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*Original article*

# Lipapheresis in the management of hyperlipidemic pancreatitis: Our experience in a series of 7 patients

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## SUMMARY

**Aim of the study : To evaluate the efficacy of lipapheresis in the management of hyperlipidemic pancreatitis (HLP).**

**Methodology : Seven patients (pts), (6 males and 1 female) with mean age 40.8 years (range: 26 - 64 years) were included. The diagnosis of pancreatitis was based upon clinical symptoms, serum and urine amylase levels and/or abdominal Computed Tomography (C/T) findings. Diagnosis of HLP was confirmed, as all pts had serum triglyceride (TG) levels of more than 1000mg/dl. All pts underwent 1-3 sessions of plasma treatment, by using double cascade filtration. During each session of plasmapheresis, three liters of plasma were exchanged. All pts were followed-up monthly after their discharge, for 6 months.**

**Results : In 3/7 (43%) a significant reduction of serum TG and pancreatic enzymes was noted, within a few hours from lipapheresis. In the remaining pts, the same results were noted after a second (2/7,28.5%) or third (2/7,28.5%) session of the procedure. Also, an impressive improvement of pts' clinical signs was observed. All sessions were well tolerated. During the follow-up period, none of the pts reported any episodes of abdominal pain or vomiting, while their serum TG levels were well below 1000mg/dl. Moreover, serum and urine amylase were within normal limits over the same period.**

**Conclusion : It seems that lipapheresis is a promising and safe treatment in pts with HLP. However, more studies with a larger patient group are needed for further evaluation of its efficacy.**


**Key words :** Pancreatitis, Hypertriglyceridemia, lipapheresis, plasma exchange

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## INTRODUCTION

Hypertriglyceridemia (HTG) is a rare cause of pancreatitis. Pancreatitis secondary to HTG presents typically, as an episode of acute pancreatitis (AP) or recurrent AP, and rarely as chronic pancreatitis.[1] It is generally thought that, a triglyceride (TG) level of more than 1000mg/dl is needed to precipitate an episode of AP.[2]

The typical clinical profile of hyperlipidemic pancreatitis (HLP) is a patient with a preexisting lipid abnormality along with a presence of a secondary factor (e.g poorly controled diabetes, alcohol abuse, or a medication) that can induce HTG. Less commonly, a patient with familial HTG, type I, IV or V (Fredrikson's classification) without a precipitating factor, presents with pancreatitis.

Interestingly, serum pancreatic enzymes (e.g amylase) may be normal or only minimally elevated, even in the presence of severe pancreatitis diagnosed by imaging studies.[3] The clinical course in HLP is not different from that of pancreatitis of other causes.

Routine management of HLP is similar to that of other causes, while reduction of TG levels to well below 1000mg/dl effectively prevents further episodes of pancreatitis. The mainstay of treatment includes dietary restriction of fat and lipid-lowering medications to manage the secondary or precipitating causes of HTG. On

the contrary, there are not sufficient data in the literature to date, concerning plasmapheresis, lipid apheresis and extracorporeal lipid elimination for the management of HLP.

We present in this study 7 patients (pts) with HLP who underwent an extracorporeal lipapheresis, resulting in impressively improvement of pancreatitis' clinical and laboratory signs.

### *Patients and Methods*

Seven pts, (6 males and 1 female) with mean age 40.8 years (range: 26-64 years) were included in our study. All of them were admitted to our hospital because of diffuse abdominal pain and vomiting. All pts underwent routine laboratory tests including serum and urine amylase, and also an abdominal Ultrasound. The diagnosis of AP was based upon clinical and laboratory tests (high levels of serum amylase), while in 3/7 (43%) diagnosis was made by abdominal Computed Tomography (C/T), which was performed during the first day of hospitalisation in all patients. The prediction of severity of AP included Ranson's criteria, APACHE II score and C-RP levels. All other common causes of AP (cholelithiasis, alcohol abuse, hypercalcemia, medications etc) were excluded by patients' history and also laboratory and imaging findings, while diagnosis of HLP was confirmed, as all patients had serum TG levels of more than 1000mg/dl.

Liver biochemistry tests, serum and urine amylase and also C-Reactive protein (CRP) were estimated every day, during hospitalisation.

When indicated, all patients underwent 1-3 sessions of plasma treatment, by using double / cascade filtration During this procedure clearance of several substances is performed according to the size of their molecules. Two special filters (Plasmaflo OP-Z5 and Cascadeflo AC1770, ASAHI) were used, which allowed dissection of lipoproteins from the figured components of blood. During each session of plasmapheresis, three liters of plasma were exchanged, and they were replaced by human albumin solution (5%). Heparin was used as anticoagulant, at a dose of 2000- 3000 u/session. A double lumen catheter in subclavicular vein was used for vascular access.

All patients were followed-up monthly after their discharge, for 6 months.

## RESULTS

Patients' history, characteristics and laboratory findings on admission, are summarized in Tables 1 and 2.

According to Ranson criteria, APACHE II score and C-RP levels, the episode of pancreatitis was classified as severe in all patients of our series (Table 3), while in all of them spiral C/T revealed several amounts of pancreatic necrosis.

The initial management of all patients included nothing by mouth, bowel rest, intravenous fluid replacement with 4 – 6 liters / day, and nasogastric tube and analgesics when necessary. Moreover, parenteral antibiotics (imipenem / cilastatin) were administered when necroses were revealed by C/T, in order to prevent septic complications. However, none of our patients showed any significant clinical or laboratory improvement within 72 hours after admission.

Thus, a session of plasma exchange was performed in all patients 48-72 hours after admission. In 3/7 (43%) a significant reduction of serum TG and pancreatic enzymes was noted, within a few hours from the procedure. In the remaining patients, the same results were noted after a

**Table 1:** Patient characteristics & history

| PATIENT | AGE | SEX | PATIENT'S HISTORY |
|---|---|---|---|
| 1 | 31 | Male | Familial combined hyperlipidemia<br>Acromegaly |
| 2 | 46 | Male | Familial combined hyperlipidemia |
| 3 | 46 | Male | Familial combined hyperlipidemia |
| 4 | 41 | Male | Familial combined hyperlipidemia |
| 5 | 26 | Male | Familial combined hyperlipidemia |
| 6 | 59 | Male | Poorly controlled diabetes<br>Alcohol abuse |
| 7 | 64 | Female | Poorly controlled diabetes<br>Arterial hypertension<br>Morbid obesity |

**Table 2:** Patients' laboratory findings on admission

| PATIENT | Serum Amylase (U/L) | Urine Amylase (U/L) | WBC | Glu mg % | LDH IU/L | PO2 mm Hg | TG mg % | Chol mg % | C-RP mg % |
|---|---|---|---|---|---|---|---|---|---|
| 1 | 1663 | 16380 | 17900 | 220 | 365 | 70 | 1566 | 451 | 119 |
| 2 | 153 | 860 | 18100 | 245 | 390 | 68 | 3565 | 604 | 85 |
| 3 | 2407 | 2898 | 17200 | 255 | 410 | 65 | 3565 | 360 | 98 |
| 4 | 115 | 778 | 18800 | 296 | 365 | 68 | 1637 | 564 | 134 |
| 5 | 1926 | 44528 | 18600 | 290 | 435 | 76 | 4400 | 654 | 159 |
| 6 | 185 | 984 | 22200 | 485 | 510 | 55 | 1135 | 265 | 165 |
| 7 | 3560 | 15865 | 20400 | 566 | 645 | 57 | 1434 | 287 | 185 |

*Serum amylase upper normal limit < 220 U/L*
*Urine amylase upper normal limit < 1200 U/L*
*C-RP upper normal limit < 8 mg/dl*

**Table 3:** Prediction of severity of our patients' pancreatitis

| PATIENT | RANSON'S CRITERIA | APACHE II SCORE |
|---|---|---|
| 1 | 3 | 8 |
| 2 | 3 | 9 |
| 3 | 3 | 9 |
| 4 | 3 | 8 |
| 5 | 3 | 8 |
| 6 | 4 | 11 |
| 7 | 4 | 12 |

second (2/7,28.5%) or third (2/7,28.5%) session of lipapheresis. The second or the third session took place 48 or 96 hours after the first one, respectively. It should be pointed out also that, an impressive improvement of clinical signs was observed in all patients.

The decrease of serum TG, cholesterol and serum amylase levels, after plasma exchange is shown in figures 1,2 and 3, while the number of lipapheresis sessions required for each patient is shown in Table 4.

All sessions of lipapheresis were well tolerated by the patients, while all of them were discharged from hospital within 8-10 days after admission. Dietary instructions were given in all patients, while drug treatment with fibrates was initiated in those with familial HTG.

During the follow-up period none of them reported any episodes of abdominal pain or vomiting, while their serum TG levels were well below 1000mg/dl. Moreover, serum and urine amylase were within normal limits at the same period. However, the abdominal U/S, which was performed two months after hospital discharge, revealed a small (of 3cm diameter) pseudocyst in one patient, which retreated spontaneously within two months.

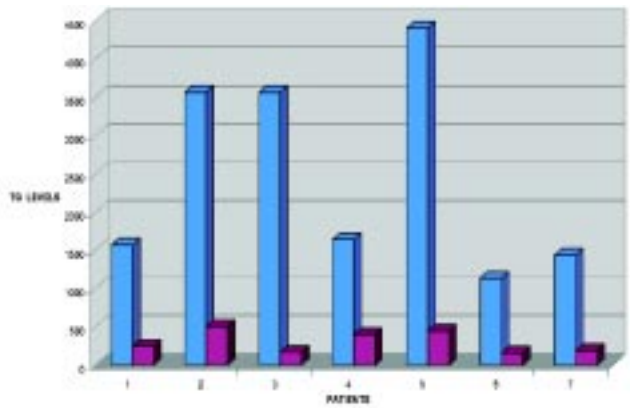

**Fig. 1.** 1-Reduction of TG levels after lipapheresis

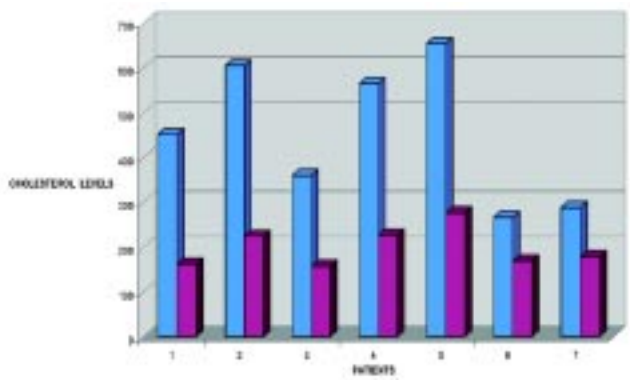

**Fig. 2.** Reduction of serum cholesterol after lipapheresis

## DISCUSSION

Patients with a preexisting abnormality in lipoprotein metabolism,usually present with significant HTG. It has been shown by several studies that patients with TG levels over 1000mg/ dl are at risk for acute pancreatitis. Two

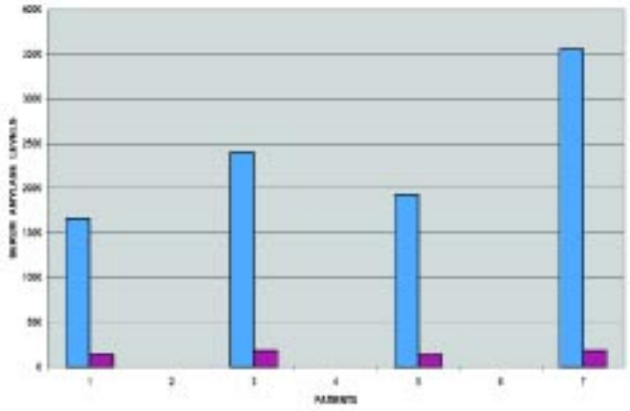

**Fig. 3.** Reduction of serum amylase levels after lipapheresis

**Table 4:** Required sessions of lipapheresis in our patients

| PATIENT | REQUIRED SESSIONS |
|---|---|
| 1 | 2 |
| 2 | 1 |
| 3 | 3 |
| 4 | 3 |
| 5 | 2 |
| 6 | 1 |
| 7 | 1 |

forms of HTG have been recognized: genetic and acquired. Among the genetic (familial) forms, patients with familial HTG of type I, IV and V (Fredrikson classification),[4] as well as, those with familial combined hyperlipidemia (with increased TG and cholesterol levels) are predisposed to develop pancreatitis. Five out of seven (71%) patients of our series had the combined type of hyperlipidemia. On the contrary, acquired forms may result from alcohol excess,[5] morbid obesity, use of several drugs (e.g estrogens, tamoxifen, retinoids, thiazides, protease inhibitors, β-blockers etc),[6,7] diabetes,[8] pregnancy,[9] chronic renal failure or hypothyroidism. It should be pointed out that acquired froms by themselves do not cause significant HTG that can be a risk factor for pancreatitis. However, in the presence of an underlying abnormality in lipoprotein metabolism, they increase TG to a significant level that may result in pancreatitis. Two of seven (28.5%) patients in our series had secondary (acquired) forms of hyperlipidemia.

The mechanism by which HTG leads to pancreatitis is not clear. A possible mechanism, proposed by Havel[10] is that, hydrolysis of TG in and around the pancreas by pancreatic lipase seeping out of the acinar cell, leads to accumulation of free fatty acids in high concentrations. Unbound free fatty acids are toxic and could produce acinar cell or capillary injury. Increased concentration of chylomicrons in the pancreatic capillaries causes capillary plugging and leads to ischemia and acidosis, and thus in that acidotic environment, free fatty acids cause activation of the trypsinogen and initiate AP.

It is well known that the diagnostic hallmark of AP is the elevated amylase and/or lipase levels in the absence of which clinicians seldom consider AP in their differential diagnosis. However, in more than 50% of patients with HLP, serum and urinary amylase levels may be normal on admission or during hospitalization. This may be due to an interference of plasma lipids with the assay or to the presence of an inhibitor in the plasma and urine that inhibits the assay.[11,12] If the serum is diluted, the increase in amylase can be appreciated and the diagnosis of AP can be made. In 3/7 (43%) of our patients, serum and urine amylase levels were within normal limits on admission, and therefore the diagnosis of AP was based upon patients' clinical features and C/T findings.

No significant differences have been reported between the course of HLP and the course of other forms of AP. However, pancreatitis due to chylomicronemia is a potentially life-threatening disorder.[13] All patients of our series had a severe form of AP, according to several scoring systems.

The initial management of HLP is similar to that for other causes of AP. The concept of the administation of lipapheresis in the management of HLP relies upon the rapid elimination of the predisposing factor (HTG) from the serum.

Plasma exchange can dramatically lower excessive lipid levels in about 2 hours. Lennertz et al[14] found that rapidly initiated plasma exchange (PE) effectively reduced TG and cholesterol levels in five patients with HLP, who had subsequent uneventful recovery. Moreover, in the study of Yeh et al.[15] 13 of 17 HLP patients (76.5%) treated with PE recovered completely. Piolot et al.[16] reported that regular monthly PE successfully prevented recurrent attacks of HLP in two cases of severe primary HTG with recurrent acute pancreatitis.

Lipapheresis is beneficial in HLP, by reducing plasma viscocity and removing of TG and toxic scavengers.[17] Also, it is thought that, during plasma exchange an immunomodulation, crucial for pacreatitis clinical course, can be achieved, dependent mainly on the filters used.

With a single session of lipapheresis, about two thirds

of serum lipids are typically cleared. An additional exchange may increase the removal rate, while it has been shown that the number of sessions is not correlated to the clinical outcome.

In our series, a significant reduction of serum lipids was achieved by 1,2 or 3 sessions of lipapheresis, in 3, 2 and 2 pts, respectively and also an impressive improvement was observed in patients' symptoms and clincal signs. All of them were discharged in excellent condition, while none of them relapsed during the follow-up period.

In some studies, fluid replacement, during the procedure, was achieved by fresh frozen plasma.[18] However, there is a possibe risk of allergic reaction and transfusion-related infection.[15] In our series, a human albumin solution was used. No adverse effects were noted during the sessions.

In conclusion, it seems that lipapheresis is a promising and safe treatment in patients with hyperlipidemic pancreatitis. However, more studies with a larger patient group are needed for further evaluation of its efficacy.

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