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Effect of plasmapheresis versus standard treatment in preventing recurrent acute pancreatitis in Chinese patients with hypertriglyceridemia

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Abstract: The present study designed to compare the effect of plasmapheresis (PPH) versus standard treatment (STD) in preventing recurrent AP in Chinese patients with severe hypertriglyceridemia. Chinese patients aged 18 to 65 years who had history of hypertriglyceridemia (>1000mg/dl) induced acute pancreatitis were assigned to plasmapheresis (up to 1.5 ml daily TG level reaches 500 mg/dl or less) or standard treatment (1:1). Standard treatment (STD) includes limited oral intake (pancreatic rest), intravenous hydration and pain management. Primary endpoint was incidence of recurrent acute pancreatitis. A total of 14% of patients in PPH group (N=50) had experienced recurrent pancreatitis as compared to 24% of patients in STD group (N=50). Also, TG clearance rate in 24 hours was substantially higher in PPH group as compared to STD. Time required to reach target TG was significantly lower in patients treated with PPH as compared to STD. Lower incidence of local complications was observed in PPH group as compared to STD. Length of stay was significantly shorter in patients of plasmapheresis group as compared to standard treatment. The results of this study recommend the use of plasmapheresis as a better alternative in preventing recurrent AP in Chinese patients with severe hypertriglyceridemia.

Keywords: Acute pancreatitis, hypertriglyceridemia, plasmapheresis.

INTRODUCTION

Acute pancreatitis (AP) is a one of most common inflammatory condition characteristics by several pelvic pain and increased level of gastric enzymes (Ahmed *et al*., 2019, Aida *et al*., 2015)]. It is accounted for financial burden to patient and their family. In most cases, the main cause of AP was due to chronic gallstones, hypertriglyceridemia (HTG), and increased intake of alcohol (Aida *et al*., 2015, Shanshan *et al*., 2020). Untreated serious conditions of AP lead to inflammatory response syndrome, damage of pancreatic tissue, and failure of multiple organs, which is the most common cause of death due to AP (Ahmed *et al*., 2019, Aida *et al*., 2015; Shanshan *et al*., 2020; Melnick *et al*., 2016). The most common treatment paradigm of AP includes administration of adequate fluid, bowel rest and controlling pain (Aida *et al*., 2015, Shanshan *et al*., 2020).

High level of TG (>1000mg/dl) is one of the most common risk factors of developing AP (Shanshan *et al*., 2020, Rajat *et al*., 2018). It is evident that severity of HTG is related with severity of AP and the development of HTG induced AP can be prevented if treatment demonstrates reduction in TG levels to less than 500mg/dl (Vipperla *et al*., 2017; Shanshan *et al*., 2020, Rajat *et al*., 2018). Thus, managing the TG levels in AP patients can alleviate the disease severity and its progression. It has been reported that insulin reduces serum TG levels in patient with HTG due to its effect on lipoprotein lipase (Meng *et al*., 2018, Cruciat *et al*., 2020, Alakel *et al*., 2019). The most common adverse event after using insulin in HTG patients was severe hypoglycemia that results in neurological complications (Vipperla *et al*., 2017; Shanshan *et al*., 2020, Rajat *et al*., 2018, Alakel *et al*., 2019). The use of standard treatment (STD) that incudes limited oral intake (pancreatic rest), hydration (IV) and pain management are commonly used to treat HTG induced AP and its recurrence. However, the standard treatment was not as effective as use of insulin. Thus, there is need of non-invasive therapy with acceptable safety profile. The use of plasmapheresis (PPH) is common nowadays in several other countries and found effective in reducing TG levels rapidly and was effective in treatment of HTG induced pancreatitis.

In China, no comparative clinical data is available on effect of PPH versus STD in preventing recurrent AP in Chinese patients with HTG. The present investigation was designed to compare the effect of PPH versus STD in preventing recurrent AP in Chinese patients with severe HTG.

MATERIALS AND METHODS

Patients and eligibility criteria

Chinese patients aged 18 to 65 years who had history of hypertriglyceridemia induced acute pancreatitis with

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history of abdominal discomfort with Triglyceride (TG) level >1000mg/dl were included at Jingmen First People's Hospital after obtaining their written, informed consent form. The study was commenced only after getting written approval from institutional review board of Jingmen First People's Hospital vide ethics committee approval # IRB/JFPH-2019/09-0129/PCT. The exclusion criteria included: The patients with AP due to any other etiology; hypersensitivity/ contraindication to plasmapheresis; patient with any infection or sepsis or sign of severe kidney injury, severe brain edema; mental disorders and other contraindicated conditions based on the judgment of treating doctor were excluded.

Study treatment and procedure

Subjects who met eligibility criteria were randomly assigned to PPH or STD in allocation ratio of 1:1. The PPH group received PPH of up to 1.5ml daily based on body weight (kg) until TG level reached 500 mg/dl or less. Standard treatment measures included oral intake (pancreatic rest), hydration (IV) and pain management.

Efficacy and safety assessment

Demography and other characteristics data were collected from each enrolled patient who were assigned either of the treatment protocol. Primary endpoint was incidence of recurrent acute pancreatitis, which was measured based on consensus criteria. The patient who had abdominal pain and elevated level of pancreatic enzyme and required hospitalization or prolongation of existing hospitalization were considered as occurrence of pancreatitis.

In addition, each patient was observed for frequency of pancreatitis and hyperamylasemia with moderate to severe severity Hyperamylasemia was defined as elevated increase level of amylase compared to baseline. Amylase levels were measured before and after procedure. Safety of both the study drugs were assessed after treatment. Clinical outcomes were assessed.

STATISTICAL ANALYSIS

Since the present study was designed as pilot study, thus, sample size calculation was not performed. However, we have taken sample size of at least 100 patients to draw the preliminary finding which may serve basis to design large clinical trial to evaluate the effect of PPH versus STD in preventing recurrent AP in Chinese patients with severe HTG in larger population. Quantitative data were analyzed using t test or Mann Whitney based on the normality of data. Categorical data were analyzed using chi-square/fisher exact test as appropriate considering the data size. P values of less than 0.05 (level of statistical significance) will be considered as statistically significant. Data analysis was done using GraphPad Prism statistical analysis software (version 8.3.0).

RESULTS

A total of 100 Chinese patients were enrolled after meeting all the eligibility criteria. All enrolled patients completed the study as per the study protocol. Demographic and baseline characteristic of treatment groups are presented in table 1. All treatment groups were found similar in terms of demographic and baseline characteristic.

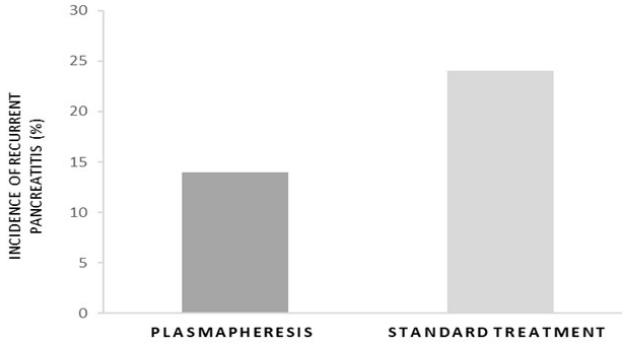

Fig. 1: Proportion of patients with recurrent pancreatitis

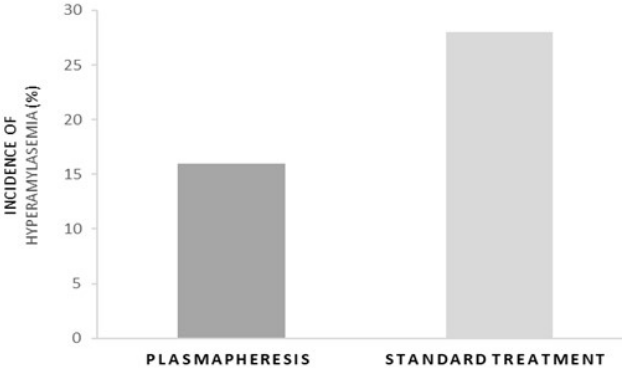

Fig. 2: Proportion of patients with hyperamylasemia

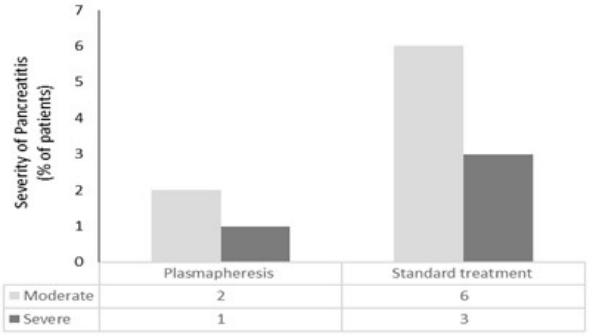

Fig. 3: Proportion of patients with moderate to severe case of pancreatitis

Proportion of patients with recurrent pancreatitis is presented in fig. 1. Among eligible patients who received either study drug protocol, 38% had recurrent pancreatitis and 42% had post hyperamylasemia. Number of patients with recurrent pancreatitis was substantially lower in PPH group as compared to STD. of total, 14% of patients in PPH had experienced recurrent pancreatitis as compared to 24% of patients in STD group.

Table 1: Demographic and baseline characteristic

Outcome variable	Plasmapheresis (N=50)	Standard treatment (N=50)	P value
Age, mean (SD)	64.5 (2.1)	61.2 (3.1)	>0.05
BMI, mean (SD)	25.1 (2.1)	24.6 (3.4)	>0.05
Gender (M/F), %	65/35	68/32	>0.05
Serum creatinine, mean (SD)	0.80 (0.2)	0.75 (0.3)	>0.05
Amylase, U/L, mean (SD)	104 (6.2)	108 (5.7)	>0.05
Pain score, mean (SD)	7.1 (2.1)	7.2 (1.8)	>0.05
Pancreatic enzyme, U/L, mean (SD)	154 (13.2)	152 (12.4)	>0.05
History of pancreatitis, %	100	100	>0.05
TG levels (mg/dl)	1232.8 (201.3)	1212.6 (212.3)	>0.05
Concomitant disease			
Nephropathy (mild), %	30	10	>0.05
Hypertension, %	40	40	
Diabetes, %	30	50	

Values are as mean (SD) for numerical variables except categorical variables. P values calculated by Man Whitney test for numerical variables, whereas chi-square test for categorical variables. P values more than 0.05 considered as statistically non-significant.

Table 2: Comparison of the effects of TG-lowering therapies

Outcome variable	Plasmapheresis (N=50) Median (IQ range)	Standard treatment (N=50) Median (IQ range)	P value
TG clearance rate in 24 hours (%)	0.68 (0.56-0.79)	0.52 (0.34-0.61)	<0.05
Amylase levels in 24 hours (U/I)	211.2 (129.1-239.2)	345.9 (231.2-520.3)	<0.05
Time required to reach target TG (h)	43 (20-64)	59 (34-82)	<0.05

Values presented as Median (IQ range). P values calculated by Man Whitney test for numerical variables, whereas chi-square test for categorical variables. P values less than 0.05 were considered as significant

Table 3: Comparison of clinical and safety outcomes

Outcome variable	Plasmapheresis (N=50)	Standard treatment (N=50)	P value
Mortality, %	0	2	<0.05
Local complications, %	20	19	>0.05
Requirement for surgery, %	3	9	<0.05
Study drug induced complications, %			
Decreased level of Potassium	1	6	<0.05
Rashes	1	6	<0.05
Thrombosis (deep vein)	0	1	<0.05
Tremor	1	4	<0.05
Length of stay (in days)	12	19	<0.05
Inflammatory response syndrome (systemic), %	4	11	<0.05
Cure, %	87	61	<0.05
P values calculated by chi-square test. P values less than 0.05 were considered as significant.			

Proportion of patients with hyperamylasemia is presented in fig. 2. The number of patients with hyperamylasemia were substantially lower in PPH group as compared to STD. Of total, 14% of patients treated with PPH had experienced hyperamylasemia as compared to 28% of patients in STD group.

The number of patients with moderate to severe case of recurrent pancreatitis were substantially lower in PPH group as compared to STD (fig. 3). Only 3% of patients treated with plasmapheresis developed hyperamylasemia of moderate (2%) to severe (1%) as compared to 9% of patients (moderate: 6%; severe: 3%) in standard treatment.

The number of patients with moderate to severe case of hyperamylasemia was substantially lower in PPH group as compared to STD (fig. 4).

Triglyceride (TG) lowering effect was compared between both the treatment group as indicated in table 2. TG clearance rate in 24 hours was substantially greater in PPH group as compared to STD. Also, similar trend of results was obtained when study treatment protocols were

compared for time required to reach target TG. Time to reach target TG was substantially higher in PPH group as compared to STD. Amylase levels in 24 hours were also significantly higher in patients treated with plasmapheresis as compared to standard treatment (table 2).

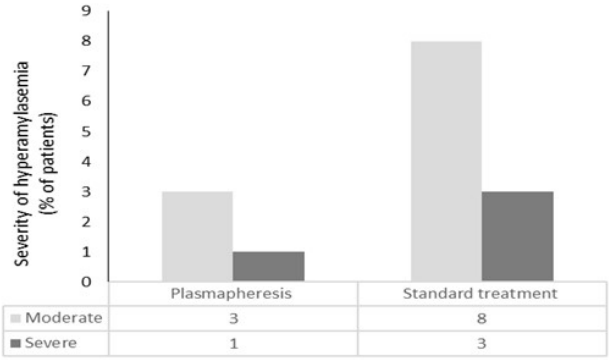

Fig. 4: Proportion of patients with moderate to severe case of hyperamylasemia

Clinical outcomes were compared between both the treatment group as indicated in table 3. There were no cases of mortality in plasmapheresis group as compared to 2% of patients in standard treatment. Incidence of local complications and drug induced complications were substantially lower in PPH as compared to STD. Length of stay was significantly shorter in patients of plasmapheresis group as compared to standard treatment. Inflammatory response syndrome (systemic) was substantially lower in PPH as compared to STD. Cure rate was significantly higher in patients of plasmapheresis group as compared to standard treatment (table 3).

Safety outcome measures such as incidence of complications/adverse events were compared and found comparable between the treatment groups.

DISCUSSION

Clinical data comparing the plasmapheresis versus standard treatment in preventing recurrent AP in patients with HTG is not available in China. Therefore, the present study was to compare the effect of PPH versus STD in preventing recurrent AP in Chinese patients with severe HTG.

In the present study, compared to standard treatment, incidence of pancreatitis and hyperamylasemia was substantially lower in PPH group. This indicated that the plasmapheresis is slightly better than standard treatment in preventing incidence of recurrent pancreatitis. Also, incidence of moderate to severe case of pancreatitis and hyperamylasemia was significantly lower in PPH group as compared to STD group. The effect of plasmapheresis in preventing recurrent pancreatitis was consistent with published studies (Kiran *et al*., 2017, Carrillo *et al*., 2015, Chang *et al*., 2016. However, there were no reports showing the comparison of plasmapheresis versus standard treatment in preventing recurrent pancreatitis. This is the first study conducted that revealed the efficacy of plasmapheresis was superior to standard treatment in preventing recurrent pancreatitis in patients with severe HTG. Betteridge et al reported that plasmapheresis administered was found effective in preventing recurrent pancreatitis among patients with severe hyper-triglyceridemia (Nasa *et al*., 2020). In the present study, TG clearance rate in 24 hours was substantially greater in patients treated with PPH as compared to STD. Also, time required to reach target TG was significantly higher in patients treated with plasmapheresis as compared to standard treatment. Overall results showed that plasmapheresis demonstrated greater TG-lowering effect as compared to standard treatment. The results of our study were consistent with the previous reports on benefits of plasmapheresis for the treatment of HTG induced AP (Kiran *et al*., 2017, Carrillo *et al*., 2015, Chang *et al*., 2016, Nasa et al., 2020). In published studies, PPH reduced TG levels by 70 to 90% (Kiran *et al*., 2017, Carrillo *et al*., 2015, Chang *et al*., 2016, Nasa *et al*., 2020). Moreover, in another published study, PPH substantially reduces TG in patients with severe HTG, and it eradicates inflammatory biomarkers that are known for progression of AP. Moreover, plasmapheresis demonstrated greater clinical outcome as compared to standard treatment.

Overall safety and efficacy results indicates that plasmapheresis and standard treatment have acceptable risk-benefit ratio and the results of this study recommend the use of plasmapheresis as a better alternative in preventing recurrent AP in Chinese patients with severe HTG. Since the present study was the first study thus, the result of this study would become benchmark for future studies in this area. Since the study was performed at single center, thus results can not be generalized to whole Chinese population.

CONCLUSION

The present study showed that treatment with plasmapheresis significantly lower incidence of pancreatitis and hyperamylasemia as compared to standard treatment in Chinese patients with severe HTG. Also, plasmapheresis demonstrated greater TG-lowering effect as compared to standard treatment. The results of this study recommend the use of plasmapheresis as a better alternative in preventing recurrent AP in Chinese patients with severe hypertriglyceridemia.

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