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Review article

The role of apheresis in hypertriglyceridemia-induced acute pancreatitis: A systematic review

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ABSTRACT

Background: Mostly published as case reports or series, the role of apheresis in hypertriglyceridemia (HTG)-related acute pancreatitis (AP) remains unclear. We performed a systematic review of available literature on this topic with specific focus on disease severity.
Methods: A search of electronic databases (PubMed, EMBASE, Cochrane) and gray literature yielded 5020 articles of which 74 met criteria for inclusion (301 unique patients). Relevant data were abstracted from full manuscripts and analyzed.
Results: Most patients were young (mean age 37.9 ± 10.4 years) and male (71.5%). About two-thirds (69.7%) received apheresis within 48 h and most required only 1 or 2 sessions (84.4%). Apheresis resulted in an average reduction of serum TG by 85.4% ($p < 0.001$). There was high variability in reporting the presence of and criteria to define severe AP (reported 221/301, 73.4%; present 85/221, 38.5%) or organ failure (reported 104/301, 34.6%; present 52/104, 50.0%). Improvement was reported in the majority of patients (reported 144/301, 47.8%, present 136/144, 94.4%) mainly by clinical symptoms or laboratory tests. Overall mortality was 7.1% (21/294) which increased to 11.8% (10/85) with severe AP and 19.2% (10/52) with organ failure.
Conclusions: Apheresis effectively reduces serum TG levels. However, due to uncontrolled data, reporting bias and lack of a comparison group, definitive conclusions on the efficacy of apheresis in reducing AP severity cannot be made. We propose which patients may be best suitable for apheresis, type of studies needed and outcome measures to be studied in order to provide empiric data on the role of apheresis in HTG-related AP.

Introduction

Hypertriglyceridemia (HTG) is a well-recognized cause of acute pancreatitis (AP). A serum triglyceride (TG) level of ≥1000 mg/dl is believed to initiate an attack of AP in some individuals. Serum TG levels fall rapidly after admission as a result of discontinuation of dietary supply from fasting and a reduction of hepatic very low density lipoprotein output due to infusion of hypocaloric intravenous fluids. Although suggested to be more severe than AP from other etiologies, definitive data on the role of HTG on AP severity is lacking due to small sample sizes and poorly defined outcomes [1].

The severity of AP is related to host factors such as age, truncal obesity, lifestyle habits such as alcohol intake, and, local and systemic response to pancreatic injury [2]. In recent studies, unsaturated fatty acids generated from lipolysis of fat within and surrounding the pancreas by pancreatic release of enzymes in AP, were noted to drive local and systemic complications [3,4]. The amount of both intrapancreatic [3] and visceral fat [6,7] have been positively correlated with obesity, which possibly explains the increased risk of severe AP in obese patients [5,8].

Abbreviations: AP, acute pancreatitis; APACHE, acute physiology and chronic health evaluation; BMI, body mass index; CT, computed tomography; CTSI, computed tomography severity index; DM, diabetes mellitus; HTG, hypertriglyceridemia; ICU, intensive care unit; LDL, low density lipoprotein; OF, organ failure; SIRS, systemic inflammatory response syndrome; TG, triglyceride.

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Most patients with HTG-induced pancreatitis receive standard treatment with pancreas rest, analgesia, supportive care for organ failure, and management directed towards local complications. TG themselves are not toxic, but serve as a source of unsaturated fatty acids. Increased production of unsaturated fatty acids from local and systemic activity of pancreatic lipase therefore may contribute to severity of AP. Hence, excess TG from the plasma can be removed with HTG-induced pancreatitis by a variety of techniques (apheresis, plasmapheresis, plasma exchange, low-density lipoprotein [LDL] apheresis) with a goal of reducing disease severity.

Over the years, numerous, mainly retrospective, case reports or small series have reported on the use of apheresis in patients with HTG-related AP. However, due to variability in patient selection and reporting of data on severity and efficacy, the role of removing excess TG from the serum in these patients remains unclear. No guidelines exist on which patients are the optimal candidates for such a treatment, and its beneficial effect on the severity of AP. In its recent guidelines, the American Society of Apheresis gave apheresis a weak recommendation as a treatment modality in AP [9].

The aim of this systematic review was to critically review the available literature on this topic with a specific focus on the role of apheresis in reducing AP severity.

Methods

Terminology

This review uses the term “apheresis” to describe all techniques (apheresis, plasmapheresis, plasma exchange, pheresis, LDL apheresis) used to remove excess TG from the serum.

Literature review and study selection

Two health sciences librarians (AK, RT) in collaboration with study author (BC) searched PubMed (1946-current), EMBASE (1947-current) and the Cochrane Database of Systematic Reviews (1995-current) databases. Gray literature search included BIOSIS Previews (1926-current), NIH RePORTER (2015 fiscal year), OAIster (dates not applicable), WHO *International Clinical Trials Registry Platform (2004-current)*, ClinicalTrials.gov (2000-current) and ProQuest Digital Dissertations (1861-current). A PubMed search query was developed combining three concepts: Plasmapheresis, Hyperlipidemia and Pancreatitis (Supplemental Appendix 1). The PubMed query was then adapted for use in the remaining databases. All databases were searched for the time period January 1, 1980–August 29, 2014, with no other limits placed on the searches. Additional articles were identified by examination of reference lists from key articles.

For inclusion in this review, an article should have been published in English language, included patients reported to have confirmed AP, identified HTG as the etiology of AP, and utilized apheresis as a treatment modality. Articles were excluded if apheresis was used as a preventative measure rather than for treatment. If more than one publication from the same authors was identified, the articles were cross-examined for replicated patient data and if an overlap existed, only unique patient-specific data was recorded and the duplicate information was excluded.

Data abstraction

Manuscripts meeting the inclusion criteria were carefully examined and data were systematically extracted by first author (BC) under supervision of the senior author with secondary review and discussion as needed on documents and data to potentially be abstracted and included (DY). Details of each study including first author, year published, country where study was conducted, study design, and number of patients were recorded. Study design was simplified to case reports (single patient) or case series (two or more patients). Patient specific information when available was recorded for age, sex, race, type of HTG (Fredrickson classification) [10], secondary risk factors (body mass index [BMI], alcohol intake, diabetes mellitus [DM], pregnancy, medications), history of prior AP, serum TG and cholesterol levels, intensive care unit [ICU] admission, apheresis details, disease severity, adjunct treatment used (insulin infusion, heparin infusion, or medications such as fibrate, statin, or niacin if started prior to or at the same time as apheresis) and disease related outcomes. Obesity was defined according to World Health Organization criteria of BMI $\geq$30 kg/m^2 and overweight as BMI 25–30 kg/m^2.

Data specific to apheresis was recorded for the type of fluid replacement used (albumin [regardless of concentration] or plasma, and in case of concurrent use, that fluid which was used more frequently was recorded), anticoagulant utilized (citrate or heparin, and if both were used, continuous infusion or anticoagulant used for greater period of time was recorded), timing of apheresis initiation, and number of sessions. Information was recorded for the first available serum TG level, total cholesterol level, and their levels after apheresis was completed. Unit conversions for TG and cholesterol levels were performed using an online lipid conversion calculator (http://www.onlineconversion.com/cholesterol.htm).

Outcomes were divided into laboratory test-oriented (lipid levels) and patient-oriented (severity parameters, mortality, length of stay, complications). Severity data included clinical setting (ICU or medical floor); AP severity criteria (Ranson, Acute Physiology and Chronic Health Evaluation [APACHE-II], computed tomography [CT] severity index, Balthazar, Japanese, Glasgow); organ failure: presence, duration (transient <48 h, persistent $\geq$48 h), and organs affected. Organ failure was recorded if laboratory and clinical information were available by the following definitions: respiratory – PaO_2 <60 mmHg or mechanical ventilation requirement; cardiovascular – systolic blood pressure <90 mmHg or diastolic blood pressure <60 mmHg or use of vasopressors; renal – increase in serum creatinine $\geq$0.3 mg/dl from baseline or $\geq$50% increase from baseline or <0.5 ml/kg/hour of urine output or requirement of hemodialysis. Other organ failure was dependent on reporting by study authors.

Episodes of AP were recorded as categorically severe if authors specifically mentioned the term “severe.” Severity criteria reported were then used to verify this description when possible by calculating criteria-specific scores. The cutoffs used to define severity included Ranson $\geq$3, APACHE-II $\geq$ 8, CTSI >5, Balthazar D-E, Japanese $\geq$2, and Glasgow $\geq$3 [11–15].

Efficacy information comprised improvement in clinical symptoms (e.g. abdominal pain, nausea, vomiting), lipid levels and other laboratory tests, severity index score, organ failure, radiographic abnormalities, length of stay and mortality. Local complications such as necrosis, fluid collections, pseudocysts, and any procedures required for treatment (drainage, laparotomy) when reported were recorded.

Analysis

A descriptive analysis was performed. Available information on individual patients was recorded and summarized as mean ± standard deviation or median and range for continuous variables and as proportions for categorical variables. Univariate comparisons were performed using student's t-test or Mann Whitney-U test for continuous variables and chi-squared or Fischer's exact test for categorical variables as appropriate using

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