Intravenous Insulin versus Conservative management in Hypertriglyceridemia associated acute Pancreatitis

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Abstract

**Context and Objective:** Hypertriglyceridemia is implicated in ~5% of cases of acute pancreatitis. It is assumed that intravenous insulin is effective in lowering triglyceride (TG) concentrations in hypertriglyceridemia associated acute pancreatitis (HAAP). However, the efficacy of intravenous insulin versus conservative management alone is not known.

**Design and Setting:** Charts of 106 patients who were admitted with HAAP and had TG concentrations >1000 mg/dL at admission were reviewed. Patients who received intravenous insulin for at least 8 hours were included in the iv insulin group, while the rest were considered to have received conservative management. We compared the change in TG concentrations from baseline in the two groups.

**Results:** Fifty-one patients received intravenous insulin while 55 patients were managed conservatively. Baseline TG concentrations were higher in iv insulin group (3307 [2106, 4425]mg/dL [median [25th, 75th percentile]) vs 2304 [1416, 2720]mg/dL, p<0.001). The TG concentrations declined rapidly in both groups, reaching below 1000 mg/dL by day 3 and <500 mg/dL by day 4. TG concentrations in iv insulin group had decreased by 69% and 85% on days 2
and 4, respectively. In comparison, the fall in conservative management group was 63% and 79%, which was not statistically different than the change in iv insulin group.

Conclusion: Our results show that iv insulin did not result in a more rapid fall in TG as compared to conservative treatment in patients with HAAP. Fasting and intravenous fluids were effective in lowering TG concentrations rapidly, with no further contribution from insulin.

Introduction

Acute pancreatitis is a common cause of morbidity and hospital admissions. Common etiologies of acute pancreatitis are alcohol consumption and gallstones. Hypertriglyceridemia is a less common, but well established cause of acute pancreatitis, accounting for ~5% of all cases of acute pancreatitis (1-3). The risk of pancreatitis increases with higher triglyceride (TG) concentrations, although there is significant inter-individual variation. Approximately 5% of patients with outpatient TG concentrations between 1000-2000 mg/dL have a history of one or more episodes of pancreatitis in past (4). The prevalence of pancreatitis increases to 20% in those with TG concentrations >2000 mg/dL (5).

The initial management of hypertriglyceridemia associated acute pancreatitis (HAAP), just as in other patients with acute pancreatitis, involves bowel rest with no oral intake, intravenous hydration and pain control. In patients with HAAP, higher TG concentrations are independently associated with a more complicated hospital course, including need for admission to intensive care units, persistent multi-organ failure and systemic inflammatory response syndrome (SIRS) (6). Hence, it is desirable to lower the TG concentrations acutely in HAAP. This can be achieved by limiting ingestion of fat and enhancing the clearance of TG. Fasting often leads to a significant reduction in TG concentrations(7). The clearance of TG from circulation is mostly
dependent upon hydrolysis of TG carried in chylomicrons and very low density lipoproteins by lipoprotein lipase enzymes. In adipose tissue, lipoprotein lipase is activated by insulin(8). This activation is impaired in those with insulin deficiency or resistance. It is worth noting that many patients with HAAP also have uncontrolled diabetes. Furthermore, fasting will also lower the insulin concentrations, thus decreasing lipoprotein lipase activation. The infusion of insulin during this scenario would be expected to be beneficial. Hence, insulin therapy is often used in the setting of HAAP (with concomitant glucose infusion in patients without diabetes) to achieve a more precipitous fall in TG as compared to fasting alone. Many case reports have suggested that insulin is effective in lowering TG concentrations in HAAP, in patients with or without diabetes (9-14). However, no systematic investigation has been done to evaluate the effect of insulin on lowering of TG in HAAP and therefore, there is no consensus regarding the use of insulin in HAAP. Most physicians utilize insulin (intravenous or subcutaneous) to treat hyperglycemia in HAAP and do not use insulin as a modality to specifically treat the elevated TG. Endocrine society guidelines do not make any recommendations regarding the use of insulin in HAAP.

In view of the above, we conducted a retrospective chart review of patients admitted with HAAP to evaluate the effect of insulin on lowering TG concentrations acutely. We hypothesized that patients with HAAP who receive intravenous insulin infusion have a greater fall in TG concentrations as compared to patients who do not receive intravenous insulin.

Methods
This is a retrospective case, control study. We sought to review charts of all patients admitted with pancreatitis and hypertriglyceridemia between January 1, 2008 and Dec 31, 2018 at SSM
Hospital system in Saint Louis, MO. The starting date was chosen based on availability of searchable electronic health records. Charts of patients who had been admitted to a hospital with acute pancreatitis and had TG concentrations >1000 mg/dL (measured within 24 hours of admission) were reviewed. International classification of diseases (ICD) codes were used to define acute pancreatitis (ICD9 code 577.0, ICD10 code K 85.00, K85.80, K85.90). The diagnosis of acute pancreatitis was confirmed on chart review by the presence of at least 2 of the following: 1) history and physical exam consistent with the diagnosis, 2) serum lipase or amylase ≥ 3 times the upper limit of normal, or 3) evidence of pancreatitis on CT scan of the abdomen.

Patients who had been admitted with recurrent episodes of pancreatitis were included only once. The episode with the highest TG concentrations at baseline was included in the analysis. To be included in the analysis, the TG concentrations should have been repeated at least once after the baseline during the hospital stay.

We reviewed patient charts of 166 episodes of acute pancreatitis who had concomitant high TG. After excluding episodes that did not meet the criteria listed above, 106 patients qualified for this analysis. Based on the therapy received, these patients were divided into two groups:

**Intravenous insulin group (n=51):** Subjects who received intravenous (iv) insulin infusion for at least 8 hours were included in this group. Serum TG concentrations immediately preceding the start of insulin infusion were considered as the baseline TG for the study.

**Conservative management group (n=55):** Subjects who did not receive iv insulin were included in this group. As part of standard care, patients with diabetes in this group received subcutaneous insulin. Those who did not have diabetes did not receive any insulin.

If available, daily serum TG concentrations were collected in both groups till day 12. In the absence of a standardized protocol for following TG concentrations during the hospital stay in...
patients with HAAP, we found that serum TG concentrations had been checked sporadically, rather than daily. Seventy % of patents in the iv insulin group and 65% of patients in the conservative management group had TG concentrations available from at least 3 distinct days. Fifty-three % of patents in the iv insulin group and 25% of patients in the conservative management group had TG concentrations available from at least 4 distinct days.

We reviewed the charts of patients to obtain baseline demographics, presence of diabetes, presence of dKA based on admitting physician notes and laboratory data. Duration of insulin infusion was calculated using the time of medication and infusion orders as well as nursing notes in patient’s charts. To assess the severity of pancreatitis, we used Bedside Index for Severity in Acute Pancreatitis (BISAP) at admission. BISAP was originally devised in 2008 and is used to predict the severity of pancreatitis based on data obtained in the first 24 hours of admission(15). BISAP score is calculated by assigning 1 point for each of the following during the first 24 hours: Blood urea nitrogen >25 mg/dL, impaired mental status, systemic inflammatory response syndrome (SIRS), age >60 years, or the presence of a pleural effusion. SIRS was considered to be present when two or more of the following are found: 1) Temperature <36°C or >38°C 2) Respirations >20/min or PaCO2 <32 mmHg 3) Heart rate >90/min 4) white blood cell count <4000/mm3 or >12,000/mm3 or more than 10% bands found on blood smear. BISAP has higher specificity but lower sensitivity for predicting severity of pancreatitis than other scores such as Ranson’s criteria or APACHE II (16). A BISAP score of 3 or more is predictive of severe acute pancreatitis (17). A BISAP score of 0-2 is associated with mortality of less than 2%. A score of 3-5 is associated with a higher mortality (>15%).
**Statistical analysis:** We compared the baseline demographics, presence of diabetes mellitus with or without diabetic ketoacidosis (dKA), duration of hospital stay and severity of pancreatitis amongst the groups with unpaired t-tests, Chi-square tests or Mann-Whitney U tests as appropriate. Non-normal continuous data were log-transformed for comparison. The primary endpoint of our study was to compare the change in TG concentrations from baseline to the concentration at day 2 amongst the two groups. Unpaired t-test was used to compare the primary endpoint between the two groups. P<0.05 was used to define statistical significance. Our study had 80% power to detect a difference of 25% (with standard deviation up to 40%) in the primary endpoint between the 2 groups. We also compared the inter-group and intra-group change in TG and blood sugar concentrations using t-test or one-way repeated measures analysis of variance (RMANOVA) followed by Holm-Sidak post hoc test. Data that were not normally distributed (Kolmogorov-Smirnov test) were log-transformed to perform the parametric statistical tests or analyzed using non-parametric tests. Data are presented as mean±SD for normally distributed data and median [25th, 75th percentile] for non-normal data. SPSS software (SPSS Inc, Chicago, Illinois) was used for the analyses.

The study protocol was approved by the Institutional Review Board of Saint Louis University.

**Results:** We identified 106 patients with HAAP who met the study criteria. 51 patients received iv insulin while 55 were managed conservatively. The mean age and BMI in the two groups were similar (table 1). Most of the patients in iv insulin group presented to the hospital with dKA. They had higher severity of pancreatitis, as assessed by BISAP scores, and stayed longer in the hospital. None of the study subjects died during the hospital stay. The median TG concentrations at baseline were higher in the iv insulin group than the conservative management
group (3307 [2106, 4425] vs 2304 [1416, 2720] mg/dl, p<0.001). Baseline TG concentrations were not related to BISAP scores (r=0.02, p=0.84) or length of stay (r= -0.06, p=0.61). BISAP scores were strongly related to the length of stay (r=0.46, p<0.001). In a multiple regression model that included BISAP score, presence of dKA and baseline TG concentrations, only BISAP score was predictive of length of stay (β=0.69, p<0.001).

The median duration of iv insulin was 45 hours [25, 90] hours. The change in TG concentrations in both groups over 12 days are shown in figure 1. TG concentrations declined rapidly in both groups (p<0.001 by one-way ANOVA in both groups). There was no difference in the % change in TG concentrations between the two groups on any day (table 2). The TG concentrations had fallen by ~50% in the first 24 hours and ~75% by day 3. Results were similar when we compared the change in TG concentrations after excluding patients whose baseline TG concentrations were <2000 mg/dL. The % fall in TG concentrations in the iv insulin group (n=41) was 48[7, 71] %, 64[45, 75] %, 78[63, 86] % and 80[75, 92] % on days 1, 2, 3 and 4 respectively. Corresponding numbers in conservative management group (n=35) were 49[26, 63] %, 71[64, 82] %, 79[69, 88] % and 86[80, 91] % (p>0.10 for comparison with the iv insulin group each day).

Six patients in the iv insulin group received insulin infusion for less than 24 hours (but more than 8 hours as per the inclusion criteria). These patients were included in the analyses above. We re-analyzed the fall in TG concentrations after excluding those patients. Five of these patients had presented with dKA. The median TG concentrations at baseline in patients who received iv insulin for at least 24 hours (n=45) were 3329 [2115, 5057] mg/dl (p= 0.002 as compared to conservative management group). The TG concentrations decreased to 1880 [735,
3369] on day 1, 1135 [535, 1703] on day 2 and 677 [531, 1359] on day 3 (p= 0.11, 0.57 and 0.67 respectively, as compared to conservative management group).

Blood glucose concentrations at admission were higher in the iv insulin group than the conservative management group but became similar after that (table 3). On day 3, the fasting blood sugars were lower in the iv insulin group. Blood glucose concentrations remained similar in the 2 groups after day 4 (data not shown).

**IV insulin group:** Since the presence of dKA necessitates the use of iv insulin, we analyzed the change in TG concentrations separately in patients with and without dKA. 30 patients presented with dKA, while 21 patients did not have dKA in the iv insulin group. A review of charts confirmed that these 21 patients without dKA received iv insulin specifically for purposes of reduction in TG concentrations. Out of 21 patients, 6 did not have diabetes. In patients with dKA, iv insulin was started due to the presence of dKA. The median baseline TG concentrations were higher in diabetic patients without dKA (4146 [3426, 8828] mg/dl) than in non-diabetic patients (3223 [1563, 4000] mg/dl, p=0.05) and in those with dKA (2953 [2067, 3502] mg/dl, p =0.003). Figure 2 shows the change in TG concentrations in patients stratified according to diabetes and dKA status. The TG concentrations had fallen by 74[64, 83] %, 70[60, 80] % and 68[56, 77] % by 48 hours in patients with diabetes but without dKA, no diabetes and no dKA, and in patients with dKA respectively (p>0.50 for comparison amongst any 2 groups).

**Conservative management group:** In this group, we compared patients who did not have diabetes and therefore did not receive any insulin, with those who had diabetes and therefore received subcutaneous insulin. The baseline TG concentrations in patients with (n=42) and
without diabetes (n=13) were similar (2019[1623, 2627] vs 2527[1292, 3072] mg/dl, p=0.52). The TG concentrations in patient with diabetes decreased by 47[-2, 65] %, 64[46, 73] %, 71[62, 79] % and 79[78, 92] % by days 1, 2, 3 and 4 respectively. Corresponding numbers in those who did not have diabetes were 41[15, 67] %, 57[56, 61] %, 78[74, 82] % and 74[70, 79] % respectively (p>0.24 for comparison each day).

The median insulin dose given on the day of admission was 13 [6, 39] units. The median insulin doses on days 1, 2 and 3 were 31 [8, 60], 35 [10, 63] and 39 [18, 74] units respectively. The insulin doses given on days 0, 1, 2 and 3 were not related to % change in TG on days 1, 2, 3 and 4 (r= 0.28, 0.36, 0.10 and 0.47 respectively, p >0.20 for all).

**Discussion**

Our data show clearly that iv insulin did not result in a more rapid fall in TG as compared to conservative treatment. The TG concentrations declined rapidly in both groups, reaching below 1000 mg/dL by day 3 and <500 mg/dL by day 4. The use of subcutaneous insulin in the conservative management group also did not induce a more rapid fall in TG concentrations as compared to fasting alone. Thus, it appears that elimination of caloric intake with intravenous hydration is the most effective management therapy to lower triglycerides, with no further contribution from insulin in the setting of HAAP.

Hypertriglyceridemia develops from the combination of dietary fat intake that is absorbed via chylomicrons, production of very low density lipoproteins in the liver and impaired clearance of chylomicrons and very low density lipoproteins (18). Clearance of TG from the circulation is predominantly dependent upon lipoprotein lipase, an enzyme that is expressed on the luminal surface of capillary endothelial cells of tissues and is activated by insulin in adipose tissue. Free
fatty acids released from the hydrolysis of TG are taken up by the adipose tissue for re-esterification into TG and stored in the adipose tissue. However, once the serum TG concentrations are >1000 mg/dL, TG clearance system is saturated, predisposing patients to very rapid increases in plasma TG in response to excess dietary intake of fats and carbohydrates (7, 19). In agreement with the “saturation hypothesis”, our data do not show a clinically meaningful impact of insulin therapy on the decrease in severe hypertriglyceridemia in the setting of HAAP.

Other therapies have been tried to reduce triglyceride concentrations rapidly, notably plasmapheresis (20). Plasmapheresis is cumbersome, expensive and not without potential complications including hypotension, vomiting, intracatheter clotting, risks arising from the infusion of blood products and air embolism. Furthermore, the TG lowering after plasmapheresis does not appear to be different than without the apheresis in patients with HAAP (21). There are reports of use of heparin to lower TG in the setting of HAAP (22, 23). Heparin causes release of lipoprotein lipase enzymes from the endothelium. Increased lipoprotein lipase activity in the circulation increases hydrolysis of TG in the lipoproteins, thus increasing circulating FFA concentrations. This would possibly contribute towards more inflammation in pancreas. Heparin may also enhance bleeding in cases of hemorrhagic pancreatitis. The Endocrine society recommends against the use of heparin or plasmapheresis in HAAP (1). None of the other triglyceride lowering drugs like niacin, fibric acids or Ω-3 fatty acids act with rapidity.

Current guidelines promote early oral feeding (within 48 hours) in mild acute pancreatitis, if tolerated. Early feeding appears to reduce length of stay and may preserve intestinal barrier (24, 25). In one case series of nine patients admitted with TG concentrations >4000 mg/dL (4 patients had pancreatitis), the effect of fasting + iv insulin (5 patients, 4 had pancreatitis) versus iv insulin...
alone (4 patients, no pancreatitis) was compared. TG concentrations decreased by 87% within 24 hours in the fasting + iv insulin group versus 40% in the group that received iv insulin alone. In our study, all patients were fasted initially. However, we did not collect data on the duration of fasting. Future studies should evaluate whether recommendations promoting early feeding in pancreatitis need to be tempered in the case of HAAP.

Our study suffers from many limitations inherent in a retrospective study. TG concentrations were not available daily in the patients. Rather they were checked sporadically during the hospital stay. The study population was heterogenous. The decisions to use insulin infusion and the duration of insulin infusion in the iv insulin group, as well as use of subcutaneous insulin in conservative management group during the hospital stay were not standardized. However, our results were consistent regardless of the baseline TG concentrations, presence or absence of dKA, or whether absolute decline or percentage decrease in TG were analyzed.

We conclude that use of intravenous insulin does not induce a greater fall in triglycerides beyond standard care in patients with HAAP. Fasting lowers TG concentrations effectively, and the use of insulin should be dictated by the requirements of glycemic management, as in patients presenting with symptomatic poorly controlled diabetes or dKA.

Author contributions: S.D. put forth the hypothesis, planned the study, analyzed data and wrote the manuscript. A.S., A.A, S.S, S.N. and S.D. collected data for the study. A.S., A.A. and S.D. conducted background literature search. S.A., A.M., R.B. and P.D. reviewed the manuscript. S.D. is the guarantor of this work and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.
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Table 1: Baseline comparisons in the two groups. *A1c was collected only in patients with diabetes. BISAP: Bedside index for severity in acute pancreatitis, dKA: Diabetic ketoacidosis.

Table 2: Columns show % decrease in TG levels on each day in both groups. Percent change was calculated only in patients who had TG concentrations available for that day. Data beyond day 4 are not shown due to the small number of subjects with available TG concentrations after 4 days.

Table 3: Blood glucose concentrations in both groups on the first 4 days *Statistical comparisons were conducted using t-test after log transformation of blood sugar concentrations.

Figure 1: Median [25th, 75th percentile] TG concentrations in iv insulin and conservative management groups over 12 days. TG concentrations were not checked daily in every patient. The number of subjects whose TG concentrations were available at each day are shown beneath the X-axis.

*p<0.001 for comparison between groups

Figure 2: Median [25th, 75th percentile] TG concentrations in patients in iv insulin group stratified with dKA and diabetes status. TG concentrations were not checked daily in every patient. The number of subjects whose TG concentrations were available at each day are shown beneath the X-axis.

*p<0.05 for comparison between groups.
Table 1: Baseline comparisons in the two groups.

|                      | Intravenous insulin group (n=51) | conservative management (n=55) | P     |
|----------------------|----------------------------------|--------------------------------|-------|
| Age (years)          | 40±11                            | 42±9                           | 0.42  |
| BMI (kg/m²)          | 33±7                             | 34±6                           | 0.57  |
| Males; n (%)         | 28 (55%)                         | 38 (69%)                       | 0.23  |
| Diabetes; n (%)      |                                  |                                |       |
| No                   | 6 (12%)                          | 4 (24%)                        | 0.03  |
| Type 1               | 9 (18%)                          | 1 (2%)                         |       |
| Type 2               | 36 (70%)                         | 41 (74%)                       |       |
| dKA at admission; n (%) | 30 (59%)                      | 1 (2%)                         | <0.001|
| HbA1c*               | 11.1± 2.2                        | 10.1± 2.4                      | 0.10  |
| h/o alcohol use; n (%) | 10 (20%)                      | 12 (20%)                       | 0.89  |
| Length of stay       | 7 [5, 17]                        | 5 [4, 7]                       | 0.003 |
| Amylase or lipase elevated > 3 times upper limit of normal; n (%) | 46 (91%) | 42 (76%) | 0.06 |
| Pancreatitis on imaging; n (%) | 46 (90%) | 50 (90%) | 0.90 |
| Organ Failure; n (%) | 14 (27%)                         | 11%                            | 0.03  |
| BISAP score          | 1 [1, 2]                         | 1 [0, 1]                       | 0.011 |
| BISAP ≥3; n (%)      | 8 (16%)                          | 0 (0%)                         | 0.02  |

*A1c was collected only in patients with diabetes.

BISAP: Bedside index for severity in acute pancreatitis, dKA: Diabetic ketoacidosis

Table 2: Columns show % decrease in TG levels on each day in both groups. Percent change was calculated only in patients who had TG concentrations available for that day. The number of subjects with paired data for each day are also shown. Data beyond day 4 are not shown due to the small number of subjects with available TG concentrations after 4 days.

|                      | Day 1       | Day 2       | Day 3       | Day 4       | P value by ANOVA on ranks |
|----------------------|-------------|-------------|-------------|-------------|---------------------------|
| iv insulin           | 48 [28, 60], n=29 | 69 [56, 80], n=39 | 76 [66, 88], n=30 | 85 [75, 88], n=29 | <0.001                   |
| conservative         | 45 [3, 67], n=20 | 63 [49, 73], n=24 | 74 [62, 81], n=17 | 79 [73, 90], n=10 | <0.001                   |
| management           |             |             |             |             |                           |
| P value by Mann-Whitney | 0.45        | 0.13        | 0.51        | 0.55        |                           |
Table 3: Blood glucose concentrations in both groups on the first 4 days

|                         | baseline       | Day 1      | Day 2      | Day 3      | Day 4      | P value by ANOVA |
|-------------------------|----------------|------------|------------|------------|------------|------------------|
| Iv insulin              | 367 [313, 468] | 205 [169, 299] | 152 [125, 199] | 146 [114, 178] | 142 [112, 184] | <0.001           |
| conservative management | 297 [159, 430] | 260 [158, 324] | 180 [133, 239] | 194 [155, 249] | 177 [121, 194] | 0.003            |
| P value*                | 0.008          | 0.87       | 0.52       | 0.02       | 0.40       |                  |

*Statistical comparisons were conducted using t-test after log transformation of blood sugar concentrations.
Figure 1

| Number of subjects | baseline | 1  | 2  | 3  | 4  | 5  | 6  | 7  | 8  | 9  | 10 | 11 | 12 |
|-------------------|----------|----|----|----|----|----|----|----|----|----|----|----|----|
| iv insulin        | 51       | 30 | 39 | 30 | 20 | 15 | 11 | 6  | 6  | 7  | 5  | 4  | 5  |
| conservative managament | 55 | 22 | 26 | 18 | 12 | 7  | 5  | 3  | 1  | 1  | 2  | 1  | 2  |
Table: Number of Subjects

|                     | baseline | 1  | 2  | 3  | 4  | 5  | 6  | 7  | 8  | 9  | 10 | 11 | 12 |
|---------------------|----------|----|----|----|----|----|----|----|----|----|----|----|----|
| No diabetes, no dKA | 6        | 6  | 6  | 5  | 4  | 2  | 2  | 2  | 2  | 2  | 1  | 1  |    |
| Diabetes, no dKA    | 15       | 10 | 12 | 8  | 8  | 4  | 5  | 1  | 2  | 3  | 1  | 1  | 1  |
| dka                 | 30       | 14 | 21 | 17 | 8  | 9  | 4  | 3  | 2  | 2  | 2  | 2  | 3  |