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Moe Thuzar, MBBS, MRCP (UK), FRACP Vasant V. Shenoy, MD, FRACP Usman H. Malabu, FRCP, FACP, FRACP Ryan Schrale, MSc, FRACP, FCSANZ, FSCAI, FESC Kunwarjit S. Sangla, MD, FRACP

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Moe Thuzar, MBBS, MRCP (UK), FRACP[1, 3, a]

Vasant V Shenoy, MD, FRACP[1, 4]

Usman H Malabu, FRCP, FACP, FRACP[1, 4]

Ryan Schrale, MSc, FRACP, FCSANZ, FSCAI, FESC[2, 4]

Kunwarjit S Sangla, MD, FRACP[1, 4, b]

[1]Department of Endocrinology and Diabetes, The Townsville Hospital, Queensland, Australia.

[2]Department of Cardiology, The Townsville Hospital, Queensland, Australia.

[3]University of Queensland, Australia

[4]James Cook University, Queensland, Australia.

[a,b]**Corresponding Authors:**

Address: 100 Angus Smith Dr, Douglas QLD 4814, Australia. Phone: +61 7 4433 2235, Fax: +61 4433 2239

[a]Email: m.thuzar@uq.edu.au , [b]Email: sanglak@health.qld.gov.au

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ABSTRACT

Extreme hypertriglyceridemia can lead to acute pancreatitis and rapid lowering of serum triglycerides (TG) is necessary in order to prevent such life threatening complication. However, there is no established consensus on the acute management of extreme hypertriglyceridemia. We retrospectively reviewed ten cases of extreme hypertriglyceridemia with mean serum TG on presentation of 101.5±23.4mmol/L (8982±2070 mg/dL) managed with insulin. Serum triglyceride decreased by 87±4% in 24 hours in those patients managed with IV insulin and fasting, and 40±8.4% in those managed with IV insulin alone (P = 0.0003). The clinical course was uncomplicated in all except one patient who subsequently developed a pancreatic pseudocyst. Thus, combination of IV insulin with fasting appears to be an effective, simple and safe treatment strategy in immediate management of extreme hypertriglyceridemia.

Keywords: hypertriglyceridemia; insulin; diabetes; dyslipidemia; pancreatitis

1. INTRODUCTION

Extreme hypertriglyceridemia (HTG) is associated with risk of acute pancreatitis [1] and should be treated promptly. The incidence of HTG-induced pancreatitis (HTGP) accounts for approximately 4-10% of all acute pancreatitis cases [1, 2]. It is generally believed that TG level of >11.3mmol/L (1000 mg/dL) triggers acute pancreatitis [1]. This threshold, however, is arbitrary and a few studies suggested a higher TG level at presentation of around 40-50mmol/L [2, 3].

Both primary (genetic) and secondary disorders of lipoprotein metabolism such as diabetes mellitus, obesity, hypothyroidism, excessive alcohol consumption and medications can lead to severe HTG [1, 2, 4].

A variety of treatment modalities including insulin, heparin and plasmapheresis have been described in the literature for rapid lowering of serum triglyceride level [1]. However, the efficacy and safety of individual modalities have not been well established and there is no consensus on the management of extreme HTG (serum TG level ≥50mmol/L) (≥4428 mg/dL) in the acute setting. Thus, cases with extremely high TG levels present a management challenge and the objective of this study is to review acute management and clinical course of patients with extreme hypertriglyceridemia.

2. METHODS

We retrospectively reviewed cases of extreme HTG (serum TG level ≥50mmol/L) (≥4428 mg/dL) presented to our institution between January 2010 and December 2013. Cases were identified from a list of inpatients for which Endocrinology consult was sought. A detailed medical records review was conducted to identify baseline epidemiological and clinical characteristics of these patients, type and effectiveness of treatment modalities used in

acute management of extreme HTG. Ethics approval was obtained from the Institutional Human Research Ethics Committee. Contiguous quantitative data were expressed as mean ± SD and were compared using two-tailed Student's t-test. Correlation was assessed by Pearson correlation coefficient. $P<0.05$ was considered statistically significant.

3. RESULTS

A total of ten patients presented with extreme HTG (serum TG level ≥50mmol/L) between January 2010 and December 2013. Half of them (5 out of 10) presented with pancreatitis. Mean serum TG level on presentation was 101.5±23.4mmol/L (112.9±19.6mmol/L in patients with pancreatitis and 90.2±21.6mmol/L in patients without pancreatitis; P = 0.09). The median age of the cohort was 39 years (range 24-55) and nine out of 10 patients were men. The group was multi-ethic with majority being Caucasians (6 out of 10 cases), one Torres Strait Islander (TSI), one Maori origin and two Indians. Mean BMI was 31.8±6.5 kg/m^2. Nine out of 10 cases were patients with type 2 diabetes, three of them were newly diagnosed with diabetes on presentation. Four of the 6 patients with known diabetes were taking insulin prior to the presentation. Mean HbA1C was 109±31mmol/mol [12.2±2.8%] and mean blood glucose level on presentation was 17.4±7mmol/L without evidence of diabetic ketoacidosis or hyperosmolar state. One patient without diabetes was thought to have L-asparaginase induced HTG. None of the patients had excessive alcohol intake. Family history of dyslipidaemia was reported only by one patient. Lipoprotein electrophoresis and Apo lipoprotein E (ApoE) genotype results were available for 5 patients. Three patients had Frederickson's type V and two had type III lipoproteinaemia. Four patients were homozygous for ApoE3 and one was heterozygous for ApoE3/4. All patients had normal thyroid and renal functions.

Nine patients were managed with IV insulin infusion (five of them were also kept fasting, four of them had pancreatitis) and one patient (patient 1) was managed with subcutaneous basal prandial insulin regimen. Five patients received subcutaneous low dose unfractionated heparin 5000 units BD or low molecular weight heparin (enoxaparin 40mg OD) as prophylaxis for deep vein thrombosis. Concurrent lipid-lowering agents [supplementary table 1] included statin (n=5), fibrate (n=10), omega-3-fish oil (n=4), ezetimibe (n=2), niacin (n=1). Five were on statin, two were on fibrate and one was on ezetimibe prior to their presentation. All patients received dietary education and low-fat diet was recommended to patients who were not fasted.

Mean serum TG levels decreased by 87±4% in the first 24 hours (from 105.1±30.1mmol/L to 13.6±4.1mmol/L) in those patients who were managed with IV insulin and fasting (Patient 3,4,5,9,10), 40±8.4% in the first 24 hours (from 94.3±18.9mmol/L to 57.6±16.2mmol/L) in those managed with IV insulin alone (Patient 2,6,7,8) (P = 0.0003) and by 23.5% (from 102 to 78mmol/L) in the patient managed with subcutaneous insulin (Patient 1). Figure 1 illustrates trends of mean serum TG levels. All patients achieved safe serum TG level <11.3mmol/L prior to discharge. Mean nadir serum TG level prior to discharge was 6.9±3.7mmol/L. The safe TG level was attained within 2.6±1.8 days in patients managed with IV insulin and fasting and within 5.7±1.5 days in patients managed with IV insulin alone (P = 0.027). Table 1 shows detailed trends of serum TG levels in individual patients.

Mean capillary glucose level during first 24 hours on IV insulin infusion was 11.5±2.5mmol/L and mean insulin infusion rate during first 24 hours was 3.3±1.6 units/hour for patients with diabetes. There was a significant positive correlation between the mean daily glucose levels and serum TG levels in all patients (r = 0.614, P<0.001). The patients with

pancreatitis in our series had uncomplicated clinical courses except one patient (patient 5) developing a pancreatic pseudocyst. Six patients returned for follow-up post discharge and mean nadir serum TG level on follow-up post-discharge was 3.3±2.2mmol/L.

4. DISCUSSION

Options for immediate management of extreme HTG include insulin (IV/SC), heparin (IV/SC) and/or plasmapheresis [1]. In this study, we found that extreme HTG can be managed effectively and safely with IV insulin. A number of case reports have also mentioned use of IV insulin in acute management of severe HTG [5-8]. In the largest report of 15 patients with less severe degree of HTG (serum triglyceride levels ranged 11-48mmol/L), the mean reduction in TG by IV insulin infusion within first 24 hours was about 40% [6]. Our patients had significantly more severe degree of HTG (range: 62.8-143mmol/L) at presentation but we found a similar degree of TG lowering by IV insulin infusion alone. Moreover, we also found that combination of IV insulin and fasting appears more effective, lowering the TG level by about 87% in 24 hours and achieving the safe TG level <11.3mmol/L in a shorter time frame.

Insulin lowers serum triglyceride level by increasing synthesis and action of peripheral lipoprotein lipase, thereby improving clearance of TG from the circulation [9]. Fasting improves triglyceridemia by reducing the chylomicron formation from the intestine [10]. It has been shown that moderate doses (30–50g) of dietary fat dose-dependently increase postprandial triglyceridemia [11, 12] and the TG response following a fat-containing meal remains elevated for 7–8 hours after the meal even in normolipidemic subjects [13]. Most meals contain 20-70g fat. Clinical studies also support that diets rich in highly digestible carbohydrate can lead to elevation in serum TG as a result of hepatic VLDL and chylomicron

remnants accumulation due to altered lipoprotein secretion and/or clearance [14, 15]. Obesity, insulin resistance and type 2 diabetes are known to be associated with exaggerated postprandial lipemia [10] and hence exclusion of dietary sources by fasting is expected to cause significant improvement of HTG in these patients.

To our knowledge, the degree of benefit of fasting in the setting of severe hypertriglyceridemia has not been reported objectively. In our study, combination of IV insulin and fasting appears to be twice as efficient in rapid lowering of serum TG level compared to IV insulin alone, indicating that fasting is at least as important as insulin in lowering serum TG level. Unfortunately, the degree of TG lowering achievable by fasting alone cannot be commented from our study since uncontrolled diabetes in almost all our cases necessitated the concomitant use of insulin.

Studies using plasmapheresis reported about 40-70% reduction of TG after one session [16, 17] and 60-80% after several sessions [16-18]. Thus, the degree of the TG lowering effect achieved by the combination of IV insulin and fasting approach (87% in 24 hours) is higher than that reported to be achievable by plasmapheresis. In addition, the combined approach is non-invasive and economical.

We found that extreme HTG is commonly associated with poorly controlled type 2 diabetes. This is consistent with previous studies [2, 4], in support of the central role of insulin resistance leading to reduced clearance and increased production of TG by the liver [19]. Use of insulin infusion in this context has added benefit for management of hyperglycemia and we found a positive correlation between the mean daily glucose levels and serum TG levels. Use of insulin in management of HTG in the absence of diabetes is limited to single case reports [7] and care needs to be taken to avoid hypoglycemia by concurrent administration of glucose in that setting.

Although the patients in our study were not completely worked up for genetic causes of HTG, it is likely that patients with extreme HTG have some form of underlying genetic defect in lipoprotein metabolism which manifests clinically on interaction with secondary causes such as diabetes, obesity [4, 20].

Our study is limited by the retrospective nature and relatively small number of cases. However, to our knowledge, this represents the largest cohort reported to date of patients with extreme hypertriglyceridemia managed with insulin. Given the paucity of literature and lack of consensus around management of extreme HTG, we hope that this paper will form a basis for conducting larger prospective studies to optimise patient outcomes in the immediate management of extreme hypertriglyceridemia.

5. CONCLUSIONS

Extreme HTG is commonly associated with poorly controlled type 2 diabetes. Combination of IV insulin and fasting appears to be a very effective, simple and safe treatment strategy in immediate management of extreme HTG.

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Table 1. Trends of Triglyceride (TG) levels in individual patients

	TG level at presentation (Day 1) (mmol/L)	TG level (Day 2) (mmol/L)	TG level (Day 3) (mmol/L)	TG level at discharge (mmol/L)	Reduction of TG level in 24hr (%)	Time to achieve TG <11.3mmol/L
IV insulin+fasting (n=5)						
-patient 3	111.1	18.2	8.5	5.8	83.6%	2 Days
-patient 4	96	15.9	15.2	10.7	83.4%	5 Days
-patient 5	109.3	N/A	N/A	6.5	N/A	4 Days
-patient 9	146.3	10.4	4.7	2.8	92.9%	1 Day
-patient 10	62.8	10	8	2.3	84%	1 Day
mean±SD	105.1±30.1	13.6±4.1	9.1±4.4	5.6±3.4	87±4%	2.6±1.8 Days
IV insulin (n=4)						
-patient 2	96	48	25.3	7.4	50%	7 Days
-patient 6	114.3	80.2	55.4	11	30%	5 Days
-patient 7	98.2	58.2	N/A	1.8	40.7%	4 Days
-patient 8	68.8	44.1	25.6	10	35.9%	7 Days
mean±SD (n=4)	94.3±18.9	57.6±16.2	35.4±17.3	7.5±4.1	40±8.4%	5.7±1.5 Days
SC insulin (n=1)						
-patient 1	102	78	46.6	11	23.5%	8 days
Comparing IV insulin+fasting Vs IV insulin alone	P=0.55	P=0.002*	P=0.03*	P=0.46	P=0.0003*	P=0.027*

*denotes statistically significant. Abbreviations: N/A= data not available

FIGURE CAPTION

Figure 1: Trends of mean triglyceride levels (Mean reduction of 87% in the first 24h in IV insulin+fasting group Vs 40% in IV insulin alone group; P=0.0003) (error bars represent standard deviations)

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Highlights:

- 10 cases of extreme hypertriglyceridemia (mean triglyceride 8982±2070mg/dL) managed by insulin.
- Compared effectiveness of combined fasting and intravenous insulin approach with intravenous insulin alone.
- Extreme hypertriglyceridaemia is commonly associated with type 2 diabetes.

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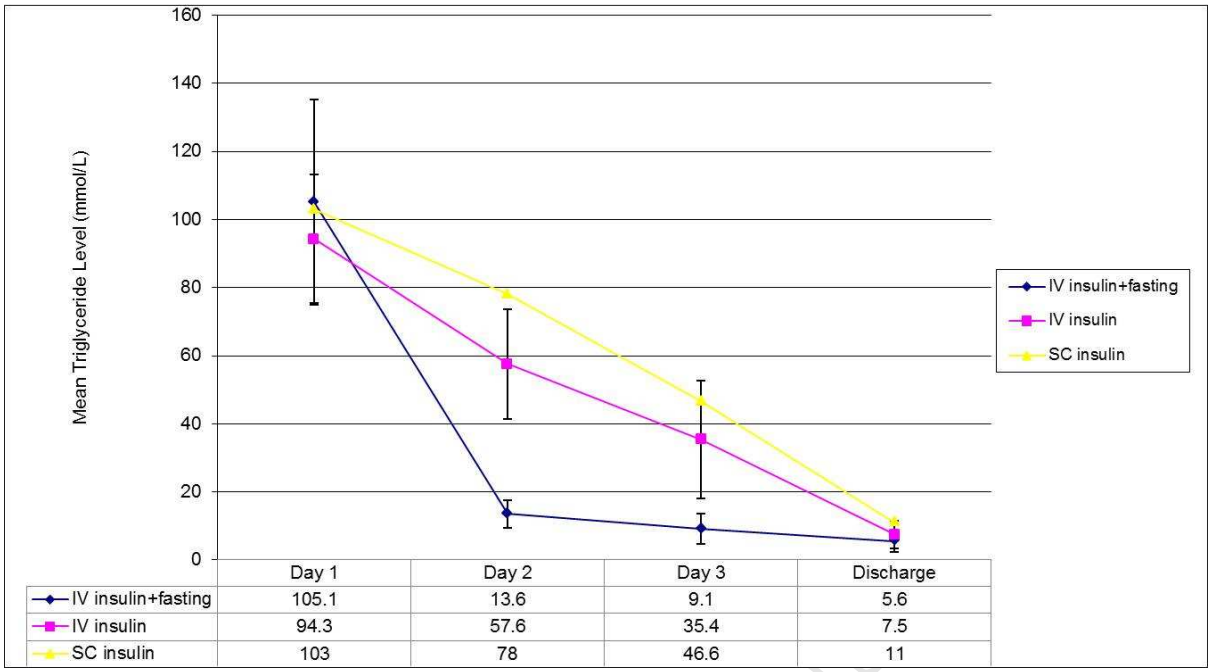

	Day 1	Day 2	Day 3	Discharge
IV insulin+fasting	105.1	13.6	9.1	5.6
IV insulin	94.3	57.6	35.4	7.5
SC insulin	103	78	46.6	11

Supplementary Table 1: Concurrent lipid lowering agents

	On presentation	During hospitalisation and on discharge
Patient 1	Rosuvastatin 20mg daily	Rosuvastatin 20mg daily Fenofibrate 145mg daily Fish oil 3g daily
Patient 2	Nil	Fenofibrate 145mg daily Fish oil 3g twice per day Nicotinic acid 500mg tds
Patient 3	Gemfibrozil 600mg twice per day Atorvastatin 80mg daily	Gemfibrozil 600mg twice per day Atorvastatin 80mg daily
Patient 4	Fenofibrate 145mg daily Atorvastatin 80mg daily	Fenofibrate 145mg daily Atorvastatin 80mg daily Fish oil 4g twice per day Ezetimibe 10mg daily
Patient 5	Nil	Fenofibrate 145mg daily
Patient 6	Atorvastatin 20mg daily Ezetimibe 10mg daily	Atorvastatin 20mg daily Fenofibrate 145mg daily Fish oil 2g three times per day Ezetimibe 10mg daily
Patient 7	Nil	Fenofibrate 145mg daily
Patient 8	Atorvastatin 40mg daily	Atorvastatin 40mg daily Fenofibrate 145mg daily
Patient 9	Nil	Fenofibrate 145mg daily
Patient 10	Nil	Fenofibrate 48mg daily

Fish oil 1g contains 300mg of omega-3 as Eicosapentaenoic acid 180mg and Docosahexaenoic acid 120mg