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Intravenous Insulin Versus Conservative Management in Hypertriglyceridemia-Associated Acute Pancreatitis

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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 intravenous insulin group, while the rest were considered to have received conservative management. We compared the change in TG concentrations from baseline in the 2 groups.

Results: Fifty-one patients received intravenous insulin while 55 patients were managed conservatively. Baseline TG concentrations were higher in the intravenous insulin group (median [25th, 75th percentile] 3307 [2106, 4425] mg/dL 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 the intravenous insulin group had decreased by 69% and 85% on days 2 and 4, respectively. The fall in the conservative management group was 63% and 79%, which was not statistically different than the change in the intravenous insulin group.

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

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Key Words: hypertriglyceridemia, insulin, intravenous, pancreatitis

1. Introduction

Acute pancreatitis is a common cause of morbidity and hospital admissions. Common etiologies of acute pancreatitis are alcohol consumption and gallstones. Hypertriglyceridemia

Abbreviations: BISAP, Bedside Index for Severity in Acute Pancreatitis; dKA, diabetic ketoacidosis; HAAP, hypertriglyceridemia associated acute pancreatitis; iv, intravenous; SIRS, systemic inflammatory response syndrome; TG, triglyceride.

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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 (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), 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 a 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 with 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 would have a greater fall in TG concentrations compared with patients who do not receive intravenous insulin.

2. 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 December 31, 2018, at the SSM Hospital system in Saint Louis, Missouri. 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 computed tomography 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 from 166 episodes of acute pancreatitis with 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:

A. 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.

B. 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 until 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 percent of patients in the iv insulin group and 65% of patients in the conservative management group had data for TG concentrations available from at least 3 distinct days. Fifty-three percent of patients 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 diabetic ketoacidosis (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 the nursing notes in patient charts. To assess the severity of pancreatitis, we used Bedside Index for Severity in Acute Pancreatitis (BISAP) at admission. The BISAP was originally devised in 2008 and is used to predict the severity of pancreatitis based on data obtained during the first 24 hours of admission (15). The 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, SIRS, age > 60 years, or the presence of a pleural effusion. SIRS was considered to be present when 2 or more of the following criteria were met: (1) body temperature < 36°C or > 38°C; (2) respirations > 20/min or PaCO2 < 32 mm Hg; (3) heart rate > 90/min; or (4) white blood cell count < 4000/mm^3 or > 12,000/mm^3 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 the Acute Physiology and Chronic Health Evaluation (APACHE II) (16). A BISAP score of 3 or more is predictive of severe acute pancreatitis (17). A BISAP score of 0 to 2 is associated with mortality of less than 2%. A score of 3 to 5 is associated with a higher mortality (> 15%).

C. Statistical Analysis

We compared the baseline demographics, presence of diabetes mellitus with or without dKA, duration of hospital stay and severity of pancreatitis among the groups with unpaired *t*-tests, Chi-square tests, or Mann-Whitney U tests as appropriate. Nonnormal 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 between the 2 groups. Unpaired *t*-test was used to compare the primary endpoint between the 2 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 glucose concentrations using *t*-test or one-way repeated-measures analysis of variance (ANOVA) 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 nonparametric tests. Data are presented as mean ± SD for normally distributed data and median [25th, 75th percentile] for nonnormally distributed 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.

3. Results

We identified 106 patients with HAAP who met the study criteria. A total of 51 patients received iv insulin and 55 were managed conservatively. The mean age and body mass index in the 2 groups were similar (Table 1). Most of the patients in the iv insulin group presented to the hospital with dKA. They had higher severity of pancreatitis, as assessed by BISAP scores, and they stayed longer in the hospital. None of the study participants died during the hospital stay. The median TG concentrations at baseline were higher in the iv insulin group than in 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 ($\beta = 0.69$; $P < 0.001$).

The median duration of iv insulin was 45 [25, 90] hours. The changes in TG concentrations in both groups over 12 days are shown in Fig. 1. TG concentrations declined rapidly in both groups ($P < 0.001$ by one-way ANOVA in both groups). There was no difference in the percentage change in TG concentrations between the 2 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 percentage 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 declines in the conservative management group (n = 35) were 49% [26%, 63%], 71%[64%, 82%], 79%[69%, 88%], and 86% [80%, 91%] on days 1, 2, 3, and 4 ($P > 0.10$ 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 with the conservative management group). The TG concentrations decreased to 1880 [735, 3369] mg/dL on day 1, 1135 [535, 1703] mg/dL on day 2 and 677 [531, 1359] mg/dL on day 3 ($P = 0.11$, $P = 0.57$, and $P = 0.67$, respectively, compared with the conservative management group).

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

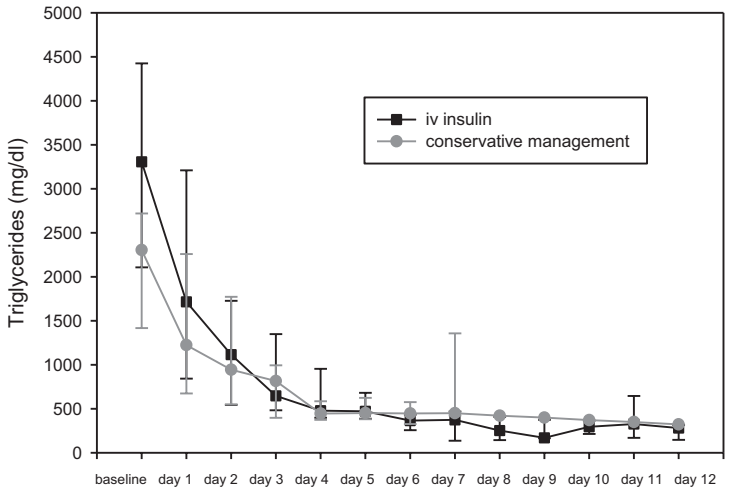
A. IV Insulin Group

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. In the iv insulin group, 30 patients presented with dKA, while 21 patients did not have dKA. A review of charts confirmed that the 21 patients without dKA received iv insulin specifically for purposes of reduction in TG concentrations. Among these 21 patients, 6 did not have diabetes. In

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/m^2	33 ± 7	34 ± 6	0.57
Males, n (%)	28 (55%)	38 (69%)	0.23
Diabetes, n (%)			0.03
No diabetes	6 (12%)	13 (24%)	
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, days	7 [5, 17]	5 [4, 7]	0.003
Amylase or lipase elevated > 3× 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
	1.5 ± 1.2	0.8 ± 0.8	
BISAP ≥ 3, n (%)	8 (16%)	0 (0%)	0.02

Abbreviations: BISAP, Bedside index for severity in acute pancreatitis; BMI, body mass index; dKA, diabetic ketoacidosis; H/o, history of.
*HbA1c was collected only in patients with diabetes.



Number of subjects	baseline	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7	Day 8	Day 9	Day 10	Day 11	Day 12
iv insulin	51	30	39	30	20	15	11	6	6	7	5	4	5
conservative management	55	22	26	18	12	7	5	3	1	1	2	1	2

Figure 1. Median [25th, 75th percentile] TG concentrations in the 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 is shown beneath the X-axis.
*$P < 0.001$ for comparison between groups

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 nondiabetic patients (3223 [1563, 4000] mg/dL; $P = 0.05$) and in those with

Table 2. Percentage Decrease in TG Levels on Each Day in Both Groups

	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 = 20	<0.001
Conservative management	45 [3, 67], n = 20	63 [49, 73], n = 24	74 [62, 81], n = 17	79 [73, 90], n = 10	<0.001
P value by Mann-Whitney	0.45	0.13	0.51	0.55	

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.
Abbreviations: ANOVA, analysis of variance; IV, intravenous.

Table 3. Blood Glucose Concentrations in Both Groups on the First 4 Days

Table 3	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	

Abbreviations: ANOVA, analysis of variance; IV, intravenous.
*Statistical comparisons were conducted using *t*-test after log transformation of blood glucose concentrations.

dKA (2953 [2067, 3502] mg/dL; $P = 0.003$). Fig. 2 shows the change in TG concentrations in patients stratified according to diabetes and dKA status. By 48 hours, the TG concentrations had fallen by 74% [64%, 83%], 70% [60%, 80%], and 68%[56%, 77%] in patients with diabetes but without dKA, patients with no diabetes and no dKA, and in patients with dKA, respectively ($P > 0.50$ for comparison between any 2 groups).

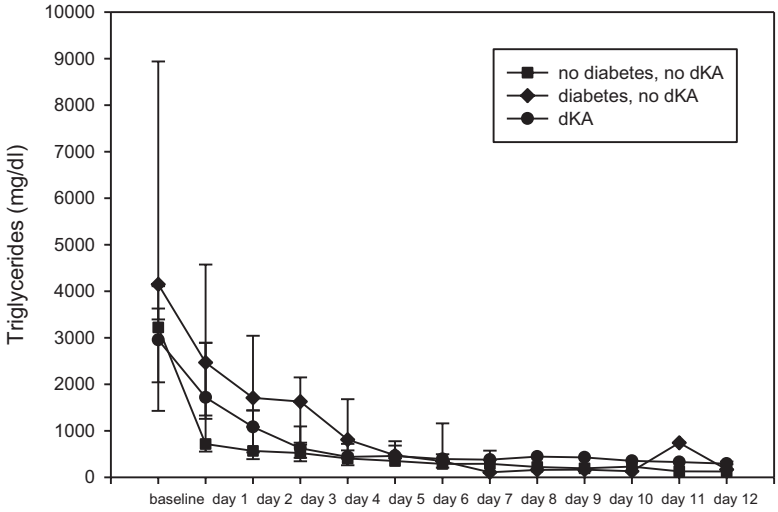
B. Conservative Management Group

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 patients 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 declines 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 percentage 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).

4. Discussion

Our data show clearly that iv insulin did not result in a more rapid decline in TG compared with conservative treatment. The TG concentrations fell rapidly in both groups, reaching



Number of subjects	baseline	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7	Day 8	Day 9	Day 10	Day 11	Day 12
No diabetes, no dka	6	6	6	5	4	2	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

Figure 2. Median [25th, 75th percentile] TG concentrations in patients in the iv insulin group stratified by 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 is shown beneath the X-axis.

*$P < 0.05$ for comparison between groups.

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 compared with fasting alone. Thus, it appears that elimination of caloric intake with intravenous hydration is the most effective management therapy to lower TG, 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 for rapid reduction of TG concentrations, 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 heparin use 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 free fatty acid 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 TG-lowering drugs, such as niacin, fibric acids, or omega-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 the intestinal barrier (24, 25). In 1 case series of 9 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. Data for TG concentrations were not available daily in the patients; rather the levels were checked sporadically during the hospital stay. The study population was heterogenous. The decisions regarding the use of insulin infusion, the duration of insulin infusion in the iv insulin group, as well as the 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 declines or percentage decreases in TG were analyzed.

We conclude that use of intravenous insulin does not induce a greater fall in TG 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.

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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.

Additional Information

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