

## Pancreatite Hipertrigliceridémica: Tratamento Convencional Versus Troca Plasmática Terapêutica

### *Hypertriglyceridemic Pancreatitis: Conventional Treatment Versus Therapeutic Plasma Exchange*

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#### Resumo

**Introdução:** A pancreatite aguda (PA) por hipertrigliceridemia (HTG) pode ser tratada com troca plasmática terapêutica (TPT), com redução rápida dos valores de triglicerídeos. Contudo, não existem estudos comparativos definitivos que comprovem o real benefício desta terapêutica.

**Objetivo:** Comparação dos métodos de tratamento (troca plasmática terapêutica versus convencional) em doentes com PA HTG, durante um período de 12 anos (2000-2012).

**Métodos:** Estudo retrospectivo descritivo e inferencial de 37 doentes, avaliando: sexo, idade, antecedentes pessoais, gravidade, valores de TG e evolução consoante o tratamento ("TPT" ou terapêutica convencional "C").

**Resultados:** Os dois grupos TPT e C mostraram-se homogêneos quanto ao sexo ( $p = 0,647$ ), idade ( $43,5 \pm 9,74$  anos TPT versus  $45,30 \pm 9,90$  anos C;  $p = 0,320$ ), pancreatite prévia (40% TPT vs 40,7% C;  $p = 1,0$ ), alcoolismo crónico (50% TPT vs 70,4% C;  $p = 0,275$ ) e gravidade pelo score de APACHE II ( $p = 0,054$ ) e Ranson às 48 horas ( $p = 0,258$ ). Dos doentes 45,95% apresentava mais de um fator de risco secundário para HTG. O grupo TPT apresentou maiores valores de TG à admissão:  $4850 \pm 2802$  mg/dL vs  $1845 \pm 1858$  mg/dL ( $p = 0,001$ ). Não se verificaram diferenças na duração do internamento  $14,2 \pm 6,8$  dias vs  $13,5 \pm 9,0$  dias ( $p = 0,56$ ) ou na taxa de mortalidade ( $p = 0,47$ ). À data de alta a redução dos TG foi superior no grupo TPT:  $4433,70 \pm 2896,08$  mg/dL - 91,41% vs  $1582,95 \pm 2051,06$  mg/dL - 83,92% ( $p = 0,002$ ). De referir seis intercorrências *minor* durante a troca plasmática terapêutica.

**Discussão/Conclusões:** Apesar do viés de seleção (estudo retrospectivo), foi constatada uma maior redução dos TG por esta técnica. As intercorrências inerentes à técnica de troca plasmática terapêutica foram de simples resolução.

**Palavras-chave:** Doença Aguda; Hipertrigliceridémia/tratamento; Pancreatite/tratamento; Troca Plasmática.

#### Abstract

**Introduction:** Acute pancreatitis (AP) induced by hypertriglyceridemia (HTG) can be treated with therapeutic plasma exchange (TPE), resulting in rapid reduction of triglyceride level. However, there are no definitive comparative studies that prove the real benefits of this therapy.

**Objectives:** Comparison of treatment methods (TPE versus conventional) in patients with HTG AP during a period of 12 years (2000-2012).

**Methods:** Retrospective, descriptive and inferential analysis of 37 patients, evaluating: gender, age, personal pathologic history, severity of disease, HTG values and evolution depending on treatment with therapeutic plasma exchange ("TPE") or with conventional therapy ("C").

**Results:** Both groups TPE and C demonstrated homogeneity considering gender ( $p = 0.647$ ), age ( $43.5 \pm 9.74$  years TPE vs  $45.30 \pm 9.90$  years C;  $p = 0.320$ ), prior AP episode (40% TPE vs 40.7% C;  $p = 1.0$ ), chronic alcohol consumption (50% TPE vs 70.4% C;  $p = 0.275$ ) and severity disease scores: APACHE II ( $p = 0.054$ ) and Ranson ( $p = 0.258$ ). More than one secondary HTG risk factor was presented in 45.95% of patients. TPE group presented higher TG levels at admission:  $4850 \pm 2802$  mg/dL vs  $1845 \pm 1858$  mg/dL ( $p = 0.001$ ). No significant statistical differences were observed considering length of hospital stay [ $14.2 \pm 6.8$  days vs  $13.5 \pm 9.0$  days ( $p = 0.56$ )] or mortality rate ( $p = 0.47$ ). At discharge, TG reduction was greater in TPE group:  $4433.70 \pm 2896.08$  mg/dL - 91.41% vs  $1582.95 \pm 2051.06$  mg/dL - 83.92% ( $p = 0.002$ ). Six minor complications associated to TPE occurred.

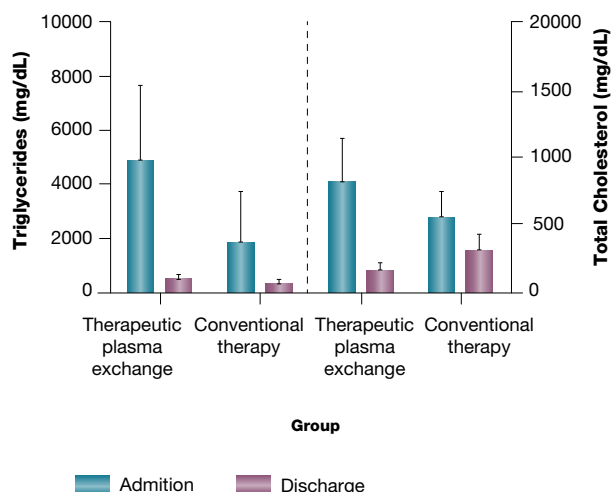
**Discussion/Conclusion:** Despite the selection bias (retrospective study), a greater TG reduction was observed with TPE technique. Complications associated with the technique were simple to resolve.

**Keywords:** Acute Disease; Hypertriglyceridemia/therapy; Pancreatitis/therapy; Plasma Exchange.

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**Figure 1:** Lipid evolution.

## Introduction

Acute pancreatitis (AP) is a potentially life-threatening condition, with a worldwide rising incidence. It is defined as an acute inflammatory process involving the pancreas, peripancreatic tissue and remote organ systems.<sup>1-4</sup> The most prevalent causes are gallstone disease, alcohol abuse and hypertriglyceridemia (HTG), with HTG accounting for 1-7% of cases, depending on the series.<sup>3,5,6</sup>

It is commonly accepted that a triglyceride (TG) level > 1000 mg/dL (> 11.3 mmol/L) is necessary to trigger an AP. However, there is no clear threshold for TG level. TG levels between 500 and 1000 mg/dL should raise a high degree of suspicion, particularly if accompanied by lactescent serum, if the evaluation of TG level has been delayed or if there is no other obvious etiology.<sup>3,5-9</sup>

HTG can be either primary (rare cases of genetic determined dyslipidemias – Frederickson Classification I, IV and V) or secondary, usually multifactorial, consequent to an association of a large number of genetic polymorphisms, and lifestyle or acquired conditions (autoimmune disease, chronic kidney disease, diabetes mellitus, drugs, hypothyroidism, metabolic syndrome, obesity and pregnancy).<sup>1,3,8,10,11</sup> The classic portrait of an AP induced by HTG is a patient with a preexisting lipid abnormality, along with the presence of a secondary factor (such as being a poorly controlled diabetic, the use of retinoids or other associated medications, alcohol abuse or pregnancy).<sup>4,5,8,12</sup>

The pathophysiologic mechanism by which HTG causes AP is still unclear. Several theories have been proposed, most of them describing free fatty acids as the cornerstone toxic molecule. Despite TG not being toxic themselves, they serve as a source of unsaturated fatty acids.<sup>3,5,7,8,13,14</sup> Hence there was a need for development of treatment forms that promote rapid removal of excessive TG, contrasting with conventional treatment (pancreas rest, analgesia, supportive care for

organ failure, and complications management). Even though the first case report of therapeutic plasma exchange (TPE) use in AP secondary to HTG dates of 1978, and most studies describe a rapid TG reduction (up to 60-80% after one or two sessions), it remains a poorly studied treatment.<sup>12,14-16</sup> This is owing to its costs, poor accessibility and fear of potential complications, which limited the studies mostly to small case series and case reports, resulting in a weak recommendation in guidelines.<sup>1,7,10,12-14,16,17</sup>

Considering what was described, the authors developed the present study to characterize and compare treatment methods (TPE versus conventional) in patients with HTG AP, during a period of 12 years (2000-2012).

## Material and Methods

A retrospective, descriptive and inferential analysis was conducted, involving patients admitted to our Hospital (Hospitais da Universidade de Coimbra) from January 2000 to December 2012 (13-year period).

A control group (conservative treatment – “C”) was obtained through the analysis of the Hospital discharge documents database, selecting patients admitted to the Internal Medicine ward with the clinical diagnosis of AP, which corresponded to 347 patients. Exclusion criteria for the control group were: gallstone disease (identified in ultrasound imaging or other imaging exam), isolated alcohol abuse, potentially iatrogenic causes (such as post endoscopic retrograde cholangiopancreatography – ERCP or associated to medications), idiopathic or not characterized etiology, TG < 500 mg/dL and patients submitted to TPE. A total of 27 patients were selected.

The TPE group (TPE treatment – “TPE”), was obtained through the analysis of the Blood Bank and Transfusion Medicine Department TPE database, with identification of 11 patients. Exclusion criteria were the same as for the control group, except these patients had to have been treated with TPE. Patients submitted to TPE for any other condition were also excluded. A total of 10 patients were selected, submitted to a total of 23 sessions. In all TPE sessions albumin was used as fluid replacement and anticoagulation was obtained with citrate.

Both groups were included in the analysis, preserving the anonymity of the patients and considering: age, sex, previous pathologic conditions, medications, clinical presentation, severity score index of AP (Ranson's criteria and APACHE II score – Acute Physiology and Chronic Health Disease Classification System II), blood analyses, including TG and total cholesterol levels, complications (associated or not to AP or its treatment), evolution and mortality.

Statistical analysis was performed using IBM SPSS Statistics 20.0®. Inferential analysis of nominal variables was performed according to Cochran rules, using Fisher's exact test or chi-square test ( $\chi^2$ ). Continuous variables were tested for normality distribution with Shapiro-Wilk's test. Analysis of con-

**Table 1:** Demographic data and secondary factors

	Conventional treatment (n = 27)	Plasmapheresis treatment (n = 10)	Test	Test value	P	df
Age (years)	45.30 ± 9.90	43.50 ± 9.74	U	106.000	0.320	N - 1
Sex			χ <sup>2</sup> (F)	-	0.647	1
Female	22.22% (6)	10.00% (1)				
Male	77.78% (21)	90.00% (9)				
BMI (kg/m <sup>2</sup> )	26.30 ± 4.85	29.73 ± 3.00	U	67.000	0.041	N - 1
Prior pancreatitis	40.74% (11)	40.00% (4)	χ <sup>2</sup> (F)	-	1.000	1
Prior knowledge of lipid disorder	51.81% (14)	80.00% (8)	χ <sup>2</sup> (F)	-	0.153	1
Secondary factor / Pathologic conditions						
Alcohol	70.37% (19)	50.00% (5)	χ <sup>2</sup> (F)	-	0.275	1
(g/day)	79.00 ± 52.99	94.20 ± 112.30	U	124.000	0.704	N - 1
Autoimmune disease	0	0				
Chronic kidney disease	0	0				
Diabetes mellitus	22.22% (6)	40.00% (4)	χ <sup>2</sup> (F)	-	0.407	1
Drugs	11.11% (3)	20.00% (2)	χ <sup>2</sup> (F)	-	0.412	1
Hypertension	25.93% (7)	40.00% (4)	χ <sup>2</sup> (F)	-	0.442	1
Hyperuricemia	7.41% (2)	20.00% (2)	χ <sup>2</sup> (F)	-	0.291	1
Hypothyroidism	0	0				
Metabolic syndrome	40.74% (11)	60.00% (6)	χ <sup>2</sup> (F)	-	0.460	1
Nephrotic syndrome	0	0				
Pregnancy	0	0				

Previous pathologic conditions and secondary factors to hypertriglyceridemia. Nominal variables are presented by relative frequency. Continuous variables are presented by mean ± standard deviation. χ<sup>2</sup> chi-squared test; df – degrees of freedom; F - Fisher's exact test; U - Mann-Whitney test; BMI - body mass index; Drugs: 2 patients with beta-blockers and 3 patients with thiazide diuretics; 3 patients with knowledge of prior lipid disorder - familiar hypercholesterolemia (2P, 1C);

tinuous variables was performed with Mann-Whitney's test (U – nonparametric test for non-normally distributed variables) or Student's t test (t – parametric test for normally distributed variables, after assessment of equality of variances using Levene's test). A *p*-value of less than 0.05 was considered to indicate statistical significance (type I error).

## Results

As presented in Table 1 most of the patients were young (mean age of 44.81 ± 9.75 years), males (81.08%), frequently with prior diagnosis of lipid disorder (3 patients with known HTG hereditary syndromes, without specific Fredrickson classification – two in the TPE group and one in the C group). The most common secondary factors were alcohol consumption (64.86%), metabolic syndrome (45.95%) and type 2 diabetes mellitus (27.03%). Considering drugs as secondary factors for HTG, two patients were on beta-blockers (one

in each group) and the remaining patients were on thiazide diuretics. One patient was diagnosed with HIV (human immunodeficiency virus) infection but only started antiretroviral treatment after the AP episode. Apart from body mass index (*p* = 0.041), the characteristics observed in Table 1 show homogeneity in both groups.

Table 2 shows the clinical presentation of the patients at admission (in all cases, the presentation in the emergency department). There were statistically significant differences in the evaluation of heart and respiratory rates (*p* = 0.017 and *p* = 0.004 respectively). Although both parameters are important for the calculation of APACHE II Score, there is no statistically significant difference between the groups as seen in Table 3 (representing also other parameters related to the initial laboratory and clinical evaluation). Eight patients (all from the TPE group) were admitted to the Gastroenterology Intensive Care Unit (UCIGE), with a mean length of stay of 6.63 ± 3.78 days.

**Table 2:** Clinical presentation at admission

	Conventional treatment (n = 27)	Plasmapheresis treatment (n = 10)	Test	Test value	P	df
Abdominal evaluation						
Guarding	18.52% (5)	20.00% (2)	$\chi^2$ (F)	-	1.000	1
Pain	100.00% (27)	100.00% (10)	$\chi^2$ (F)	-	1.000	1
Altered lung auscultation	14.81% (4)	40.00% (4)	$\chi^2$ (F)	-	0.179	1
Fever	40.74% (11)	40.00% (4)	$\chi^2$ (F)	-	1.000	1
Auricular temperature (°C)	37.08 ± 0.98	37.16 ± 1.04	U	133.500	0.959	N - 1
Arterial blood pressure (mmHg)						
Systolic blood pressure	136.60 ± 18.77	144.00 ± 18.63	U	93.000	0.242	N - 1
Diastolic blood pressure	84.12 ± 12.15	85.70 ± 15.67	U	102.500	0.410	N - 1
Mean arterial pressure	101.61 ± 12.37	105.13 ± 15.44	t	0.708	0.484	33
Tachycardia	37.04% (10)	60.00% (6)	$\chi^2$ (F)	-	0.457	1
Heart rate (bpm)	94.67 ± 13.04	107.60 ± 15.03	t	2.520	0.017	32
Tachypnea	29.63% (8)	80.00% (8)	$\chi^2$ (F)	-	0.009	1
Respiratory rate (bpm)	20.56 ± 7.79	30.30 ± 8.72	U	52.500	0.004	N - 1
Xanthomas / Xanthelasma	0	10.00% (1)	$\chi^2$ (F)	-	0.278	1

Nominal variables are presented by relative frequency. Continuous variables are presented by mean ± standard deviation.  $\chi^2$  chi-squared test; df – degrees of freedom; F - Fisher's exact test; U - Mann-Whitney test; t - student-t test; °C - degrees Celsius; bpm (heart rate) - beats per minute; bpm (respiratory rate) - breaths per minute; mm Hg - millimeter of mercury.

A total of 23 TPE sessions were performed (minimum of one session and maximum of four sessions), with the decrease in TG level being represented in Fig. 1 (as well as TG variation of the C group and total cholesterol variation in both groups). Complications were identified in 26.09% (six patients) of all TPE sessions (Table 4). All were quickly and effectively solved: an anxiety attack solved by stopping the session, paresthesia treated with calcium gluconate, urticaria treated with clemastine and treatment induced pain worsening treated with different analgesics. No other complications related to TPE were documented. TG levels after the first TPE cycle were only available for eight patients. For these eight patients, a single cycle of TPE was responsible for a TG lowering of 80.97% (TG values after one session: 635.88 ± 261.25 mg/dL).

A total of eleven patients were treated with fibrate drugs, with four from TPE group and seven from the C group. Fibrates were early introduced during treatment in six cases (two patients from TPE group and four from the C group).

One patient from the TPE group was discharged against medical advice, prior to optimal lipid care, and one patient (also from the TPE group) was transferred to another hospital (closer to the area of residence of the patient) to continue treatment.

## Discussion

This study included 37 patients (Table 1) most of them were young males, with prior diagnosis of lipid disorder. Seventeen patients had more than one secondary risk factor (45.95%), which demonstrates higher risk compared to other populations (data from a systematic study demonstrates accumulation of risk factors in 9.4% of the patients).<sup>7</sup> All our other demographic data is coincident with previous studies (including a recent systematic review of 301 patients)<sup>7,16</sup> and there are no statistically significant differences between the two groups (apart from body mass index,  $p = 0.041$ , but with both groups presenting overweight/obesity), demonstrating homogeneity between groups TPE and C.

At clinical presentation (Table 2), some differences between groups C and TPE are apparent, but merely considering heart rate and respiratory rate ( $p = 0.017$  and  $p = 0.004$ ). As AP usually presents as an acute onset of abdominal pain, homogeneity between groups was expected. Clinical signs and symptoms associated with initial laboratory evaluation (Table 3) allow calculation of scores like APACHE II and Ranson, that accurately predict outcome of patients with acute pancreatitis.<sup>18</sup> Although there was no statistically significant

**Table 3:** Initial laboratory and clinical evaluation

	Conventional treatment (n = 27)	Plasmapheresis treatment (n = 10)	Test	Test value	P	df
Complete blood count						
White blood cell count (x 10 <sup>9</sup> cells/L)	11.42 ± 3,95	14.58 ± 3.36	U	70.000	0.026	N -1
Hemoglobin (g/dL)	15.22 ± 2,18	17.19 ± 1.85	U	61.500	0.012	N -1
Hematocrit (%)	38.70 ± 4,18	42.68 ± 3.61	U	59.000	0.009	N -1
Biochemistry						
Glucose (mg/dL)	152.33 ± 72,11	165.80 ± 81.88	t	0.487	0,630	35
Calcium (mg/dL)	8.91 ± 0,83	8.83 ± 0.67	U	125.500	0.745	N -1
Blood urea nitrogen (mg/dL)	11.60 ± 3,51	11.06 ± 2.48	U	124.000	0.705	N -1
Creatinine (mg/dL)	0.72 ± 0,15	0.84 ± 0.20	U	91.500	0.133	N -1
Lactate dehydrogenase (U/L)	357.19 ± 214,20	242.40 ± 116.37	U	94.000	0.161	N -1
C-reactive protein (mg/dL)	565 ± 8,74	6.62 ± 10.14	t	0.287	0.776	35
Amylase (U/L)	318.84 ± 311,34	373.50 ± 240.31	U	102.000	0.401	N -1
Lipase (U/L)	597.60 ± 572,38	1055.40 ± 931.20	U	17.000	0.327	N -1
Lipids						
Triglycerides (mg/dL)	1854.22 ± 1858.13	4850.40 ± 2802.58	U	36.000	0.001	N -1
Total cholesterol (mg/dL)	546.63 ± 200,73	809.00 ± 332.60	t	2.859	0.007	34
HDL cholesterol (mg/dL)	51.24 ± 26.13	89.50 ± 109.98	U	80.000	0.845	N -1
Scores						
APACHE II	6.55 ± 2.86	9.56 ± 4.82	U	49.500	0.054	N -1
Ranson	2.55 ± 1.43	3.56 ± 2.35	U	66.500	0.258	N -1

Continuous variables are presented by mean ± standard deviation. df – degrees of freedom; U - Mann-Whitney test; t - student-t test; HDL - High-density lipoprotein; APACHE II - Acute Physiology and Chronic Health Disease Classification System II.

differences between the scores of groups C and TPE ( $p = 0.054$  for APACHE II and  $p = 0.258$  for Ranson) calculated scores should be analyzed in more detail. The group submitted to TPE presented APACHE II scores of  $9.56 \pm 4.82$ , much higher than the same value for C group –  $6.55 \pm 2.86$ , associated to a potentially higher hospital mortality. As the present study is retrospective, this type of bias was expected, as patients in worst clinical state are treated more aggressively and, therefore, most promptly selected for TPE (this kind of bias was present also in a systematic review of cases<sup>7</sup>). In this case, the low number of patients included in the study is probably the reason why there are no statistical differences.

Another expected bias is TG total level at admission. As previously stated, standard treatment of AP includes pancreas rest, analgesia, supportive care for organ failure, and management of complications. However, a rapid decrease in TG levels is essential to the successful management of HTG induced pancreatitis.<sup>10</sup> Several studies report decreases in TG levels after only one session of TPE in up to 60% of patients, and up to 60-80% in one or two sessions.<sup>3,7,10,12,16</sup> Considering these results,

a bias of selection of patients with high TG levels at admission to TPE is logical (as well as a selection bias for the patients admitted in the UCIGE). Similar reduction results were obtained in our study (Table 4), with decrease in TG up to 80.97% in one session (results considering data from eight patients) and up to 91.41% at the end of all sessions for patients submitted to more than one treatment (six patients). Similar results were obtained for total cholesterol level decrease. Regardless of selection bias and premature discharge of two patients in the TPE group (one patient against medical advice and one patient transferred to another hospital), the relative reduction achieved in the TPE treatment group was greater than in the conventional treatment group ( $p = 0.002$  both in TG and total cholesterol levels reduction), demonstrating that TPE is a useful tool for achieving an early decrease of TG to safer levels. The benefits of this treatment acquire a greater importance given that some studies demonstrate that TG levels < 500 mg/dL represent a safe therapeutic target, not only to prevent AP recurrences, but also to prevent other clinical events (cardiovascular, diabetes and renal) and to reduce overall costs.<sup>12</sup>

**Table 4:** Clinical evolution

	Patients on Conventional treatment (n = 27)	Patients on Plasmapheresis treatment (n = 10)	Test	Test value	P	df
Length of stay (days)	13.48 ± 9.03	14.20 ± 6.76	U	118.000	0.560	N - 1
Death	3.70% (1)	10.00% (1)	χ <sup>2</sup> (F)	-	0.473	1
Complications relating plasmapheresis (n = 23 sessions)		26.09% (6)				
Anxiety	-	4.35% (1)	-	-	-	-
Paresthesias	-	4.35% (1)	-	-	-	-
Treatment induced pain worsening	-	13.04% (3)	-	-	-	-
Urticaria	-	4.35% (1)	-	-	-	-
Complications (all other causes)	37.04% (10)	90.00% (9)	χ <sup>2</sup> (F)	-	<b>0.008</b>	1
Acute gout attack	3.70% (1)	20.00% (2)	χ <sup>2</sup> (F)	-	0.172	1
Chronic pancreatitis	0	10.00% (1)	χ <sup>2</sup> (F)	-	0.270	1
Diabetes mellitus onset	0	10.00% (1)	χ <sup>2</sup> (F)	-	0.270	1
Diabetic ketoacidosis	3.70% (1)	0	χ <sup>2</sup> (F)	-	1.000	1
Hypovolemic shock	0	10.00% (1)	χ <sup>2</sup> (F)	-	0.270	1
Multiple organ failure	3.70% (1)	10.00% (1)	χ <sup>2</sup> (F)	-	0.473	1
Nosocomial pneumonia	0	10.00% (1)	χ <sup>2</sup> (F)	-	0.270	1
Oropharyngeal candidiasis	0	10.00% (1)	χ <sup>2</sup> (F)	-	0.270	1
Pancreatic abscess	3.70% (1)	0	χ <sup>2</sup> (F)	-	1.000	1
Pancreatic pseudocyst	14.81% (4)	0	χ <sup>2</sup> (F)	-	0.557	1
Pulmonary atelectasis	3.70% (1)	0	χ <sup>2</sup> (F)	-	1.000	1
Refractory hypokalemia	0	10.00% (1)	χ <sup>2</sup> (F)	-	0.270	1
Withdrawal syndrome	3.70% (1)	0	χ <sup>2</sup> (F)	-	1.000	1
Lipid evolution: Triglycerides						
Triglycerides at admission (mg/dL)	1854.22 ± 1858.13	4850.40 ± 2802.58	U	36.000	0.001	N - 1
Triglycerides after one session of plasmapheresis (mg/dL)*	-	635.88 ± 261.25	-	-	-	-
Triglycerides after one session of plasmapheresis reduction	-	80.97%	-	-	-	-
Triglycerides at discharge (mg/dL)	296.65 ± 109.66	416.70 ± 187.65	U	62.000	0.094	N - 1
Triglycerides total reduction	83.92%	91.41%	U	31.000	0.002	N - 1
Lipid evolution: Total cholesterol						
Total cholesterol at admission (mg/dL)	546.63 ± 200.73	809.00 ± 332.60	t	2,859	0.007	34
Total cholesterol after one session of plasmapheresis (mg/dL)*	-	195.50 ± 50.35	-	-	-	-
Total cholesterol after one session of plasmapheresis reduction	-	75.83%	-	-	-	-
Total cholesterol at discharge (mg/dL)	298.05 ± 121.28	153.70 ± 50.30	U	22,500	0.001	N - 1
Total cholesterol total reduction	54.52%	81.00%	U	24.000	0.002	N - 1

Nominal variables are presented by relative frequency. Continuous variables are presented by mean ± standard deviation.  
χ<sup>2</sup> Chi-squared test; df – degrees of freedom; F - Fisher's exact test; U - Mann-Whitney test; t - student-t test; \* - results considering 8 patients.

Although TPE has proven effective in achieving significant reductions in TG levels, most studies are case reports and small case series. Randomized controlled trials are lacking

and, consequently, guidelines such as the latest from the American Society for Apheresis classifies TPE as a category III indication in HTG induced AP.<sup>19</sup> These studies are lacking



not only because of the limited availability of this kind of treatment and low prevalence of the disease, but also because of the fear of potential complications. Some complications of TPE are bleeding/hematoma, catheter site infection, hemothorax, hypofibrinogenemia, hypotension, nausea, paresthesia (associated to the use of citrate as anticoagulation therapy and consequent hypocalcemia), pneumothorax, urticaria, vasovagal reactions and vomiting.<sup>17</sup> However, studies have demonstrated that the occurrence of truly important complications is rare, and that most complications, like clinical manifestation of hypocalcemia by paresthesia is easily treated.<sup>6,10</sup> This data is concurrent with that of our study, with only minor complications associated to TPE being documented.

It is also important to consider the length of the study (13 years), as it entails technological and practical changes that may represent a bias, not only in the rate of complications but also on the clinical evolution.

Considering the length of hospital stay and mortality, no statistically significant differences were achieved between both groups [ $p = 0.560$  and  $p = 0.473$  respectively (Table 4)]. These data are similar to a previous study, by Chen *et al.*<sup>20</sup> that showed no clear benefit of apheresis in reducing severity and improving outcomes in AP.<sup>12,15,16</sup> Nevertheless, it is important to emphasize that study presented similar bias and limitations as our present study: it is also a retrospective study, with small groups (60 patients treated with TPE; 34 patients treated otherwise) and single center experience (as it was designed for the evaluation of the clinical outcomes in HTG induced AP before and after the availability of apheresis at their institution). On the other hand, major AP complications (pancreatic pseudocyst and pancreatic abscess) were more commonly seen in the group treated with conventional therapy. Although the number of cases is too small in order to properly achieve definitive considerations, rapid removal of TG may reduce damage to the pancreas. Still, further studies are needed.

Many questions remain unanswered, not only considering the real benefit of the use of TPE, but also considering variations on the technique (a recent study found a significant reduced mortality using citrate anticoagulation as compared to heparin anticoagulation).<sup>3</sup>

## Conclusions

Apart from the greater burden of secondary factors, our study reported a population that has general demographic data similar to what has been previously published in studies about AP induced by HTG. This can potentially illustrate greater incidence and/or more severe cases, conclusions that require further studies.

We also reported how therapeutic plasma exchange can effectively and quickly reduce TG levels, to a safe therapeutic target without major complications associated to the treatment. There was no statistically significant differences

between patients treated with or without TPE, regarding length of hospital stay and mortality, but the small sample in this study may contribute to this result. Well design randomized controlled trials with an adequate sample size are necessary for further analyses and to determine the benefits of this procedure.

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