# Heparin and insulin in the management of acute hypertriglyceridemic pancreatitis

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## Abstract

Hypertriglyceridemic pancreatitis (HTGP) is the third cause of acute pancreatitis in most studies, with a triglyceride (TG) risk value of more than 1000 mg/dL. The pathophysiological mechanism involves triglyceride hydrolysis by pancreatic lipase and the release of fatty acids which cause damage by producing free radicals. The reduction of TGs below 500 mg/dL is the treatment goal, based on increased lipoprotein lipase activity and chylomicron degradation. We present the case of a patient with HTGP with an adequate response to concomitant insulin and heparin therapy. (Acta Med Colomb 2020; 45. DOI: https://doi.org/10.36104/amc.2020.1491).

**Key words:** *triglycerides, acute pancreatitis, heparin, insulin, lipoprotein lipase*.

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## Introduction

Acute pancreatitis is an inflammation of the glandular parenchyma of the retroperitoneal organ which leads to injury with or without subsequent destruction of the pancreatic acinus (1). The incidence of pancreatitis varies from one population to another (4.9-35 per 100,000 inhabitants). The average age of onset is 53 years, with equal distribution between the sexes, although in the last few years there has been a rise in women under the age of 35. The average inpatient stay is seven days, which suggests that most cases are mild. However, one out of five cases may develop organ damage with or without complications, classifying them as severe cases. Patients with severe pancreatitis who recover from the first phase of the disease may develop secondary infection in the necrotic pancreas. Mortality for patients with infected necrosis or organ failure has been reported at 30-40%, increasing with age (2).

Gallstones are the most common cause, making up 40-70% of cases. Population studies indicate that 3-7% of individuals with gallstones develop pancreatitis. Alcohol consumption is the second most common cause, at 25-41%. Hypertriglyceridemia is the third cause, accounting for up to 10% of all cases, increasing to 50% in pregnancy. Severity and complication rates tend to be greater (3); thus, prompt medical management to decrease the TGs is essential. The following case shows one management method which is considered to be cost effective.

## Case presentation

A 30-year-old patient was admitted due to a two-day history of epigastric pain radiating to the sternal and precordial region and 10 food vomiting episodes; he denied having a fever. On admission to the emergency room he was dehydrated and tachycardic with a normal blood pressure. On physical exam he had no pain on abdominal palpation and his neurological exam was within normal limits. His glucose level on admission was 352 mg/dL, and blood gases revealed partially compensated metabolic acidosis without impaired oxygenation (ph 7.25, $HCO_3$ 14, $PaCO_2$ 29, $PaO_2$ 63, BE -10). Laboratory tests showed a complete blood count within normal limits, amylase 648 U/L, hyponatremia at 120 mmol/dL (corrected for glucose level: 124 mmol/dL) and 14.10% glycosylated hemoglobin. Management was begun with crystalloids in the context of diabetic ketoacidosis (new-onset diabetes), implementing crystalloid resuscitation and initiating insulin infusion therapy. He was also diagnosed with Marshall 2, APACHE II 10 pancreatitis. Hepatobiliary ultrasound ruled out pancreatic lithiasis, and triglycerides were ordered since he did not have a history of alcohol consumption. The triglyceride results were 6,700 mg/dL with total cholesterol of 1,071 mg/dL. Plasmapheresis was not available, therefore a bolus of 80 units/kg of unfractionated heparin was added to the insulin treatment and was continued at 18 U/kg/hour. Abdominal tomography was compatible with Balthazar B (Figure 1). The metabolic acidosis was corrected, and adequate glucose control was achieved. Dextrose, insulin and heparin infusions were continued, with the heparin maintaining a PTT 2.5 times the institution´s reference value. The patient showed clinical improvement of the abdominal pain and daily follow up of the triglycerides showed a significant decrease. The patient tolerated oral

ingestion, and fenofibrate was begun as complementary treatment. The infusion treatment was maintained for four days, his triglycerides were below 500 mg/dL on the fifth day, and he was transferred to the regular floor without complications (Table 1).

## Discussion

Hypertriglyceridemic pancreatitis (HTGP) is a disease which presents in people with lipid metabolism disorders, mainly in those with triglycerides above 1,000 mg/dL. It is generally seen in men and in the fifth decade of life (46.9±11.5 years) (4).

The pathophysiological mechanism has not been well defined, but there are three recognized theories. The first is the most accepted and proposes that chylomicrons occlude the pancreatic capillaries and their hydrolysis releases high concentrations of free fatty acids which exceed the capacity of albumin to bind them in micelles with detergent properties. These fatty acid-micelle complexes damage the endothelium and the pancreatic acinar cells (5, 6). The resulting ischemia creates an acid environment which generates more free fatty acids and toxicity, leading to the release and activation of pancreatic lipase and proteases, and autodigestive injury (4). The second theory speaks of hyperviscosity which leads to selective ischemia of the pancreatic acinar cells. The third is the genetic theory, based on genetic polymorphisms which have been identified in patients with severe hypertriglyceridemia with pancreatits, and have not been found in individuals with hypertriglyceridemia without pancreatitis (4).

The clinical course of HTGP is similar to that of other causes of acute pancreatitis, but the complication and mortality rates are significantly higher (4). Four groups of HTGP individuals are generally described throughout the clinical presentation: first, patients with poorly controlled diabetes (in this case the patient had new-onset diabetes) with or without a history of hypertriglyceridemia. Second, alcoholic patients with milky plasma. Third, non-obese, non-alcoholic patients with hypertriglyceridemia secondary to medications or diet, and, last, patients with familial hypertriglyceridemia without secondary factors (5).

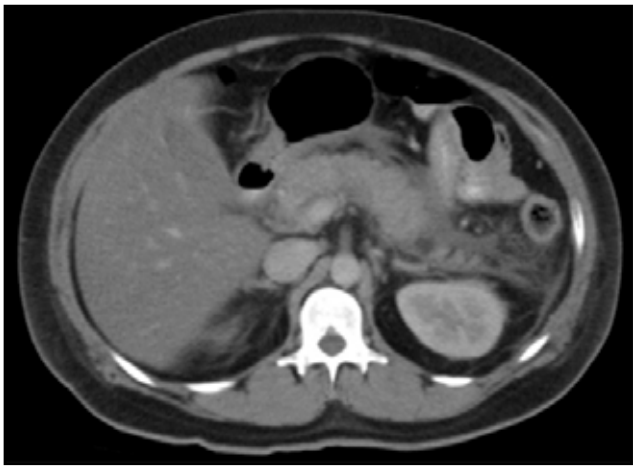

**Figure 1.** *Diffuse increase in pancreatic size, with irregular borders and heterogenous attenuation.*

Acute treatment (within the first 14 days) is key to management as 50% of mortality occurs during this time (possibly due to systemic inflammation and multiple organ failure). Treatment is similar to the management of acute pancreatitis due to other causes, and consists of bowel rest by withholding oral intake, intravenous fluid resuscitation, pain control and symptom management. Crystalloids should be administered with isotonic fluids at an infusion rate of 250-500 mL/h for 24-48 hours. Enteral feeding plays an important role in the management of acute pancreatitis, offering nutritional support to the patient, thus maintaining bowel function and protecting against systemic inflammatory response syndrome (3). There is currently no specific treatment for hyperlipidemia, but various therapies such as the administration of insulin, heparin, apheresis/plasmapheresis, fibrates and omega 3 fatty acids have been employed to lower serum TG levels.

**Table 1**. *Laboratory records.*

| | Day 1 | Day 2 | Day 3 | Day 4 | Day 5 |
|---|---|---|---|---|---|
| Triglycerides mg/dL | 6,700 | 3,250 | 1,770 | 749 | 454 |
| Total cholesterol mg/dL | 1,071 | 850 | 577 | 435 | 325 |
| Leucocytes cells/$\mu$L | 14,580 | 10,510 | 8,530 | 9,550 | 7,520 |
| Hgb g/dL | 16.2 | 15 | 12.3 | 12.5 | 13 |
| Hematocrit % | 40 | 41 | 36 | 37 | 37.9 |
| Platelets cells/$\mu$L | 302,000 | 310,000 | 226,000 | 297,000 | 206,200 |
| Sodium mmol/L | 128 | 132 | 136 | 135 | 138 |
| Potassium mmol/L | 3.32 | 3.5 | 3.58 | 3.78 | 3.65 |

We emphasize the importance of lipoprotein lipase (LPL), an enzyme expressed in the capillary endothelial cells of muscle and fatty tissue which plays an important role in fat metabolism by hydrolyzing TGs, and thus is an important factor in their reduction. Insulin fosters the synthesis and activation of this enzyme, reducing TG levels, and increases the breakdown of chylomicrons. It may be administered subcutaneously or parenterally, although its parenteral use is preferable due to the ease of titration and its pharmacokinetics. It is used in various infusion schemes, depending on whether the patient has diabetes, reducing triglycerides to less than 1,000 mg/dL within 72-96 hours of infusion. In the reported case, it was used from the beginning due to diabetic ketoacidosis.

In a case series (10 patients), intravenous insulin was associated with a 40% decrease in TGs in 24 hours in severe hypertriglyceridemias, and an 87% decrease in patients treated with insulin plus fasting, while subcutaneous administration of insulin caused a 23% reduction in triglycerides in 24 hours (6). Insulin therapy has proven to be safe and effective in the treatment of HTGP (4, 5).

Heparin, a widely used medication in multiple diseases due to its anticoagulant effect, has been proven to alter the HTGP inflammatory process due to its effect on endothelial cells, blocking platelet and leucocyte adhesion to the endothelium and reducing leucocyte recruitment, thus leading to suppression of the inflammatory response (7). Heparin was shown to reduce mortality and improve the Balthazar score in a multi-center study performed by Lu XS (a study with limited statistical power) (7). In addition, like insulin, it activates LPL; heparin causes endothelial LPL to be released into the circulation (6), resulting in decreased serum TGs. The process following endothelial LPL release requires that LPL be synthesized again, which is a slow process; thus, two events occur: first, effectiveness is lost after the first dose, and second, rebound hypertriglyceridemia may present after discontinuing heparin. Therefore, it is recommended that heparin be used after the standard treatment of fasting, intravenous fluid infusion and insulin infusion (9). Consequently, heparin would not be the treatment of choice as monotherapy (6). Heparin may be administered subcutaneously or parenterally, the latter by infusion or in boluses. There is insufficient evidence to give a clear recommendation in this regard, but according to the case reports, parenteral bolus administration could be recommended, as it is more effective (18 units/kg/dose every 4-6 hours) (6). In addition, the risk of bleeding should be considered, although this has not been reported in HTGP patients in the literature.

With regard to the concomitant use of insulin and heparin, we highlight Henzen et al.´s report in which the reduction range was from 3,822 mg/dL to 888 mg/dL in 2.8 days with simultaneous administration of these medications in five patients (10). In the four-case series by Kuchay et al., the mean decrease was from 3,800 mg/dL to 849.7 mg/dL over a period of 72 hours; the pancreatitis resolved in all the cases (11). In Berger et al.´s five-case series, the TGs were below 500 mg/dL at three days (12). In our case, they decreased by 3,450 mg/dL in the first 24 hours, and levels under 500 mg/dL were not achieved until day five. However, the initial level was higher than many of the cases reported in the literature.

The use of therapeutic plasma exchange has been reported mainly in patients with TG levels over 2,000 mg/dL, with rapid clinical improvement not just due to its effect in decreasing TGs but also due to its effect on the inflammatory mediators (4). A session of plasmapheresis has been shown to decrease serum TG levels up to 70% in patients with severe hypertriglyceridemia (13), and in patients with pancreatitis due to hypertriglyceridemia a greater than 80% decrease has been shown in two sessions of plasmapheresis (14).

In 2016, He WH et al. carried out a controlled, randomized study with 66 HTGP patients, finding that the early use of high-volume hemofiltration can decrease TG levels, but is not superior to insulin and low-weight heparin therapy with regard to local pancreatic complications, the need for surgery, mortality and length of hospital stay (15).

## Conclusion

Management with insulin and heparin is a safe, economical alternative for HTGP treatment compared to plasmapheresis, which is not available in many institutions. However, most of the available literature is based on case series; therefore, studies with better statistical power are needed.

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