mg/dL. **Methods:** This was a retrospective case series from March 2018 to March 2020 at a single rural academic medical center. 23 patients were included who received weight-based intravenous insulin at 0.1 units/kg/hour through a hypertriglyceridemia management order-set over a two-year period. **Results:** The median triglyceride level at initiation of the insulin infusion was 3759 mg/dL with an interquartile range of 5555. The median time to a triglyceride level less than 1000 mg/dL and 500 mg/dL was 45 hours (1.8 days) and 75 hours (3.1 days) respectively. Patients remained on intravenous insulin for a median of 60 hours (2.5 days). **Conclusions:** In this largest case series to date evaluating the use of intravenous insulin for the treatment of hypertriglyceridemia, a weight-based insulin infusion demonstrated reduction of triglyceride levels to less than 1000 mg/dL in approximately 2 days and less than 500 mg/dL in approximately 3 days.

INTRODUCTION

Patients with severe hypertriglyceridemia (HT), defined as a triglyceride level greater than 1000 mg/dL, are at risk for development of acute pancreatitis, premature atherosclerosis, or cardiovascular disease (1,2). HT is reported to cause 1 to 7% of acute pancreatitis events in individuals of all ages, secondary only to alcohol and gallstones (3-6). It is hypothesized that HT causes pancreatitis by damaging acinar cells and microvascular membranes from elevated free fatty acid and lysolecithin formation in the pancreatic bed (7). In severe cases, HT can lead to significant morbidity including pancreatic necrosis, abscess formation, and sepsis that can be life-threatening (6,8).

Despite severe sequelae of HT, there is limited data on how to acutely manage HT. Medical therapies such as apheresis, heparin, insulin, and other lipid lowering agents such as niacin, statins, fish oil and fenofibrate derivatives have been utilized. While there are no formal guidelines, a goal triglyceride (TG) level less than 500 mg/dL has been shown as a surrogate marker for clinical improvement (9). Other reviews indicate that targeting triglyceride levels less than 1000 mg/dL

may be sufficient to decrease pancreatitis symptoms and complications (10).

There are no preferred treatment or clinical practice guidance for the management of HT. Previous studies have demonstrated the efficacy of apheresis (PLEX therapy) for acutely lowering TG levels (11-14). However, its cost and feasibility are prohibitive and not commonly used. PLEX therapy requires central venous access, plasma replacement, and transfer to a dialysis unit or intensive care unit and this invasive level of treatment is often not feasible at smaller institutions without the above capabilities. Other treatment modalities such as insulin or heparin infusions are thought to enhance lipoprotein lipase activity, hydrolyze triglycerides into fatty acids and glycerol, and thereby lower serum triglyceride concentrations (7). While theorized to decrease triglycerides, limited clinical evidence exists for either of these therapies (15,16). Since the anticoagulation effects of heparin infusions increase the risk of bleeding, we chose to utilize insulin infusions for the treatment of HT at our institution. To date, there has only been one randomized trial comparing the efficacy of insulin and heparin to apheresis for the treatment of HT (15).

The largest case series evaluating the use of intravenous insulin for hypertriglyceridemia induced pancreatitis includes only 12 patients (16). However, additional guidance is needed for insulin infusion therapy as the overall efficacy, dosing recommendations, and glucose replacement requirements are not known.

At our institution, an aggressive, provider-titrated hypertriglyceridemia insulin infusion order-set was implemented in March 2018 for acute lowering of serum triglycerides. Given the robust use of this high-dose insulin therapy protocol at our institution and the paucity of data in current clinical practice, the purpose of this case series is to provide novel data on the use of intravenous insulin therapy in combination with subcutaneous heparin and oral lipid lowering therapies for the treatment of hypertriglyceridemia.

METHODS

Study population

All adult patients who received insulin via the hypertriglyceridemia insulin infusion order-set from March 2018 to March 2020 were included in this case series. Patients were excluded if they received insulin for less than 12 hours, had an initial triglyceride level less than 500 mg/dL, were less than 18 years of age, or received apheresis. While apheresis can be considered in the management of hypertriglyceridemia, these patients were excluded from this case series in order to better ascertain the triglyceride lowering effects of insulin monotherapy.

Study design

This case series was designed as a retrospective electronic chart review of patients who received insulin via the hypertriglyceridemia insulin infusion order-set from March 2018 to March 2020. Institutional review board authorization was obtained and granted. Data points collected and analyzed included patient age, gender, length of stay, pancreatitis, pseudocyst, abscess, ascites, or pleural effusion on admission, history of diabetes, triglyceride levels throughout admission, concomitant use of lipid lowering therapies, total time on insulin therapy, time to triglyceride level less than 1000 mg/dL and 500 mg/dL and need for an endocrine consult service. Pancreatitis, pseudocyst, abscess, and ascites were validated on abdominal imaging at admission.

The primary endpoint was time to a triglyceride level less than 500 mg/dL. Secondary

endpoints included time to a triglyceride level less than 1000 mg/dL, utilization of subcutaneous heparin, and concomitant use of oral lipid lowering therapies. Oral lipid lowering therapies were defined as a statin, niacin, fenofibrate, or fish oil derivative.

The hypertriglyceridemia infusion order-set begins with an insulin infusion at a rate of 0.1 units/kg/hour based on actual body weight (Figure 1). This order-set includes concomitant nursing orders for titration of dextrose-containing intravenous fluids or as needed boluses to maintain blood glucose to prevent hypoglycemia. Maintenance fluids are selected based on initial blood glucose levels of less than 150mg/dL, 150 to 250mg/dL and greater than 250mg/dL. Upon initiating the insulin infusion, serum glucose levels are checked every 1 hour. If the serum glucose level remains 100 to 140 mg/dL for 3 hours in a row, serum glucose checks move to every 2 hours. If at any time the serum glucose decreases to less than 70 mg/dL, 12.5 grams of dextrose 50% is administered. If the serum glucose remains below 70 mg/dL despite three administrations of dextrose 50%, the insulin drip is discontinued. Triglyceride levels are checked at minimum every 24 hours, and more frequently at provider discretion. The insulin infusion may be increased by 0.1 units/kg/hour per provider discretion at a minimum of once every 24 hours to a maximum infusion rate of 0.4 units/kg/hour. Current recommendations are to discontinue the insulin infusion permanently when the triglyceride level is less than 500 mg/dL though this is ultimately up to provider discretion.

Statistical analysis

Descriptive statistics, including medians with interquartile ranges were utilized for both the primary and secondary endpoints. Because the collected data had a skewed distribution, median was selected as the measure of central tendency.

RESULTS

A total of 30 patients received intravenous insulin through the hypertriglyceridemia order-set over a two-year period. 7 patients were excluded from the study analysis given receipt of PLEX therapy (n = 5) or insulin less than 12 hours (n = 2). Baseline demographics are depicted in Table 1. The average age of patients in this case series was 41 years with a range of 21 to 63. 35% of patients (n = 8) were female and the average length of stay was 7 days. 91% of patients (n = 21) presented with pancreatitis and had

Hypertriglyceridemia Insulin Infusion Medication Management Aggressive Treatment Panel Order-Set	
<p>Nursing orders:</p> <ul style="list-style-type: none"> <input type="checkbox"/> Perform point-of-care (POC) whole blood glucose checks every 1 hour <ul style="list-style-type: none"> • If POC glucose <70 mg/dL, administer 12.5g of dextrose 50% (D50) • If POC glucose <70 mg/dL x 3 results (and treated with D50), then stop insulin drip and call provider <input type="checkbox"/> If blood glucose is stable 100-140 mg/dL x 3 hours, then monitor POC glucose every 2 hours <input type="checkbox"/> Notify MD if potassium level is less than 3.5 mmol/L 	<p>Medication Management:</p> <p>Insulin Therapy:</p> <ul style="list-style-type: none"> <input type="checkbox"/> Insulin regular 250 units in 250 mLs of normal saline infusion <ul style="list-style-type: none"> • 0.1 units/kg/hour <input type="checkbox"/> Dextrose 50% (0.5 g/mL) injection <ul style="list-style-type: none"> • 25 mL (12.5 g) intravenous every 1 hour as needed for blood sugar below 70 mg/dL <p>IV Fluid Therapy:</p> <ul style="list-style-type: none"> - If serum potassium is less than 4.5 mmol/mL, choose a potassium-containing fluid - All fluids started at an initial rate of 75mL/hr <p><input type="checkbox"/> IV fluids for patients with blood sugars greater than or equal to 250 mg/dL</p> <ul style="list-style-type: none"> • 1/2 NS 1000 mL with potassium chloride 20 mEq premix infusion at 75mL/hr • NS premix infusion <p><input type="checkbox"/> IV fluids for patients with blood sugars between 150 and 250 mg/dL</p> <ul style="list-style-type: none"> • D5W 1/2 NS 1000 mL with potassium chloride 20 mEq premix infusion • D5W 1/2 NS premix infusion

Figure 1: Hypertriglyceridemia insulin infusion medication management order-set. The hypertriglyceridemia infusion order-set begins with an insulin infusion at a rate of 0.1 units/kg/hour based on actual body weight. This order-set includes concomitant nursing orders for titration of dextrose-containing intravenous fluids or as needed boluses to maintain blood glucose to prevent hypoglycemia.

a prior history of diabetes. Upon admission to the hospital, 70% of patients (n = 16) had an endocrine consult placed and 83% (n = 19) received subcutaneous heparin 5000 units three times daily as venous-thromboembolism prophylaxis. The other four patients that did not receive subcutaneous heparin received either enoxaparin (n = 2) or apixaban (n = 2).

On admission, the median triglyceride level was 3759 mg/dL with an interquartile range of 5555. Patients remained on intravenous insulin for a median of 60 hours (2.5 days) as depicted in Table 2. The median time to a triglyceride level less than 1000 mg/dL and 500 mg/dL was 45 hours (1.8 days) and 75 hours (3.1 days) respectively. To note, 39% of patients (n = 9) never had a documented triglyceride level less than 500 mg/dL prior to discharge (Table 2). For these patients, it was assumed that discharge was time to triglyceride level less than 500 mg/dL.

Median time on insulin and time to a triglyceride level less than 1000 mg/dL and 500 mg/dL were stratified by initial triglyceride level as a surrogate marker for severity of disease in Table 3. Initial triglyceride levels (mg/dL) were divided into 5 groups: 500 to 1000, 1000 to 2000, 2000 to 3000, 3000 to 4000, and greater than 5000. Across the 5

different groups, there was no correlation of time on insulin therapy or time to triglyceride lowering less than 1000 mg/dL and 500 mg/dL.

During the admission, one patient developed a pancreatic pseudocyst, and one patient developed a pancreatic abscess. There were no mortalities. The insulin infusions were never stopped due to hypoglycemia. On discharge, 96% of patients (n = 22) were prescribed oral lipid lowering therapies (Table 4). There were eight different oral regimens consisting of a combination of a statin medication, niacin, fenofibrate, and fish oil. 35% of patients (n = 8) received triple therapy with a statin, fenofibrate, and fish oil. Full results of each oral regimen are detailed in Table 4.

DISCUSSION

This is the largest case series to date investigating intravenous insulin for the lowering of serum triglycerides. The results showed an aggressive intravenous insulin infusion can be used to acutely lower triglycerides in patients with hypertriglyceridemia. Weight-based insulin dosing at 0.1 units/kg/hour demonstrated safety and efficacy

for the management of hypertriglyceridemia similar to previous smaller case reports.

Table 1: Baseline demographics.

Endpoint	Patients (N = 23)
Average age, year (range)	41 (21 – 63)
Female gender, No. (%)	8 (35)
Average length of stay, day (range)	7 (3 – 28)
Pancreatitis on admission, No. (%)	21 (91)
History of diabetes, No. (%)	21 (91)
Endocrine service consulted, No. (%)	16 (70)
Subcutaneous heparin use, No. (%)	19 (83)

Previous case reports highlight the benefit of initiating intravenous insulin therapy alone or in combination with heparin. A 1998 case report involving an adolescent male with HT (TG = 4575 mg/dL) demonstrated that intravenous insulin at a dose of 0.1 units/kg subcutaneously was effective in immediately lowering the TG level over 4 hours, though the effect was difficult to maintain (17). Alagozlu and colleagues published a similar case report in 2006 and treated a 44-year-old male with diabetes and an initial TG level of 1707 mg/dL with an intravenous insulin infusion initiated at 3 units/hour in combination with 5% dextrose to prevent hypoglycemia (18). Within 24 hours, the patient's TG level was 713 mg/dL, and within 4 days was below the targeted goal of 500 mg/dL (18).

Given the benefit demonstrated with continuous infusion insulin, further studies were conducted evaluating weight-based intravenous insulin infusions. Two separate case reports published by Twilla and Tong utilized an intravenous insulin infusion at a rate of 0.1 units/kg/hour in combination with dextrose (19-20). It was theorized that because there were favorable effects seen with TG reduction with continuous insulin, higher weight-based dosing of insulin would provide additional benefit in time to triglyceride lowering. In both of these single patient case reports, TG lowering less than 1000 mg/dL occurred between 3 to 5 days with no significant hypoglycemia (19-20).

The largest case series to date evaluating the use of intravenous insulin for hypertriglyceridemia-

induced pancreatitis included only 12 patients (16). The series showed a serum TG level decrease to less than 500 mg/dL within 2 to 3 days but did not report the dose of insulin utilized or the median time required to decrease TG levels below that target. This makes reproduction for clinical use difficult. Our case series included similar weight-based continuous insulin infusion management to these smaller cases. However, in our review, the median time to triglyceride lowering less than 1000 mg/dL was only 1.8 days (45 hours) which was faster than previously reported literature (16, 21-22). This may be explained by our utilization of a hypertriglyceridemia order-set which included directions, insulin titration parameters, and a hypoglycemia treatment plan if needed (Figure 1). Further, the inclusion of our order-set details may aid to assist clinicians in the management of HT where information was previously limited.

Table 2: Clinical endpoints - triglyceride levels and insulin duration.

Endpoint	Patients (N = 23)
Median triglyceride level on admission, mg/dL (IQR)	3759 (5555)
Median length of insulin infusion, hours (IQR)	60 (63)
Median time to triglyceride level < 1000 mg/dL, hours (IQR)	45 (30)
Median time to triglyceride level < 500 mg/dL, hours (IQR)	75 (32)
Triglyceride level never at goal < 500 mg/dL, No. (%)	9 (39)

IQR = interquartile range

Interestingly, in our case series, the median time on the insulin infusion was shorter than the time duration to a triglyceride level less than 500 mg/dL. For the majority of these patients, insulin therapy was discontinued due to resolution of pancreatitis symptoms. This explains why 39% of patients (n = 9) were discharged before TG decreased below 500 mg/dL. This finding supports the hypothesis that patients may actually achieve control of their pancreatitis symptoms at a triglyceride level less than 1000 mg/dL compared to 500 mg/dL.

Furthermore, a patient's initial triglyceride level did not predict the time on intravenous insulin

Table 3: Clinical endpoints stratified by triglyceride level on admission.

Initial triglyceride level, mg/dL	Number of Patients	Median time on insulin, hours (IQR)	Median time to TG < 1000, hours (IQR)	Median time to TG < 500, hours (IQR)
500 - 1000	1	42	36	72
1000 - 2000	4	30 (35)	14 (16)	69 (15)
2000 - 3000	3	80 (27)	24 (7)	78 (25)
3000 - 4000	4	95 (125)	73 (47)	306 (198)
> 5000	11	60 (64)	59 (28)	63 (34)

TG = triglyceride; IQR = interquartile range

and time duration to a triglyceride level less than 1000 mg/dL. The patient group who had an initial triglyceride level of greater than 5000 mg/dL had both a shorter duration on insulin and time to a triglyceride level less than 1000 mg/dL when compared to patients who presented with a triglyceride level of 3000 to 4000 mg/dL. These findings are consistent with a 2006 hypertriglyceridemia review concluding that at a TG level greater than 1000mg/dL, there was no relationship between TG level and the severity of disease course or complications (10).

Heparin has previously been studied as a potential treatment for hypertriglyceridemia as monotherapy and in combination with insulin and other modalities. Intravenous heparin causes an initial rise in circulating lipoprotein lipase levels, it is quickly followed by increased hepatic degradation which subsequently contributes to further depletion in plasma stores of lipoprotein lipase (23-24). Previous literature has a variety of different dosing regimens for heparin including therapeutic heparin infusions as well as prophylaxis dosing. Because of the transient effects seen on lipoprotein lipase and because of an increased risk of bleeding, the use of an intravenous heparin infusion as monotherapy for treatment is very low. To date, there has been only one randomized trial comparing the efficacy of insulin and heparin to apheresis for the treatment of HT (15). The trial showed a non-inferior decrease in TG level after the first plasma exchange session ($66.9\% \pm 21.5\%$) compared to one day of insulin and heparin therapy ($75.0\% \pm 14.6\%$). The medical cost during hospitalization and adverse events were significantly lower in the insulin and heparin group than in the plasma exchange group ($p < 0.05$). However, the study did not report insulin doses, the therapeutic protocol utilized, or hourly decreases in TG levels. While our case series did not compare to apheresis, our explicitly stated dosing scheme and

results of rapidly decreased TG levels reviewed by the hour, support insulin therapy as an effective alternative.

Table 4: Patient complications and discharge medications.

Endpoint	Patients (N = 23)
Pancreatic pseudocyst development, No. (%)	1 (4)
Pancreatitis abscess development, No. (%)	1 (4)
Concomitant lipid lowering therapy on discharge, No. (%)	22 (96)
Fish oil, n	1
Statin and fenofibrate, n	2
Niacin and fish oil, n	2
Statin and fish oil, n	1
Statin, fenofibrate, and fish oil, n	8
Niacin, fenofibrate, and fish oil, n	2
Statin, niacin, and fish oil, n	2
Statin, niacin, fenofibrate, and fish oil, n	4

On discharge, 96% of patients ($n = 22$) received oral lipid lowering therapies for long-term maintenance of triglycerides. Previous case series have not reported maintenance regimens for this specific sub-set of patients and there are no guidelines to dictate one therapy over another. While there were eight different oral regimens prescribed, 35% of patients ($n = 8$) received triple therapy with a statin, fenofibrate, and fish oil. Long-term patient follow-up was not assessed in this case series, but future research could evaluate the success of

combination lipid lowering therapy to prevent subsequent triglyceride elevation, pancreatitis, and hospital admission.

Limitations to this study include the retrospective design and single center conduction. Though note was taken that the insulin drip was commonly stopped early due to resolution of pancreatitis symptoms, this was difficult to collect due to limitations in electronic medical record documentation. Resolution of pancreatitis symptoms therefore were not distinctly assessed and only lowering of triglyceride levels were reviewed. Other major clinical outcomes such as mortality, development of pancreatitis if not already present, pancreatic pseudocyst development, pancreatic necrosis development, and pancreatic abscess formation were reviewed.

In this largest case series to date evaluating the use of intravenous insulin for the treatment of hypertriglyceridemia, a weight-based insulin infusion at 0.1 units/kg/hour demonstrated reduction of triglyceride levels to less than 1000 mg/dL in approximately 2 days and less than 500 mg/dL in approximately 3 days. Future research should be done to evaluate the utility of dual therapy with heparin and long-term oral lipid lowering therapies.

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