HYPERTRIGLYCERIDEMIC PANCREATITIS (HTGP)

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CLINICAL ASPECTS

Hypertriglyceridemia occurs in almost half of patients with acute pancreatitis. In order to attribute pancreatitis to hypertriglyceridemia the patient should have a triglyceride concentration of over 1,000 mg/dL at initial evaluation and no other cause of pancreatitis identified. By this definition, the condition occurs in 9% cases of pancreatitis occurring in the general population. During pregnancy HTGP was reported to represent up to half of the cases of pancreatitis. Conversely in patients referred for marked hypertriglyceridemia 14% had pancreatitis. The median triglyceride level is 2,622 mg/dl and the median age of the patients is 47 years. Two thirds of the patients are men. Among patients with HTGP there is an increased proportion of obesity, fatty liver and type 2 diabetes. HTGP is associated with spurious laboratory abnormalities due to interference of elevated triglycerides with colorimetric methods of laboratory techniques and to reduction of water soluble media in the serum. Abnormalities include spuriously normal amylase and lipase.

PATHOGENESIS

The relationship between hypertriglyceridemia and pancreatitis is not understood. Hypotheses include local accumulation of free fatty acids (FFA) and serum hyperviscosity. Both may result in capillary stasis, hypoxia and ultimately in edema and necrosis. FFA concentration is increased through hydrolysis of excess triglycerides by pancreatic lipase resulting in toxicity to the acinar cell through increased oxidation and acidosis. Acute pancreatitis may be precipitated by infection, dehydration and hypotension. Pancreatitis may be associated with genetic or acquired hypertriglyceridemia. The latter could be transient if attributable to a rich meal, alcohol binge, drugs, or uncontrolled diabetes. The genes associated with HTGP are those encoding factors involved in triglyceride metabolism: LPL, apo C-II, apo A5, apo E2, circulating antilipoprotein lipase antibody, lipase maturation factor 1, glycosylphosphatidylinositol-anchored high-density lipoprotein-binding protein and cystic fibrosis transmembrane conductance regulator. Genetic disorders resulting in extreme increase of triglyceride concentration such as homozygous LPL deficiency (Fredrickson type 1 hyperlipidemia) may cause HTGP in children. Less severe genetic disorders contribute to the risk of HTGP later in life in combination with causes of increased triglyceride production such as obesity, diabetes and metabolic syndrome. Pregnancy and drugs affecting triglyceride metabolism may cause HTGP. Drugs frequently associated with HTGP are: estrogens, protease inhibitors, antiretroviral therapy, retinoids, antipsychotics, and tamoxifen.

DIAGNOSIS AND DIFFERENTIAL DIAGNOSIS

Patients with pancreatitis present with sudden onset of abdominal pain, nausea and vomiting. The pain is very severe, stabbing, localized in the upper abdomen and may radiate to the back. Differential diagnosis includes biliary colic, acute gastritis, perforated peptic ulcer, and acute myocardial infarction. The diagnosis of pancreatitis is confirmed by marked elevations of serum amylase and lipase. Unfortunately, amylase and to lesser extent lipase could be in the normal range in HTGP and one must rely on contrast-enhanced CT scan of the pancreas for diagnosis. The presence of lactescent serum will establish that serum triglycerides are markedly elevated. In some case series HTGP was more severe than more common forms of pancreatitis and more frequently associated with hyperglycemia, hypoalbuminemia, hypocalcemia, high APACHE score, hypotension and renal failure. In others, there was no association between triglyceride level and degree of severity.

THERAPY

Evaluation of Severity

Within 72 hours of admission the patients are classified according to the severity of pancreatitis into mild or severe. APACHE II Score $\geq$8 and Ranson Score $\geq$3 have a high predictive value for severe pancreatitis. The Balthazar Score using imaging for evaluation of severity is a viable alternative. Patients need to be re-evaluated daily and a decreasing APACHE score is predictive of a mild episode while an increasing score predicts severe pancreatitis. APACHE score can be modified for patients with high body mass index to reflect their increased risk. Hematocrit higher than 44% has a high sensitivity and specificity for necrotizing pancreatitis. Patients with severe pancreatitis, organ failure and/or high hematocrit require ICU admission. Other indications for ICU admission include obtundation, presence of infiltrates or pleural effusions on chest X ray, labored breathing, tachycardia >120 bpm, oliguria (<50 ml/hour) and C reactive protein >150mg/L.

Management of Hypertriglyceridemia

In HTGP a decrease in triglyceride concentration is a management priority. Rapid triglyceride concentration lowering is obtained by plasmapheresis (PLPH), insulin (INS), heparin (HEP) or insulin and heparin (INS-HEP). No randomized trial between PLPH and INS-HEP has been conducted. Some case reports document pain relief concurrent with drastic decreases in triglyceride level. Only few studies report rapid objective improvement. If hypertriglyceridemia is attributed to a drug it should be discontinued. In severe cases this medication will never be re-prescribed but in moderate cases successful resumption under monitoring has been reported.

Plasmapheresis

For treatment of severe HGTP, plasmapheresis is indicated whenever available. American Society of Apheresis guidelines classify apheresis for HTGP as grade III, class 2C recommendation, acknowledging that the evidence of benefit is based only on a few case reports. A small randomized trial showed that plasmapheresis is more efficient in lowering triglycerides but did not improve clinical outcomes. Additional benefit might be attributed to removal of circulating proteases and inflammatory

markers and reduction of plasma hyperviscosity. If the procedure is associated with fresh frozen plasma administration, additional benefits have been attributed to replacement of consumed protease inhibitors and supplemental LPL activity. The following technical recommendations have been made:

Centrifugal or double membrane filtration have been used to treat HTGP. A comparison of these two methods found greater removal with centrifugal methods because of slightly higher efficiency, tendency of the TG to clog the pores of the filters and an increased risk of hemolysis.

Replacement of removed plasma: Plasma is usually replaced with albumin 4-5% or fresh frozen plasma (FFP). In some situations there are compelling recommendations for use of FFP because of coexisting comorbidity. Otherwise albumin is safer because of lower risk of allergic and infectious.

Anticoagulant: Reports have recommended the use of heparin as anticoagulant for these procedures because of its ability to release LPL which should enhance TG reduction. Some authors have used citrate or nafamostat mesylate with similar TG reductions and possibly superior clinical outcomes.

Volume exchanged is usually 1 to 1.5 total plasma volumes. Reported values are 4,890 $\pm$ 1,300 ml. or 70 ml/Kg for men and 65 ml/Kg for women.

Timing, duration and number of procedures: It is recommended that decision for use of PLPH be made early, within 48 hours of admission, although there is no evidence supporting this recommendation. A triglyceride concentration reduction of 60% is expected from a single procedure. PLPH is continued until a triglyceride concentration lower than 500 mg/dl has been reached. The following equation was proposed for estimation of number of plasmapheresis required: *Percent triglyceride reduction = 100 (1-$e^{-PV/PPV}$),* where PV is the exchanged plasma volume and PPV the estimated patient plasma volume. The frequency of repeat PLPH is daily to twice a week.
Vascular access used is a double luminal catheter in a central or peripheral vein.

Usual duration of the procedure is 3.5 $\pm$ 2.0 hours.

Usual blood flow is 102 $\pm$ 23 ml/min.

Heparin and/or Insulin

If the patient is hyperglycemic or if PLPH is not available, INS, HEP or INS-HEP are used. The mechanism of action of HEP is activation of LPL resulting in accelerated triglyceride hydrolysis. INS administration contributes to the synthesis of LPL de novo. In addition, it diminishes FFA flow resulting in diminished toxicity to pancreatic tissue and decreased triglyceride synthesis.

INS could be administered intravenously or subcutaneously. The recommended dose is variable depending on the level of glycemia and the level of insulin resistance. INS is titrated to maintain plasma glucose 120-160 mg/dl. The initial dose recommended is 0.1 units/Kg/hour followed by a decrease to 0.05 units/Kg/hour, once triglyceride level <1,000 mg/dl is reached, followed by 0.025 units/Kg/hr and discontinuation. If the patient does not have hyperglycemia at baseline, hypoglycemia is prevented and

managed by changing the rate of glucose infusion rather than by changing INS dose. Electrolytes must be monitored as well.

HEP is also administered intravenously or subcutaneously. The dose of HEP used is 10-12,000 units per day, sufficient to lower triglycerides without affecting coagulation. Low molecular weight HEP (enoxaparin 40 mg/day, sc) has been used with satisfactory results. The duration of effective HEP use is not clearly established.

INS alone has been used successfully. HEP alone has also been used but some authors have expressed concern since HEP infusion can result in increased degradation and exhaustion of LPL stores resulting in a paradoxical increase in triglycerides.

Nutritional Support

Oral feeding is withheld initially. Fasting is well tolerated for this duration if associated with proper hydration. In addition to resting the bowel in the setting of acute inflammation, acute fasting serves to cut off the exogenous and endogenous supply of triglycerides. Mild pancreatitis is treated with resumption of oral feeding in a timely manner, usually within 5-7 days of the admission. Severe pancreatitis requires enteral (EN) or parenteral (TPN) nutrition.

Type of nutrition: Multiple small-randomized clinical trials have shown the superiority of EN over TPN in patients with acute pancreatitis but not in HTGP. Use of EN is associated with significant reductions of the risk of death, multiple organ failure, systemic infection and operative interventions. There is a trend towards decrease of local septic complications, other local complications and length of hospital stay. Based on this, in patients with severe pancreatitis EN is preferred to TPN, providing that ileus is not present. Combinations of EN and TPN can be used if EN is only partially tolerated or cannot provide sufficient nutrients. Tube feeding should be initiated early if the patient is unlikely to resume oral intake for prolonged time.

Access: There is no significant benefit from the use of nasojejunal versus nasogastic feeding,

Nutrient: Many enteral nutritional regimens have been proposed but, in general, there is no benefit from “immunomodulating” versus standard feeding or “semi-elemental” versus polymeric feeding and no advantage from using “probiotic” feeding. The principles of nutritional support in acute pancreatitis apply to HTGP with one exception: since triglycerides should never be allowed to exceed 400 mg/dL, fat supplementation is temporarily eliminated from TPN and reduced to 10-15% of total daily caloric intake in oral and enteral management until hypertriglyceridemia has resolved. Medium chain triglycerides and omega 3 fatty acids have been shown to rapidly decrease triglyceride concentrations in patients with extreme hypertriglyceridemia and are the preferred source of fat for enteral feeding after HTGP but there are no publications documenting this use.

Monitoring: Since the main source of calories is usually dextrose, frequent monitoring of plasma glucose is essential. The risk of hyperglycemia is higher in TPN. In patients receiving fat-free TPN for long duration, monitoring of triene/tetraene ratio is necessary in order to diagnose and correct essential fatty acid deficiency.

FOLLOW-UP

Oral Drugs Addressing Hypertriglyceridemia

As soon as oral intake is established, oral medications aimed at decreasing triglyceride levels are recommended. They include fibrates, omega 3 fatty acids, niacin, statins and pioglitazone, in that order. Combination therapy using drugs from these classes are usually necessary and sufficient (For additional details see chapter in Lipid and Lipoprotein section on Triglyceride Lowering Drugs). Newer drugs are or will be available but have not been tested in this context (lomitapide, volanesorsen, alipogene tiparvovec) Bariatric surgery is effective in patients with severe hypertriglyceridemia and morbid obesity.

Prevention of Recurrence

HTGP has a higher likelihood of recurrence than other forms of pancreatitis. Patients should be educated on the importance of compliance with drug therapy addressing hypertriglyceridemia. Long-term dietary modification in patients with hypertriglyceridemia should include restriction of dietary fat, simple carbohydrates and alcohol. Medium-chain triglycerides have been used successfully. In extreme cases, long term plasmapheresis has been performed. Patients should also avoid drugs associated with hypertriglyceridemia.

GUIDELINE

None applicable

REFERENCES

Al-Omran M, et al. *Enteral versus parenteral nutrition for acute pancreatitis.* Cochrane Database Syst Rev. 2010 Jan 20;(1). PMID:20091534

Cole RP. Heparin treatment for severe hypertriglyceridemia in diabetic ketoacidosis. Arch Intern Med. 2009 Aug 10;169(15):1439-41. PMID: 19667310

Scherer J.et al Issues in Hypertriglyceridemic Pancreatitis: An Update. J Clin Gastroenterol. 2014 Mar;48(3):195-203. PMID: 24172179

Stefanutti C. et al Severe hypertriglyceridemia-related acute pancreatitis Ther Apher Dial. 2013 Apr;17(2):130-7 PMID:23551669

Tsuang W, et al. Hypertriglyceridemic pancreatitis: presentation and management. Am J Gastroenterol. 2009 Apr;104(4):984-91. PMID:19293788