Original Research

Case Series- Intravenous Insulin Infusion Therapy in Management of Hypertriglyceridemia of Various Etiologies

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Received: 29 November, 2023 Accepted: 24 December, 2023

Abstract
Intravenous insulin infusion has demonstrated its efficacy in reducing triglyceride levels, particularly in cases of pancreatitis. This case series explores the application of intravenous insulin therapy in diverse clinical scenarios, where hospitalized patients presented with hypertriglyceridemia concurrent with various ailments. Remarkably, all patients exhibited positive responses to the treatment, resulting in the successful reduction of triglyceride levels to within the near-normal to normal range. This study sheds light on the broader potential of intravenous insulin in managing hypertriglyceridemia across different medical conditions, presenting a promising avenue for therapeutic intervention.

Introduction

Hypertriglyceridemia refers to a fasting plasma triglyceride measurement that is increased, typically above the 95th percentile for age and sex, although additional quantitative or qualitative lipoprotein abnormalities can also be present. Elevated plasma triglyceride concentrations contribute to an increased risk of cardiovascular disease, both directly and because such elevations are associated with associated risk factors such as obesity, metabolic syndrome, proinflammatory and prothrombotic biomarkers, and type 2 diabetes mellitus. [2] When looking at dementia subtypes, it was also observed that high total cholesterol and triglycerides (TG) may increase the future risk of Alzheimer's disease (AD), with a pooled RR of 1.13 (95% CI: 1.06–1.21) and 1.10 (95% CI: 1.04–1.15), respectively. [10]Atherogenic dyslipidemia can be observed in a large majority of patients with NAFLD and results from hepatic and peripheral insulin resistance along with associated alterations of the hepatic glucose and lipoprotein metabolism, gut dysbiosis, and genetic factors.[11] The increased risk of acute pancreatitis is an additional consideration when a patient's triglyceride level is very high (typically > 10 mmol/L).The clearance of TG from circulation is mostly dependent upon the hydrolysis of TG carried in chylomicrons and very low-density lipoproteins by lipoprotein lipase enzymes. In adipose tissue, lipoprotein lipase is activated by insulin.[3.] This activation is impaired in those with insulin deficiency or resistance. Insulin decreases triglycerides by stimulating lipoprotein lipase activity, which degrades triglycerides into fatty acids and glycerol. [9]. Furthermore, fasting will also lower 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 hypertriglyceridemia-associated acute pancreatitis (HAAP) with concomitant glucose infusion in patients without diabetes to achieve a more precipitous fall in TG as compared with fasting alone.

Methodology

Patients presenting with high triglyceride levels or admitted patients found to have high triglyceride levels in Jaipur Golden Hospital, Rohini, New Delhi, were included in the study after obtaining verbal consent for the said modality of treatment. IV insulin was started at 0.1 to 0.3 IU/kg body weight/hour for 24 to 48 hours.

Observation and Result

Table no.a: The data on individual cases of HTGP on epidemiology, clinical presentation, diagnosis, management, and clinical outcomes are summarized

Case no.	Clinical Presentation	Comorbidity	Initial TG level (mg/dL)	Treatment	TG post-treatment (mg/dL)	Duration of treatment (days)	Outcome
1	upper abdomen	DM-2	1273	IV insulin infusion	288	2	Recovered
2	right upper quadrant of the abdomen	NA	632	Dextrose drip along with an IV insulin infusion	181	1	Recovered
3	Abdomen pain	DM-2	890	IV insulin	262	1	Recovered
4	Abdomen pain	DM-2, HTN	3687	IV insulin	1329	2	Recovered
5	Acute gastroenteriti	DM-2	1136	IV insulin	413	2	Recovered
6	Forgetfulness	DM-2, HTN	1053	IV insulin	283	2	Recovered
7	Fullness on the right side of the abdomen	NA	1388	IV insulin along with a dextrose drip	177	2	Recovered
8	Severe pain in the abdomen with nausea vomiting	NA	2440	Intravenous insulin, glucose	1133	3	Recovered

Patient demographics and clinical presentations

In the present review, HTGP involved all age groups, with a mean age of 46 years (range: 39–68 years). There was no clear gender preponderance (male, n = 5; female, n = 3). The typical presentation was acute-onset abdominal pain, while other notable symptoms included nausea and vomiting. Cutaneous signs of hypertriglyceridemia, such as eruptive xanthomas over the extensor surfaces of the arms, legs, and buttocks, were also noted in a few patients. A majority of patients had comorbid conditions and risk factors like moderate-to-severe hypertriglyceridemia, hypertension, diabetes mellitus, dyslipidemia, and obesity. It was an interesting observation that the initial triglyceride levels causing acute pancreatitis were more than 1000 mg/dL in all cases included in this review.

Diagnosis

The diagnostic criteria for HTGP include the presence of at least two out of three following findings: (a) acute-onset severe epigastric pain radiating to the back; (b) serum lipase or amylase elevated three or more times the upper reference limit; and (c) the three characteristic findings of acute pancreatitis on imaging investigations such as computed tomography, magnetic resonance imaging, or transabdominal ultrasonography. Another major clue for the diagnosis of HTGP includes a biochemical evaluation remarkable for serum triglyceride levels greater than 1000 mg/dL. The risk factors for hypertriglyceridemia are obesity, family history of hypertriglyceridemia, poorly controlled diabetes mellitus, and alcoholism. It is important to mention here that a thorough clinical history, including family history of lipid metabolic aberrations and physical examination to identify eruptive xanthomas, can help to channel the biochemical and radiological investigations toward a timely etiology establishment.

Insulin therapy

Currently, there are no clear therapeutic guidelines for HTGP. Insulin therapy has previously been used in these patients as a minimally invasive and economical strategy with promising outcomes. The mechanism by which insulin lowers the level of serum triglycerides is by triggering the enzymatic activity of lipoprotein lipase and inhibiting hormone-sensitive lipase. Lipoprotein lipase metabolizes chylomicrons and VLDLs into free fatty acids and glycerol. Therefore, it ultimately decreases serum triglyceride levels. Decreasing the activity of hormone-sensitive lipase causes decreased adipocyte-triglyceride breakdown, resulting in a decreased release of free fatty acids into the circulation, which controls the toxic effects on the pancreas, limiting its active inflammation. In this review, the initial symptomatic management is comprised of bowel rest, intravenous fluids, and analgesics. In regard to the

emergency management of HTGP, insulin infusion as monotherapy or part of a combination regimen was the most effective option in settings where plasmapheresis was not available or as an alternative approach for patients who could not tolerate apheresis. It was usually given intravenously at a rate of 0.1–0.3 units/kg/hour. Serum triglyceride levels were monitored every 12 hours. With insulin therapy, it was pivotal to measure blood glucose levels, and an adjuvant 5% dextrose infusion was required when the blood glucose level fell below 200 mg/dL.

Discussion

Hypertriglyceridemia, characterized by fasting serum triglyceride levels exceeding 150 mg/dL, poses a spectrum of risks where levels between 150 and 1000 mg/dL are considered moderately high and levels surpassing 1000 mg/dL are deemed severely high, associated with potential complications. Notably, the risk of acute pancreatitis escalates significantly when triglyceride levels exceed 2000 mg/dL, reaching an approximate incidence of 10% to 20%. The mechanism behind lipotoxicity in acute pancreatitis is rooted in the breakdown of triglycerides into toxic free fatty acids by pancreatic lipases.The pathogenesis of hypertriglyceridemia-induced acute pancreatitis (HTG-AP) remains elusive, yet the proposed mechanism implicates the toxic effects of free fatty acids liberated during triglyceride breakdown. Triglyceride-rich lipoproteins, such as chylomicrons and VLDL, become abundant in hypertriglyceridemia, potentially obstructing pancreatic capillaries and altering cellular structure. This process prompts the release of pancreatic enzymes, including lipase, initiating the breakdown of lipid-rich molecules, thereby intensifying local oxidative stress and contributing to pancreatic inflammation.Treatment guidelines for severe HTG-AP are not well-established. However, the literature suggests the use of insulin, heparin, and plasmapheresis. Insulin, identified as noninferior and cost-effective compared to plasmapheresis, targets the stress-induced release of fatty acids, promotes intracellular triglyceride generation within adipocytes, and facilitates fatty acid metabolism in insulin-sensitive cells. This multifaceted approach aims to mitigate the toxic effects of fatty acids on the pancreas, often observed in the context of diabetes and peripheral insulin resistance.

Initiation of oral lipid-lowering agents becomes viable when a patient can tolerate oral intake. Following the 2012 Endocrine Society guidelines for hypertriglyceridemia management, fibrates are recommended as the first-line treatment for severe and very severe cases. Complementary oral agents, such as niacin, N-3 fatty acids, and statins, may be employed in conjunction with fibrates, with careful consideration of potential side effects and the necessity for patient counseling. Emphasizing aggressive lifestyle modifications alongside regular triglyceride level monitoring is crucial to prevent recurrent episodes of acute pancreatitis. This comprehensive approach underscores the importance of tailoring treatment strategies to the severity of hypertriglyceridemia and its associated complications.

Clinical outcomes

According to the results of the outcome analysis of this review, the overall prognosis of HTGP was good, with a vast majority of patients recovering completely with intensive insulin therapy. It is quite reassuring that in emergency clinical settings, intravenous insulin was used as a salvage therapy, even in patients with severe HTGP, resulting in a remarkable recovery. In three to five days of insulin therapy, most patients demonstrated a good clinical response; serum triglyceride levels decreased to less than 500 mg/dL, after which the treatment was discontinued. A number of patients received insulin as a combination therapy with lipid-lowering drugs. This fatal outcome re-emphasizes that patients with HTGP are more likely to encounter organ failure as compared to the other causes of pancreatitis. Therefore, urgent and appropriate management is essentially important.

Long-term management

Patients with HTGP clinically improve when their serum triglyceride levels fall below 500 mg/dL. However, in order to prevent recurrent episodes and subsequent complications of HTGP, long-term management is warranted to maintain the level of triglycerides below 200 mg/dL. It is particularly tailored to lifestyle modifications with dietary fat and sugar restriction, aerobic exercises, weight loss, and blood sugar control. Hypolipidemic medications like gemfibrozil and fenofibrate lower serum triglyceride levels and reduce the recurrence risk of HTGP.

Conclusion

This case series investigated hospitalized patients with elevated triglyceride levels, irrespective of comorbidities such as diabetes mellitus, hypertension, obesity, or complications like acute pancreatitis or atherosclerosis. Intravenous (IV) insulin emerged as a promising and effective treatment modality for triglyceride reduction, demonstrating quicker results compared to other interventions. Despite not being currently recognized by the Endocrine Society, our findings suggest that IV insulin is not only effective in diabetic patients but also in those without diabetes, making it a valuable tool for triglyceride management. Particularly in peripheral hospitals where options like plasmapheresis may be unavailable, IV insulin proves to be a cost-effective and accessible alternative, highlighting its practical utility in acute settings. As we strive to refine treatment approaches, the role of IV insulin in managing hypertriglyceridemia deserves further consideration within the medical community.

Footnotes: Declaration of Conflicting Interests: The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Financial Support and Sponsorship Section: The author(s) received no financial support for the research, authorship, and/or publication of this article.

Ethics Approval: Our institution does not require ethical approval for reporting individual cases or case series.

Informed Consent: Verbal informed consent was obtained from the patient(s) for their anonymized information to be published in this article.

Authors statement:- All authors have read this manuscript and is approved by all. All believes that this represent our honest work.

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