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Ian N. Monk

Wayne State University School of Medicine, inmonk@wayne.edu

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High-volume hemofiltration is not preferred for hypertriglyceridemia-induced pancreatitis

IAN N. MONK, Wayne State University School of Medicine, imonk@med.wayne.edu

ABSTRACT A critical appraisal and clinical application of He WH, Yu M, Zhu Y, et al. Emergent triglyceride-lowering therapy with early high-volume hemofiltration against low-molecular-weight heparin combined with insulin in hypertriglyceridemic pancreatitis: A prospective randomized controlled trial. *J Clin Gastroenterol.* 2016;50(9):772-778. doi: [10.1097/MCG.0000000000000552](https://doi.org/10.1097/MCG.0000000000000552).

Keywords: Pancreatitis, hypertriglyceridemia, insulin, heparin, plasmapheresis

Clinical Context

Our patient is a 23-year-old man who presented to the emergency department due to an acute episode of sharp epigastric pain. The patient complained of associated nausea but no vomiting. Physical exam was significant for exquisite tenderness in the epigastric area on palpation. Labs drawn in the emergency department revealed a lipase of 4084 units/L and triglycerides of 1014 mg/dL. The patient was diagnosed with hypertriglyceridemia-induced pancreatitis (HTGP) based on the clinical picture and lab findings. The patient was started on IV insulin at 8 units/hour and subcutaneous heparin at 5000 units/8 hours in the MICU. One consultant recommended the use of plasmapheresis as potential therapy for HTGP.

Clinical Question

Is plasmapheresis superior to insulin and heparin for the acute treatment of hypertriglyceridemia-induced pancreatitis?

Research Article

He WH, Yu M, Zhu Y, et al. Emergent triglyceride-lowering therapy with early high-volume hemofiltration against low-molecular-weight heparin combined with insulin in hypertriglyceridemic pancreatitis: A prospective randomized controlled trial. *J Clin Gastroenterol.* 2016;50(9):772-778. doi: [10.1097/MCG.0000000000000552](https://doi.org/10.1097/MCG.0000000000000552).

Related Literature

A literature review began by exploring the American College of Gastroenterology and American Gastroenterology Association websites to determine if there is a recommended treatment for patients with HTGP. This search did not yield any definitive guidelines from either group. The literature search continued with articles referenced on UpToDate® on the "Hypertriglyceridemia-induced acute pancreatitis" webpage regarding the treatment of this condition. Many of the articles concerning the various

IAN MONK is a 3rd year medical student at the Wayne State University School of Medicine.



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treatment strategies were case reports¹⁻⁶ or clinical reviews⁷, and no randomized controlled trials were referenced. The patients managed in these case reports had a wide variety of triglyceride levels (1000 mg/dL to >10000 mg/dL) and lipase levels (300 units/L to >7000 units/L) but most patients showed improvement with several different types of therapy and could be discharged from the hospital with no long-term morbidities. Three of the case reports used insulin and heparin therapy, two used plasma exchange therapy, and one used a combination of fish oil, insulin, and gemfibrozil. An observational cohort study⁸ referenced on UpToDate[®] examined the differences between heparin and citrate use in plasmapheresis therapy and found that heparin was associated with a higher mortality.

Further literature review was conducted on PubMed using the search terms “hypertriglyceridemia,” “pancreatitis,” and “treatment.” This search yielded a meta-analysis⁹ that analyzed thirty-eight studies with 1979 patients. This analysis found that plasmapheresis reduced concentrations of triglycerides by up to 85%, but that this did not affect morbidity or mortality.

The term “treatment” was changed to “insulin” in the PubMed review after exhausting a search for a randomized controlled trial. This change only revealed one prospective randomized controlled study regarding the management of hypertriglyceridemia-induced pancreatitis (HTGP) and, thus, this was the article chosen for critical appraisal. The He, et al. trial¹⁰ compared high-volume hemofiltration (HVHF) (a type of plasmapheresis) against low-molecular-weight-heparin (LMWH) combined with insulin in the treatment of HTGP. The major advantage of the He, et al. study is that it is the only randomized controlled clinical trial regarding HTGP treatment. It also directly compared the treatment that our patient received (insulin and heparin) with another (plasmapheresis) that is highly regarded as good as or better than insulin and heparin in treating HTGP.

Critical Appraisal

The study by He, et al. is a randomized controlled trial (N = 66) that seeks to compare the efficacy of the combination of LMWH and insulin versus HVHF in the early treatment of HTGP based on each treatment’s efficiency in lowering serum triglycerides, the clinical outcomes, adverse effects of the treatments, and the changes in APACHE II scores, serum C-reactive protein, and serum procalcitonin over the course of the treatments. The study falls under a level 2b evidence according to the Oxford Centre for Evidence-Based Medicine. The trial was conducted from August 2011 to October 2013 at the Department of Gastroenterology of The First Affiliated Hospital of Nanchang University in China. The study was self-funded (by The First Affiliated Hospital of Nanchang University) and it had no other sponsors. The authors of the article did not report any conflicts of interest. Of the 1160 patients that presented to the hospital and were admitted with a diagnosis of acute pancreatitis in the designated time period, 136 fulfilled the diagnostic criteria of HTGP. Patients were included in the study if they presented within 72 hours of the onset of their symptoms, were not pregnant, and agreed to participation in the study. The patients were randomly assigned to either the HVHF group (N = 32) or LMWH and insulin group (N = 34) (control), however neither the researchers nor the patients were blinded. While the patients would not be able to be blinded due to the functional differences in the technical aspects of the two treatments, the researchers analyzing the data could have been blinded. Patients in the HVHF group received hemofiltration as soon as possible and the hemofiltration was discontinued once the triglyceride level decreased to < 500 mg/dL. Patients in the control group received 4000 units of LMWH every 12 hours for 3 days and a micropump of insulin until blood glucose was controlled to a level between 140 to 200 mg/dL. Patient characteristics including age, sex, BMI, alcoholism, coexisting conditions, and triglyceride levels were similar between the groups.

Patients in the HVHF group had a higher incidence of persistent non-pancreatic organ failure but no statistically significant difference in local pancreatic complications, requirement of surgical intervention, or mortality. No significant differences existed between the two groups in triglyceride levels following treatment but the HVHF group did show a quicker initial drop in triglyceride levels. The number needed to harm (NNH) for the HVHF group concerning the non-pancreatic organ failure was calculated to be 15.5. HVHF treatment did not improve the length of stay in the hospital compared to the control and it was associated with an approximately 2-fold increase in hospital charges for patients in the group. To classify the severity of the pancreatitis, the authors used at least 2 SIRS criteria at presentation as a predictor of severe acute pancreatitis (SAP). The SIRS criteria has been demonstrated in other studies^{11,12} to be a good predictor of outcomes in patients who present with pancreatitis. There was no difference in the outcomes of SAP patients between the two study groups. The APACHE II disease classification system is a point-based method to evaluate the general severity of a disease and risk of death.¹³ The APACHE II scores, CRP levels, and PCT levels did not show statistically significant differences between the two treatment groups on days 1, 2, and 5 of treatment.



A significant strength of the He, et al. study is that it is a prospective, randomized controlled trial that directly assesses two different treatment modalities for HTGP. This is a first step toward defining what treatments are best for patients.

There are several flaws that must be considered with the He, et al. trial. Firstly, the patient population is small and as such, the conclusions reached must not be taken out of proportion. Larger, multicenter trials are necessary to fully assess the efficacy of HVHF and other types of plasmapheresis compared to insulin and LMWH. Secondly, the researchers were not blinded from the two different treatments. Therefore, intervention bias cannot be ruled out in this case. The authors openly address both flaws in the discussion section of the article.

A final point to consider is that the actual costs to patients for treatments may differ. HVHF will always cost more than LMWH and insulin due to the machinery necessary, the separate staff needed, etc. However, the twofold increase in cost associated with HVHF referenced in the article may not hold true in other places or situations and may be dependent on several factors.

Clinical Application

The study by He, et al. concluded that while HVHF can lower triglyceride levels more rapidly than LMWH and insulin, HVHF was not found to be superior in terms of clinical outcomes and costs to patients. There was also an increased statistically significant incidence of non-pancreatic organ failure associated with HVHF treatment. This study supports the use of an older, cheaper therapy, and applying these results, in spite of the small size of the study, would likely be beneficial. However, larger multicenter trials are necessary to draw more certain conclusions regarding the treatment of HTGP.

Our patient had HTGP and could have been included in this study based on the selection criteria. Plasmapheresis was not felt to be beneficial for this patient. He received a similar therapy to LMWH and insulin and responded more quickly and had a shorter hospital stay than average when compared to patients in the He, et al. trial. It is important to note that his triglyceride levels were significantly lower than average in the LMWH and insulin group (1014 and 1971 mg/dL, respectively). Ultimately, he was transferred to the general medicine floor 24 hours later upon clinical improvement and decrease of his triglycerides to <500 mg/dL. The patient was discharged one day after being transferred to the medicine service and he was scheduled for a follow up appointment with the gastroenterology service for prevention of future episodes of acute pancreatitis and genetic testing for disorders of lipid metabolism.

Take-home points:

1. Treatment with HVHF was not shown to improve clinical outcomes in patients diagnosed with HTGP versus treatment with LMWH and insulin, but it is more expensive,
2. there is a great need for clinical trials investigating the treatment of HTGP, and
3. a thorough evaluation of a patient's clinical outcomes with different modalities (SIRS criteria, APACHE II score, CRP, PCT, morbidities, and mortality in this study) is beneficial in evaluation of treatment efficacy.

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