Digestive Diseases

Pancreas: Research Article

Dig Dis 2023;41:647–655
DOI: 10.1159/000529975

Received: June 7, 2022
Accepted: February 20, 2023
Published online: March 4, 2023

Therapeutic Plasma Exchange in ICU Patients with Acute Hypertriglyceridemia-Induced Pancreatitis Improves Patient Outcomes

Lea U. Krauß[a] Andreas-M. Brosig[b] Sophie Schlosser[a] Vlad Pavel[a] Alexander Mehrl[a] Karsten Gülow[a] Arne Kandulski[a] Martina Müller[a] Stephan Schmid[a]

[a]Department of Internal Medicine I, Gastroenterology, Hepatology, Endocrinology, Rheumatology and Infectious diseases, University Hospital Regensburg, Regensburg, Germany; [b]Institute of Clinical Chemistry and Laboratory Medicine, Transfusion Medicine, University Hospital Regensburg, Regensburg, Germany

Keywords
Acute pancreatitis · Hypertriglyceridemia · Therapeutic plasma exchange · Plasmapheresis · Intensive care medicine

Abstract
Background: Acute severe pancreatitis is associated with high morbidity and mortality. Hypertriglyceridemia is the third most common cause of acute pancreatitis and higher triglyceride levels increase the risk for severe acute pancreatitis. Plasma exchange is an effective treatment method to lower triglycerides. Our study aimed to investigate the efficiency of plasma exchange as a treatment option for acute hypertriglyceridemia-induced pancreatitis (HTGP), the impact on mortality assessed by the SOFA, SAPS II, BISAP Score, Ranson's, and Glasgow-Imrie Criteria, as well as the overall length of stay in hospital and ICU. ***Methods:*** In this retrospective single-center cohort study, triglycerides before and after plasma exchange were compared. SOFA and SAPS II were taken on ICU admission and at discharge. To further characterize the patient cohort, BISAP Score (on admission), Ranson's Criteria (on admission and after 48 h), and the Glasgow-Imrie Criteria (48 h after admission) were calculated. ***Results:*** The study included 11 patients (91% male; median age 45 years). Triglycerides were reduced from 4,266 ± 3,560.6 to 842 ± 575.9 mg/dL during plasmapheresis ($p < 0.001$). The median ICU length of stay was 3 ± 4.2 days. In-hospital mortality was 0%. The SOFA score was significantly reduced from 4 ± 3.4 points on admission to 2 ± 2.1 points at discharge ($p = 0.017$). Triglycerides and cholesterol decreased from 3,126 ± 3,665 to 531 ± 273 mg/dL ($p = 0.003$) and from 438 ± 137.9 to 222 ± 59.5 mg/dL ($p = 0.028$), respectively. The BISAP Score on admission was 3 ± 0.5 points, Ranson's Criteria were 3 ± 1.5 points (48 h after admission, cumulative), and Glasgow-Imrie Criteria 3 ± 1.3 points (48 h after admission). ***Conclusion:*** Plasmapheresis is an efficient and safe treatment method for ICU patients with acute HTGP and significantly reduces triglycerides. Furthermore, plasmapheresis significantly improves the clinical outcomes of patients with HTGP.

Introduction

Acute pancreatitis is a common gastrointestinal disorder with significant associated morbidity and mortality [1, 2]. In

karger@karger.com
www.karger.com/ddi

Correspondence to:
Stephan Schmid, stephan.schmid@ukr.de

Western countries, the incidence has been rising over the last 50 years [3]. Hypertriglyceridemia (HTG) is the third most common cause of acute pancreatitis [4]. Affected patients usually present with preexisting dyslipidemia and often a secondary condition such as uncontrolled diabetes or alcohol abuse [5]. Severe and very severe HTG (>1,000 mg/dL) is associated with a significant risk for acute pancreatitis [6, 7]. Elevated triglyceride levels multiply the rates of severe acute pancreatitis and are associated with the prognosis of the disease [8]. Although the pathomechanisms are not fully understood, the hydrolysis of triglycerides into free fatty acids by pancreatic lipases with a toxic effect on acinar cells and pancreatic endothelium plays an important role in lipotoxicity and associated inflammation [9, 10]. Early recognition and treatment initiation of hypertriglyceridemia-induced pancreatitis (HTGP) can reduce complications and prevent further episodes. The general management of acute pancreatitis primarily includes fluid resuscitation and early enteral nutrition as well as relief of often severe visceral pain [4, 11, 12]. In addition, plasma exchange is an effective and fast treatment option to lower the serum level of triglycerides [9]. An additional treatment option is the application of insulin. A prospective randomized controlled trial of 66 patients with hypertriglyceridemic pancreatitis showed that early high-volume hemofiltration was superior to combination therapy with low-molecular-weight heparin and insulin [9]. However, no differences regarding mortality and duration of hospitalization were observed in this study. In general, randomized controlled trials comparing insulin therapy and plasmapheresis in the treatment of acute HTGP are lacking. Currently, the trial "intensive insulin therapy versus plasmapheresis in the management of hypertriglyceridemia-induced acute pancreatitis" (Bi-TPAI trial) is comparing those two treatment regimens with the primary endpoint of lowering triglycerides and – among others – the secondary endpoints intensive care unit (ICU) and hospital length of stay as well as mortality. The study is currently recruiting [13]. The role of apheresis in HTGP, particularly in lowering triglyceride levels, has been investigated before [10, 14–16]. However, data on mortality are still limited. The aims of this study were (1) to evaluate the efficiency of early therapeutic plasma exchange, i.e., plasmapheresis, as a treatment option for acute HTGP, (2) to analyze the impact of HTGP on mortality assessed by the Sepsis-related Organ Failure Assessment (SOFA) [17], new Simplified Acute Physiology Score (SAPS II) [18], Revised Atlanta Classification [19], BISAP (Bedside Index for Severity in Acute Pancreatitis) Score [20], Ranson's [21], and Glasgow-Imrie Criteria [22], and (3) to determine the overall length of intensive care stay and hospital stay.

Materials and Methods

Study Design and Patient Characteristics

To investigate plasmapheresis as a therapeutic option in acute HTGP and its impact on hospital length of stay as well as mortality, a retrospective single-center cohort study was conducted in our medical ICU of the Department of Internal Medicine I at the University Hospital of Regensburg between 2016 and 2022. The study was approved by the Ethics Committee of the University of Regensburg, Regensburg, Germany (trial registration number 22-2935-104). The study included 11 patients treated in the ICU for acute HTGP. Plasma exchange was performed with a cell separator Spectra Optia (Terumo BCT, Lakewood, CO), using only therapeutic plasma as the exchange fluid and acid citrate dextrose for anticoagulation. In general, the goal was to exchange at least 1.5 times the patient's total plasma volume. A triglyceride level of 1,000 mg/dL was set as the target value for plasma exchange. A second exchange was performed if the target value was exceeded or at individual clinical discretion.

Clinical and Laboratory Data

To evaluate the clinical outcomes, we calculated the SOFA score and the SAPS II score on admission and at discharge as well as Revised Atlanta Classification, BISAP Score, Ranson's Criteria, Glasgow-Imrie Criteria, and length of stay in the hospital and ICU. To determine the length of stay, each day started was counted as a full day.

Demographic data, i.e., age and gender, were collected. Laboratory data were retrieved from medical records on admission and at discharge: lipase in U/L, C-reactive protein (CRP) in mg/L, procalcitonin (PCT) in ng/mL, creatinine in mg/dL, serum urea in mg/dL (for SAPS II score converted to mmol/L [serum urea mg/dL/6,006]), triglycerides in mg/dL, cholesterol in mg/dL, and calcium in mmol/L. Data of plasmapheresis protocol including triglyceride levels before and after apheresis were collected. In 3 patients, plasmapheresis was performed twice. Therefore, data from 14 therapy protocols were included. In addition, the time from onset of symptoms to plasmapheresis was assessed. Previous diseases and discharge status were also documented.

The SOFA score predicts ICU mortality based on laboratory results and clinical data. For each patient, the "worst value" in a 24-h period was calculated at admission and discharge. The "worst" measurement was defined as the measure that correlated to the highest number of points. The following parameters were included: paO2 in mm Hg, FiO2 in % (room air = 21%; nasal cannula 1 L/min = 25%, 2 L/min = 29%, 3 L/min = 33%, 4 L/min = 37%, 5 L/min = 41%, ≥6 L/min = 45%; high flow = 30–100%), mechanical ventilation (yes/no), platelets × 10^3/μL (≥150 = 0; 100–149 = 1; 50–99 = 2; 20–49 = 3; <20 = 4 points), Glasgow Coma Scale (GCS; 15 = 0; 13-14 = 1; 10–12 = 2; 6–9 = 3; <6 = 4 points), bilirubin in mg/dL (<1.2 = 0; 1.2–1.9 = 1; 2.0–5.9 = 2; 6.0–11.9 = 3; ≥12.0 = 4 points), mean arterial pressure or administration of vasoactive agents required (no hypertension = 0; mean arterial pressure <70 mm Hg = 1; dopamine ≤5 μg/kg/min or dobutamine = 2; dopamine >5 μg/kg/min, epinephrine ≤0.1 μg/kg/min or norepinephrine ≤0.1 μg/kg/min = 3; dopamine >15 μg/kg/min, epinephrine >0.1 μg/kg/min or norepinephrine >0.1 μg/kg/min = 4 points), and creatinine in mg/dL (<1.2 = 0; 1.2–1.9 = 1, 2.0–3.4 = 2; 3.5–4.9 = 3; ≥5.0 = 4 points). If only venous pO2 was available, paO2 was defined as "90 mm Hg."

The SAPS II score estimates mortality of ICU patients based on laboratory results and clinical data. Again, the "worst" value within a 24-h period at admission and discharge was calculated for each patient. The following data were integrated: age in years (<40 = 0; 40–59 = 7; 60–69 = 12; 70–74 = 15; 75–79 = 16; ≥80 = 18 points), heart rate (<40 = 11; 40–69 = 2; 70–119 = 0; 120–159 = 4; ≥160 = 7 points), systolic blood pressure in mm Hg (<70 = 13; 70–99 = 5; 100–199 = 0; ≥200 = 2 points), temperature ≥39°C (yes/no), GCS (14–15 = 0; 11–13 = 5; 9–10 = 7; 6–8 = 13; <6 = 26 points), paO2/FiO2 if on mechanical ventilation or CPAP in mm Hg/% (<100 = 11; 100–199 = 9; ≥200 = 6; not on mechanical ventilation in the last 24 h = 0), serum urea in mmol/L (<10 = 0; 10–29.6 = 6; ≥30 = 10 points), urine output in mL/24 h (<500 = 11; 500–999 = 4; ≥1,000 = 0 points), sodium in mmol/L (<125 = 5; 125–144 = 0; ≥145 = 1 points), potassium in mmol/L (<3.0 = 3; 3.0–4.9 = 0; ≥5.0 = 3 points), bicarbonate in mmol/L (<15 = 6; 15–19 = 3; ≥20 = 0 points), bilirubin in mg/dL (<4.0 = 0; 4.0–5.9 = 4; ≥6.0 = 9 points), white blood cells × 10^3/mm^3 (<1.0 = 12; 1.0–19.9 = 0; ≥20.0 = 3 points), chronic disease (metastatic cancer = 9; hematologic malignancy = 10; AIDS = 17; none = 0 points), type of admission (scheduled surgical = 0; medical = 6; unscheduled surgical = 8 points).

The severity of acute pancreatitis was classified according to the Revised Atlanta Classification [19]. For a precise assessment, the BISAP Score was calculated on admission [20]. With this 5-point scoring system, patients can be classified within the first 24 h of admission into distinct groups of mortality. Mortality rises with BISAP Scores ≥3 (mortality 5–20%). Therefore, BISAP Scores of ≥3 points identify patients at a high risk for unfavorable outcomes.

Ranson's Criteria [21] is a scoring system for predicting the prognosis and mortality risk of patients with acute pancreatitis, based on initial and 48-h laboratory values, as well as age and fluid requirements. The following parameters were collected at admission: white blood cell >16k (1 point), age >55 years (1 point), glucose >200 mg/dL (1 point), AST >250 U/L (1 point), and LDH >350 U/L (1 point). Forty-eight hours after admission, the following parameters were additionally obtained (worst value within 48 h): hematocrit drop >10% (1 point), serum urea increase >10.8 mg/dL (1 point), calcium <2 mmol/L (1 point), paO2 < 60 mm Hg (1 point), base deficit >4 mg/dL (1 point), fluid needs >6 L (1 point). A total score of ≥3 points correlates with a severe pancreatitis.

The Glasgow-Imrie Criteria were calculated 48 h after admission [22]. Comprising a range of 0–8 points, the Glasgow-Imrie Criteria represent a reliable tool to identify a group of patients at high risk for major complications and mortality. PaO_2, age, white blood count, calcium, blood urea nitrogen, LDH, albumin, and glucose are included in the score. Glasgow-Imrie Criteria ≥3 points identify patients with a high risk of severe pancreatitis.

Statistical Analyses

Data were obtained from MetaVision (iMDsoft) and SAP Software and analyzed with Microsoft Excel 2016. Quantitative data were expressed as median or mean ± standard deviation and range, and categorical variables were expressed as absolute quantities and percentages. SOFA, SAPS II, BISAP Score, Ranson's, and Glasgow-Imrie Criteria were calculated with MDCalc®. IBM SPSS Statistics ® (version 28.0.1.1.) was used for comparative tests. The triglyceride levels before and after plasmapheresis were compared with paired-sample *t* test and presented in a line graph. Laboratory data, SOFA and SAPS II scores were compared between ICU admission and ICU discharge with Wilcoxon test. The significance level was set to a *p* value <0.05.

Results

Characteristics of the Study Population

Between February 2016 and March 2022, a total of 11 patients with acute hypertriglyceridemic pancreatitis were admitted to the ICU. The patients were predominantly male and had a median age of 45 years. One-third of the study population was diagnosed with hyperlipidemia or HTG prior to admission. Three patients had a past medical history of recurrent pancreatitis. Two patients had diabetes mellitus type 2 and 1 patient had obesity. Clinical characteristics are listed in Table 1.

The median length of stay in the ICU was 3 ± 4.2 days; the overall hospital stay was 10 ± 23.3 days. From the onset of symptoms of acute pancreatitis, no more than 2 days elapsed until the initiation of plasmapheresis. None of the patients died during the hospital stay. Six patients were discharged, whereas 5 patients were transferred to the general ward or an external hospital.

Nine patients had moderately severe acute pancreatitis, and two had severe acute pancreatitis, according to the Revised Atlanta Classification. On admission, the median BISAP Score was 3 ± 0.5 points. Patients with a BISAP Score of ≥3 points have a higher mortality of 5–20% [20]. Of note, in our cohort, all patients survived and had an excellent outcome after a short stay at the ICU. 48 h after admission, the median Ranson's Criteria added up to cumulative 3 ± 1.5 points, and the median Glasgow-Imrie Criteria yielded 3 ± 1.3 points. Therefore, analyses of Ranson's and Glasgow-Imrie Criteria again highlight that the patients included in our study were at a high risk of severe pancreatitis.

Data of Plasmapheresis

Plasmapheresis lasted approximately 2.17 h and was performed with citrate anticoagulation. Within this time, triglycerides decreased from 4,266 ± to 842 ± 575.9 mg/dL (shown in Fig. 1). The delta value of triglycerides showed a mean decrease of 75.8 ± 9.3%. The one-tailed paired sample *t* test showed a significant decrease with a *p* value <0.001. Consumed plasma during the apheresis was 5,176 ± 1,112.3 mL. Details are summarized in Table 2.

Table 1. Clinical characteristics of the study population

Characteristics	Total study population (n = 11)
Age: median±SD [range], years	45±9.8 [30–64]
Sex, *n* (%)	
Female	1 (9)
Male	10 (91)
ICU stay: median±SD [range], days	3±4.2 [2–16]
Overall hospital stay: median±SD [range], days	10±23.3 [2–84]
Preexisting diseases, *n* (%)	
Recurrent/chronic pancreatitis	3 (27.3)
Hyperlipidemia/HTG	4 (36.4)
Diabetes mellitus type 2	2 (18.2)
Obesity	1 (9.1)
Alcohol abuse	6 (54.5)
Nicotine abuse	3 (27.3)
Hyperuricemia	2 (18.2)
Steatosis hepatitis	2 (18.2)
Arterial hypertension	1 (9.1)
Chronic cholecystitis	1 (9.1)
Carcinoma in medical history	1 (9.1)
Ranson's Criteria: median±SD [range], points	
On admission	1±0.6 [0–2]
48 h after admission (cumulative)	3±1.5 [0–6]
BISAP Score: median±SD [range], points	
On admission	3±0.5 [2–3]
Glasgow-Imrie Criteria: median±SD [range], points	
48 h after admission	3±1.3 [1–4]
Time from onset of symptoms to plasmapheresis: median±SD [range], points	2±1.1 [1–4]
Discharge status, *n* (%)	
Outpatient	6 (54.6)
Transfer to general ward	2 (18.2)
Transfer to external hospital	3 (27.3)

Ranson's Criteria: range on admission: 0–5 points; range 48 h after admission: 0–11 points (cumulative); BISAP, Bedside Index for Severity in Acute Pancreatitis: range 0–5 points; Glasgow-Imrie Criteria: range 0–8 points.

Clinical and Laboratory Data on Admission and at Discharge

Data are shown in Table 3. The SOFA score was calculated with 4 ± 3.4 points on ICU admission and 2 ± 2.1 points at ICU discharge (p = 0.017). As calculated by the SOFA score, mortality risk could significantly be reduced from 36.1% to 5.4% during the ICU stay. One of the patients displayed a considerably higher SOFA score on admission compared to the other patients (12 points) but was discharged with a SOFA score of 2 points, which was in line with the median SOFA at discharge.

The SAPS II score summed up to 22 ± 6.4 points on ICU admission and 17 ± 6.6 points at ICU discharge (p = 0.058). This corresponds to a reduction of in-hospital mortality from 4.7% to 2.6%. The inflammation markers CRP and PCT decreased from 121 ± 181.2 to 100 ± 107.4 mg/dL (p = 0.131) and from 0.44 ± 1.11 to 0.15 ± 0.58 ng/mL (p = 0.43), respectively. Serum calcium increased significantly from 1.92 ± 0.34 to 2.18 ± 0.29 mmol/L (p = 0.008). Triglycerides and cholesterol dropped significantly from 3,126 ± 3,665 to 531 ± 273 mg/dL (p = 0.003) and from 438 ± 137.9 to 222 ± 59.5 mg/dL (p = 0.028), respectively. Lipase (p = 0.068), creatinine (p = 0.374), and serum urea (p = 0.888) showed no significant differences between ICU admission and discharge.

Discussion

This is one of the few studies that investigated the effect of plasma exchange on serum triglyceride levels in ICU patients with acute HTGP and its impact on mortality. As previous studies have shown, the patients admitted with

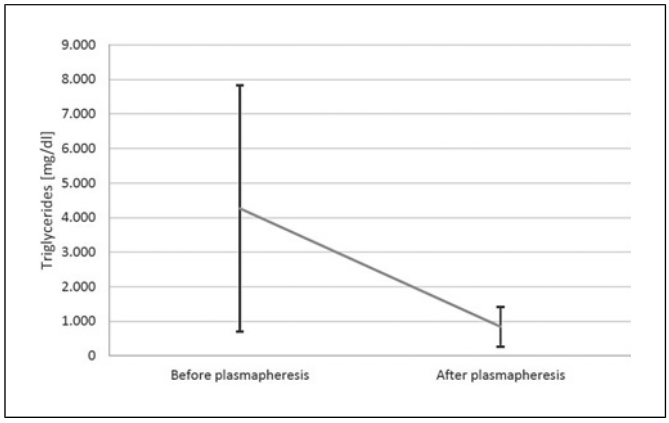

Fig. 1. Reduction of triglycerides during plasmapheresis. 3 of 11 patients completed plasmapheresis twice (n = 14). Data are shown as mean ± standard deviation. p value <0.001 in one-tailed paired-sample t test.

HTGP often had preexisting underlying co-morbidities such as dyslipidemia, diabetes mellitus, obesity, and alcohol abuse that probably contributed to the development of the disease [5, 23, 24]. Epidemiological studies show an increase in the rate of acute pancreatitis linear to an increase in triglycerides.

A small group of patients with HTGP has rare hereditary metabolic defects, comprising lipoprotein lipase deficiency, and hyperlipoproteinemia types I, IV, and V, according to Frederickson [25]. The antisense oligonucleotide volanesorsen significantly lowered triglyceride levels in patients with familial chylomicronemia syndrome in a randomized trial and reduces the rate of triglyceride-induced pancreatitis in familial chylomicronemia by approximately 30% [7, 26]. So far, this medical treatment is only available for this specific subgroup of patients with HTGP. In our study, no patient would have qualified for medical treatment. Therefore, all patients included in our study underwent therapeutic plasma exchange.

Approximately one-third of our study population had recurrent or chronic pancreatitis. Among these patients, two had a known dyslipidemia and one had a history of alcohol abuse. For chronic pancreatitis, excessive alcohol consumption is the most common risk factor [27, 28]. Most of our patients were male (91% of the study population). This observation is in accordance with a systematic review by Click et al. [14], who reported that 71.5% of 301 patients with acute pancreatitis were male. This may be related to a higher incidence of metabolic syndrome [29] and, in particular, alcohol-related HTG in the male gender [30, 31]. Moreover, they demonstrated that triglycerides were effectively reduced by plasma exchange [14], as did several other studies [10, 32–34]. These findings are comparable to the results of our study. We have shown that there is a significant reduction in triglycerides during plasmapheresis. In addition to an effective reduction of triglycerides, Gubensek et al. [10] reported that the use of citrate anticoagulation during plasma exchange was associated with reduced mortality. The overall in-hospital mortality was 5%. In the citrate group, it was 1%, whereas in the heparin group it was 11%. In our study, we did only use citrate anticoagulation and none of the patients died during the hospital stay. In our study, plasma exchange with citrate anticoagulation led to a significant reduction in mortality in patients with acute HTGP. In contrast, another study comparing the overall mortality and morbidity of HTGP treated with plasma exchange versus medical treatment found no significant difference in the outcome, even if severe cases calculated by Ranson's Criteria were analyzed separately [35]. Another study comparing high-volume hemofiltration with low-molecular-weight heparin in combination with insulin in a prospective randomized controlled trial demonstrated that hemofiltration lowered triglyceride levels more efficiently but was not superior in terms of clinical outcomes such as mortality and duration of hospitalization [9].

To predict mortality, previous studies often used the APACHE II score [9, 35]. In a study with 10 patients with HTGP, the median APACHE II decreased by 3% after therapeutic plasma exchange. However, the difference was not significant [15]. In a large retrospective cohort analysis, SOFA, qSOFA, and SIRS criteria were evaluated for their prognostic accuracy for in-hospital mortality in critically ill adult ICU patients. In this comparison, the SOFA score had a significantly greater prognostic accuracy than the other two scores [36]. For assessment of ICU patients, SOFA is an established score, whereas qSOFA represents the simplified version with fewer parameters to be included. By combining the qSOFA with the laboratory parameters blood urea nitrogen and CRP (emergency room assessment of acute pancreatitis), the authors of another cohort study reported an outstanding prognostic validity for multiorgan dysfunction and mortality in patients with acute severe pancreatitis [37]. A comparison of APACHE II and SOFA in critically ill patients in a cross-sectional study found a comparable sensitivity and specificity between those two scores [38].

In our study, we used SOFA, SAPS II, BISAP Score, Ranson's, and Glasgow-Imrie Criteria. Based on these scoring systems, we were able to show that the risk of death during the stay in the ICU was significantly reduced

Table 2. Data of plasmapheresis

Data of plasmapheresis protocol	Total study population (n = 14)
Height: median±SD [range], cm	171±3.7 [165–180]
Weight: median±SD [range], kg	79.5±15.8 [65–110]
Patient blood volume: median±SD [range], mL	4,996±626.6 [4,022–6,285]
Patient plasma volume: median±SD [range], mL	3,267±285.3 [2,735–3,708]
Hematocrit: median±SD [range], %	33.5±5.0 [30–45]
Inlet volume: median±SD [range], mL	10,163±3,085.2 [5,892–15,883]
Outlet plasma volume: median±SD [range], mL	5,253±1,068.1 [3,328–6,906]
Consumed plasma: median±SD [range], mL	5,176±1,112.3 [3,218–6,709]
Ratio of consumed and patient plasma: median±SD [range]	1.65±0.3 [1.0–2.0]
Duration: median±SD [range], min	130±30.8 [77–177]
Average inlet speed: median±SD [range], mL/min	84.7±12.2 [60.3–101.7]
Average plasma outlet speed: median±SD [range], mL/min	39.9±5.6 [32.4–47.9]
Plasma rate: median±SD [range], %	78.1±7.6 [60.5–89.7]
Triglycerides: mean±SD [range]	
Before plasmapheresis, mg/dL	4,266±3,560.6 [685–10,777]
After plasmapheresis, mg/dL	842±575.9 [171–2,006]
Delta value, %	75.8±9.3 [58.2–92.2]*

Analysis includes 11 patients; 3 patients completed plasmapheresis twice (n = 14).
*$p < 0.001$ in one-tailed paired-sample t test.

Table 3. Clinical and laboratory data on admission and at discharge

Clinical Scores and laboratory data	On admission (n = 11)	At discharge (n = 11)	p value
SOFA: median±SD [range], points	4±3.4 [0–12]	2±2.1 [0–7]	0.017
SAPS II: median±SD [range], points	22±6.4 [16–36]	17±6.6 [7–27]	0.058
Lipase: median±SD [range], U/L	1,106±2,448 [68–6,887]	2,093±1,375 [58–3,093]	0.068
CRP: median±SD [range], mg/L	121±181.2 [5.6–480]	100±107.4 [14.2–389]	0.131
PCT: median±SD [range], ng/mL	0.44±1.11 [0.16–3.21]	0.15±0.58 [0.09–1.46]	0.043
Creatinine: median±SD [range], mg/dL	0.72±0.18 [0.38–1.02]	0.73±0.17 [0.57–1.13]	0.374
Serum urea: median±SD [range], mg/dL	16±11.6 [9–45]	22±11.4 [7–45]	0.888
Triglycerides: median±SD [range], mg/dL	3,126±3,665 [1,038–10,777]	531±273 [171–1,116]	0.003
Cholesterol: median±SD [range], mg/dL	438±137.9 [262–703]	222±59.5 [161–330]	0.028
Calcium: median±SD [range], mmol/L	1.92±0.34 [1.18–2.32]	2.18±0.29 [1.58–2.64]	0.008

SOFA, Sepsis-related Organ Failure Assessment (predicts ICU mortality based on laboratory results and clinical data); SAPS II, new Simplified Acute Physiology Score (estimates mortality in ICU patients); CRP, C-reactive protein; PCT, procalcitonin.

by plasma exchange. Of clinical relevance, all the patients included in our study suffered from moderate to severe acute pancreatitis and following therapeutic plasma exchange had an excellent outcome, all patients survived. This highlights that plasmapheresis is a valuable therapeutic option for patients with HTGP.

The SOFA score decreased significantly between ICU admission and ICU discharge, whereas the difference for SAPS II was not significant. Therefore, SOFA might be a more useful score to predict mortality in patients with acute HTGP.

In our study population, HTG was accompanied by high cholesterol levels and plasmapheresis also significantly reduced cholesterol levels. These results correlate well with previous studies in patients with hyperlipidemia and hypercholesterinemia. In patients with severe hyperlipidemia refractory to diet and lipid-lowering drugs, apheresis is the therapy of choice. There is a

large body of literature that demonstrates that apheresis is a very effective and safe treatment for lowering cholesterol levels [32, 33, 39–41]. In this context, Chen et al. [42] showed that plasmapheresis was more effective in terms of lowering triglycerides for patients with HTGP and high cholesterol levels (>12.4 mmol/L) compared to low cholesterol levels. They suggested that total cholesterol could be a potential biomarker to predict the triglyceride-lowering effect of plasmapheresis in patients with HTGP.

Our data showed a significant increase in calcium levels to the normal range within the ICU stay. Most of the patients presented with lowered calcium levels on ICU admission. This reflects the severity of the acute pancreatic disease and the critical clinical status of the patients at the time of admission. Decreased levels of ionized calcium are seen in critically ill patients [43–46] and thus, hypocalcemia is more frequent in severe cases of acute pancreatitis [47, 48]. A retrospective cohort study demonstrated a significant association between lower serum calcium on admission and persistent organ failure in patients with acute pancreatitis [49]. In patients with HTGP, it was shown that ionized serum calcium was lower than in patients with pancreatitis of other etiologies [50].

Elevated CRP is an indicator for inflammation [51] and can be used as a prognostic marker for severe acute pancreatitis [52, 53]. In a previous study, high CRP was also a risk factor for severe acute pancreatitis in patients with HTGP [50]. PCT is regarded as a specific biomarker in cases of bacterial infection [54]. Our analyses showed considerably elevated CRP and mildly increased PCT levels at the time of ICU admission. Considering the study population with mainly severe cases of pancreatitis calculated by Ranson's Criteria, high CRP levels at the time of admission were not unexpected. PCT decreased significantly during the ICU stay and at the time of ICU discharge it was just slightly elevated. We assume that this is linked to the low incidence of infected pancreatic necrosis in our patients.

Several studies have demonstrated that severe HTG might be associated with severity and progressive disease of HTGP, and in these cases plasmapheresis should be performed as early as possible [35, 55]. In a retrospective study with 13 patients with acute HTGP, all patients received therapeutic plasma exchange within a median of 19 h after the onset of symptoms [56]. All patients survived with a mean hospital stay of 9.5 days and no plasma exchange-related complications had occurred. In line with these results, our patients were all treated within the first 2 days of ICU admission and none of them died during the hospital stay. One of the most recent trials compared plasma exchange with citrate anticoagulation and insulin treatment in patients with acute HTGP with regard to triglyceride reduction and clinical outcome [57]. The authors reported a trend toward a greater decrease in triglycerides within 24 h after admission in the plasma exchange group, but no significant difference was found. Length of hospital stay was comparable in both groups and survival was 100%. The results of this study question if plasma exchange is superior to other therapeutic options in patients with HTGP. In contrast to our analysis, this study specifically included patients with nonsevere prognosis. In contrast, our results clearly show that early therapeutic plasma exchange improves clinical outcome in patients with severe HTGP admitted to the ICU. Therefore, further studies with a larger study population and comparison of the two treatment regimens – early therapeutic plasma exchange versus medical treatment – in cases of severe acute pancreatitis are needed.

Limitations

This study is a single-center study with a relatively small study population. Furthermore, our study mainly included male patients because this is a disease which has been shown to predominantly affect men [14]. Therefore, the outcome in female patients may be different.

Conclusion

In patients with severe acute HTGP, early plasma exchange is an effective and safe treatment option to efficiently lower serum triglycerides. Calculated by the SOFA score, mortality risk was reduced significantly in all patients treated with plasma exchange. The survival rate of the patients after plasma exchange was 100%.

Acknowledgments

We thank the interprofessional team of the medical intensive care unit of the Department of Internal Medicine I and the team of the Department of Transfusion Medicine at the University Hospital Regensburg, Regensburg, Germany, for continuous support.

Statement of Ethics

This study was reviewed and approved by the Ethics Committee of the University of Regensburg, Regensburg, Germany (application number 22-2935-104). This is a retrospective study. All patient-related data were acquired from our hospital databases and were subsequently pseudonymized. Because of the retrospective character of the study, written informed consent was not required.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

Funding Sources

There was no external funding involved.

Author Contributions

Study concept and supervision: Prof. Dr. med. Martina Müller-Schilling, MHBA, and Dr. med. Stephan Schmid, MHBA. Introduction/data collection/statistical analyses/interpretation/discussion/formatting: Dr. med. univ. Lea U. Krauß. Data collection plasmapheresis: Dr. med. Andreas-M. Brosig. Critical review and writing of the manuscript: Prof. Dr. med. Martina Müller-Schilling, MHBA, Dr. med. Stephan Schmid, MHBA, PD Dr. rer. nat. Karsten Gülow, PD Dr. med. Arne Kandulski, Dr. med. Vlad Pavel, Dr. med. Alexander Mehrl, and Dr. med. Sophie Schlosser.

Data Availability Statement

All data generated or analyzed during this study are included in this article. Further inquiries can be directed to the corresponding author.

References

1 Machicado JD, Gougol A, Tan X, Gao X, Paragomi P, Pothoulakis I, et al. Mortality in acute pancreatitis with persistent organ failure is determined by the number, type, and sequence of organ systems affected. United European Gastroenterol J. 2021 Mar;9(2):139–49.

2 Jinno N, Hori Y, Naitoh I, Miyabe K, Yoshida M, Natsume M, et al. Predictive factors for the mortality of acute pancreatitis on admission. PLoS One. 2019 Aug;14(8):e0221468.

3 Iannuzzi JP, King JA, Leong JH, Quan J, Windsor JW, Tanyingoh D, et al. Global incidence of acute pancreatitis is increasing over time: a systematic review and meta-analysis. Gastroenterology. 2022 Jan;162(1):122–34.

4 Forsmark CE, Vege SS, Wilcox CM. Acute pancreatitis. N Engl J Med. 2016 Nov;375(20):1972–81.

5 Yang AL, McNabb-Baltar J. Hypertriglyceridemia and acute pancreatitis. Pancreatology. 2020 Jul;20(5):795–800.

6 Berglund L, Brunzell JD, Goldberg AC, Goldberg IJ, Sacks F, Murad MH, et al. Evaluation and treatment of hypertriglyceridemia: an endocrine society clinical practice guideline. J Clin Endocrinol Metab. 2012;97(9):2969–89.

7 Mayerle J, Jansen PL, Lorenz P, Beyer G, Hoffmeister A, Lerch MM. S3-Leitlinie Pankreatitis - editorial der Deutschen Gesellschaft für Gastroenterologie, Verdauungs- und Stoffwechselkrankheiten (DGVS) (September 2021 - AWMF Registernummer 021-003) - neue Leitlinie zur akuten und chronischen Pankreatitis. Z Gastroenterol. 2022 Mar;60(3):297–8.

8 Wan J, He W, Zhu Y, Zhu Y, Zeng H, Liu P, et al. Stratified analysis and clinical significance of elevated serum triglyceride levels in early acute pancreatitis: a retrospective study. Lipids Health Dis. 2017 Jun;16(1):124.

9 He WH, Yu M, Zhu Y, Xia L, Liu P, Zeng H, et al. Emergent triglyceride-lowering therapy with early highvolume hemofiltration against low-molecular-weight heparin combined with insulin in hypertriglyceridemic pancreatitis a prospective randomized controlled trial. J Clin Gastroenterol. 2016;50(9):772–8.

10 Gubensek J, Buturovic-Ponikvar J, Romozi K, Ponikvar R. Factors affecting outcome in acute hypertriglyceridemic pancreatitis treated with plasma exchange: an observational cohort study. PLoS One. 2014 Jul;9(7):e102748.

11 Yasuda H, Horibe M, Sanui M, Sasaki M, Suzuki N, Sawano H, et al. Etiology and mortality in severe acute pancreatitis: a multicenter study in Japan. Pancreatology. 2020 Apr;20(3):307–17.

12 Mayerle J, Simon P, Lerch MM. Medical treatment of acute pancreatitis. Gastroenterol Clin North Am. 2004;33(4):855–69.

13 Song X, Shi D, Cui Q, Yu S, Yang J, Song P, et al. Intensive insulin therapy versus plasmapheresis in the management of hypertriglyceridemia-induced acute pancreatitis (Bi-TPAI trial): study protocol for a randomized controlled trial. Trials. 2019 Jun;20(1):365.

14 Click B, Ketchum AM, Turner R, Whitcomb DC, Papachristou GI, Yadav D. The role of apheresis in hypertriglyceridemia-induced acute pancreatitis: a systematic review. Pancreatology. 2015 Jul;15(4):313–20.

15 Nakhoda S, Zimrin AB, Baer MR, Law JY. Use of the APACHE II score to assess impact of therapeutic plasma exchange for critically ill patients with hypertriglyceride-induced pancreatitis. Transfus Apher Sci. 2017 Apr;56(2):123–6.

16 Kyriakidis AV, Karydakis P, Neofytou N, Pyrgioti M, Vasilakakis D, Digenis P, et al. Plasmapheresis in the management of acute severe hyperlipidemic pancreatitis: report of 5 cases. Pancreatology. 2005;5(2–3):201–4.

17 Vincent JL, Moreno R, Takala J, Willatts S, De Mendonça A, Bruining H, et al. The SOFA (Sepsis-related Organ Failure Assessment) score to describe organ dysfunction/failure. On behalf of the Working Group on Sepsis-Related Problems of the European Society of Intensive Care Medicine. Intensive Care Med. 1996;22(7):707–10.

18 Le Gall JR, ., Lemeshow S, Saulnier F. A new Simplified Acute Physiology Score (SAPS II) based on a European/North American multicenter study. JAMA J Am Med Assoc. 1993 Dec;270(24):2957–63.

19 Sarr MG, Banks PA, Bollen TL, Dervenis C, Gooszen HG, Johnson CD, et al. The new revised classification of acute pancreatitis 2012. Surg Clin North Am. 2013;93(3):549–62.

20 Wu BU, Johannes RS, Sun X, Tabak Y, Conwell DL, Banks PA. The early prediction of mortality in acute pancreatitis: a large population-based study. Gut. 2008;57(12):1698–703.

21 Ranson JH, Rifkind KM, Roses DF, Fink SD, Eng K, Spencer FC. Prognostic signs and the role of operative management in acute pancreatitis. Surg Gynecol Obstet. 1974 Jul;139(1):69–81.

22 Blamey SL, Imrie CW, O'Neill J, Gilmour WH, Carter DC. Prognostic factors in acute pancreatitis. Gut. 1984;25(12):1340–6.

23 Zafrir B, Saliba W, Jubran A, Hijazi R, Shapira C. Severe hypertriglyceridemia-related pancreatitis: characteristics and predictors of recurrence. Pancreas. 2019 Feb;48(2):182–6.

24 Mosztbacher D, Hanák L, Farkas N, Szentesi A, Mikó A, Bajor J, et al. Hypertriglyceridemia-induced acute pancreatitis: a prospective, multicenter, international cohort analysis of 716 acute pancreatitis cases. Pancreatology. 2020 Jun;20(4):608–16.

25 Pedersen SB, Langsted A, Nordestgaard BG. Nonfasting mild-to-moderate hypertriglyceridemia and risk of acute pancreatitis. JAMA Intern Med. 2016;176(12):1834–42.
26 Witztum JL, Gaudet D, Freedman SD, Alexander VJ, Digenio A, Williams KR, et al. Volanesorsen and triglyceride levels in familial chylomicronemia syndrome. N Engl J Med. 2019;381(6):531–42.
27 Löhr JM, Dominguez-Munoz E, Rosendahl J, Besselink M, Mayerle J, Lerch MM, et al. United European Gastroenterology evidence-based guidelines for the diagnosis and therapy of chronic pancreatitis (HaPanEU). United Eur Gastroenterol J. 2017 Mar;5(2):153–99.
28 Kleeff J, Whitcomb DC, Shimosegawa T, Esposito I, Lerch MM, Gress T, et al. Chronic pancreatitis. Nat Rev Dis Primers. 2017 Sep;3:17060.
29 Hadaegh F, Hasheminia M, Lotfaliany M, Mohebi R, Azizi F, Tohidi M. Incidence of metabolic syndrome over 9 years follow-up; the importance of sex differences in the role of insulin resistance and other risk factors. PLoS One. 2013 Sep;8(9):e76304.
30 Lee K. Gender-specific relationships between alcohol drinking patterns and metabolic syndrome: the korea national health and nutrition examination survey 2008. Public Health Nutr. 2012 Oct;15(10):1917–24.
31 Waśkiewicz A, Sygnowska E. Alcohol intake and cardiovascular risk factor profile in men participating in the WOBASZ study. Kardiol Pol. 2013;71(4):359–65.
32 Yeh JH, Chen JH, Chiu HC. Plasmapheresis for hyperlipidemic pancreatitis. J Clin Apher. 2003;18(4):181–5.
33 Zheng H, Wang D, Wang X, Lin Y, Lu Z, Chen Y, et al. Dynamic changes of lipid profile in severe hypertriglyceridemia-induced acute pancreatitis patients under double filtration plasmapheresis: a retrospective observational study. Lipids Health Dis. 2020 Sep;19(1):206.
34 Al-Humoud H, Alhumoud E, Al-Hilali N. Therapeutic plasma exchange for acute hyperlipidemic pancreatitis: a case series. Ther Apher Dial. 2008 Jun;12(3):202–4.
35 Chen JH, Yeh JH, Lai HW, Liao CS. Therapeutic plasma exchange in patients with hyperlipidemic pancreatitis. World J Gastroenterol. 2004 Aug;10(15):2272–4.
36 Raith EP, Udy AA, Bailey M, McGloughlin S, MacIsaac C, Bellomo R, et al. Prognostic accuracy of the SOFA score, SIRS criteria, and qSOFA score for in-hospital mortality among adults with suspected infection admitted to the intensive care unit. JAMA. 2017 Jan;317(3):290–300.
37 Rasch S, Pichlmeier EM, Phillip V, Mayr U, Schmid RM, Huber W, et al. Prediction of outcome in acute pancreatitis by the qSOFA and the new ERAP score. Dig Dis Sci. 2022 Apr;67(4):1371–8.
38 Kumar S, Gattani SC, Baheti AH, Dubey A. Comparison of the performance of APACHE II, SOFA, and mNUTRIC scoring systems in critically ill patients: a 2-year cross-sectional study. Indian J Crit Care Med. 2020 Nov;24(11):1057–61.
39 Apstein CS, Zilversmit DB, Lees RS, George PK. Effect of intensive plasmapheresis on the plasma cholesterol concentration with familial hypercholesterolemia. Atherosclerosis. 1978;31(2):105–15.
40 Bambauer R, Schiel R, Latza R. Low-density lipoprotein apheresis: an overview. Ther Apher Dial. 2003 Aug;7(4):382–90.
41 Kadikoylu G, Yavasoglu I, Bolaman Z. Plasma exchange in severe hypertriglyceridemia a clinical study. Transfus Apher Sci. 2006 Jun;34(3):253–7.
42 Chen Z, Huang X, Han N, Guo Y, Chen J, Ning Y, et al. Total cholesterol concentration predicts the effect of plasmapheresis on hypertriglyceridemic acute pancreatitis: a retrospective case–control study. BMC Gastroenterol. 2021 Dec;21(1):3.
43 Sanaie S, Mahmoodpoor A, Hamishehkar H, Shadvar K, Salimi N, Montazer M, et al. Association between disease severity and calcium concentration in critically ill patients admitted to intensive care unit. Anesth Pain Med. 2018 Feb;8(1):e57583.
44 Byrnes MC, Huynh K, Helmer SD, Stevens C, Dort JM, Smith RS. A comparison of corrected serum calcium levels to ionized calcium levels among critically ill surgical patients. Am J Surg. 2005;189(3):310–4.
45 Zaloga GP. Hypocalcemia in critically ill patients. Crit Care Med. 1992;20(2):251–62.
46 Zivin JR, Gooley T, Zager RA, Ryan MJ. Hypocalcemia: a pervasive metabolic abnormality in the critically ill. Am J Kidney Dis. 2001;37(4):689–98.
47 Mentula P, Kylänpää ML, Kemppainen E, Jansson SE, Sarna S, Puolakkainen P, et al. Early prediction of organ failure by combined markers in patients with acute pancreatitis. Br J Surg. 2005 Jan;92(1):68–75.
48 He F, Zhu H-M, Li B-Y, Li X-C, Yang S, Wang Z, et al. Factors predicting the severity of acute pancreatitis in elderly patients. Aging Clin Exp Res. 2021 Jan;33(1):183–92.
49 Peng T, Peng X, Huang M, Cui J, Zhang Y, Wu H, et al. Serum calcium as an indicator of persistent organ failure in acute pancreatitis. Am J Emerg Med. 2017 Jul;35(7):978–82.
50 Yu S, Wu D, Jin K, Yin L, Fu Y, Liu D, et al. Low serum ionized calcium, elevated high-sensitivity C-reactive protein, neutrophil-lymphocyte ratio, and body mass index (BMI) are risk factors for severe acute pancreatitis in patients with hypertriglyceridemia pancreatitis. Med Sci Monit. 2019 Aug;25:6097–103.
51 Sproston NR, Ashworth JJ. Role of C-reactive protein at sites of inflammation and infection. Front Immunol. 2018 Apr;9:754.
52 Pongprasobchai S, Jianjaroonwong V, Charatcharoenwitthaya P, Komoltri C, Tanwandee T, Leelakusolvong S, et al. Erythrocyte sedimentation rate and C-reactive protein for the prediction of severity of acute pancreatitis. Pancreas. 2010 Nov;39(8):1226–30.
53 Cardoso FS, Ricardo LB, Oliveira AM, Canena JM, Horta DV, Papoila AL, et al. C-reactive protein prognostic accuracy in acute pancreatitis: timing of measurement and cutoff points. Eur J Gastroenterol Hepatol. 2013 Jul;25(7):784–9.
54 Sager R, Kutz A, Mueller B, Schuetz P. Procalcitonin-guided diagnosis and antibiotic stewardship revisited. BMC Med. 2017 Jan;15(1):15.
55 Stefanutti C, Labbadia G, Morozzi C. Severe hypertriglyceridemia-related acute pancreatitis. Ther Apher Dial. 2013 Apr;17(2):130–7.
56 Gavva C, Sarode R, Agrawal D, Burner J. Therapeutic plasma exchange for hypertriglyceridemia induced pancreatitis: a rapid and practical approach. Transfus Apher Sci. 2016 Feb;54(1):99–102.
57 Gubensek J, Andonova M, Jerman A, Persic V, Vajdic-Trampuz B, Zupunski-Cede A, et al. Comparable triglyceride reduction with plasma exchange and insulin in acute pancreatitis: a randomized trial. Front Med. 2022 Apr;9:870067.