

Manuscript number: 65666

Title: "Therapeutic Plasma Exchange for Hyperlipidaemic Pancreatitis: Current Evidence and Unmet Needs"

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Dear Editors and Reviewers:

Thank you very much for your attention and comments on our paper "Therapeutic Plasma Exchange for Hyperlipidaemic Pancreatitis: Current Evidence and Unmet Needs". Those comments are all valuable and very helpful for revising and improving our paper. We have revised the manuscript according to your kind advices and the detailed suggestions. Revised portion are marked in red in the paper. The responses to the reviewer's comments are as following:

Responses to the reviewer's comments:

Response to Reviewer #1

1 The grammar could be improved

Response: 2 grammatical errors have been corrected, 2 sentences have been modified,

Before: It is believed that the risk and severity of HLAP **increase with increasing** levels of serum triglycerides (TG)

After: It is believed that the risk and severity of HLAP **increase with rising** levels of serum triglycerides (TG)

Before: **Till date**, numerous reports and several studies revealing the effectiveness of TPE in reducing TG levels have been published.

After: **To date**, numerous reports and several studies revealing the effectiveness of TPE in reducing TG levels have been published.

Before: In their report, a total of 132 patients with HLAP were analyzed. 43 patients underwent TPE; the 24-h TG clearance rate **is** 71% (62%-84%).

After: In their report, a total of 132 patients with HLAP were analyzed. In 43 patients underwent TPE, the 24-h TG clearance rate **was** 71% (62%-84%).

Before: A **retrospectively** review reported by Fei Fei et al.

After: A retrospective review reported by Fei F et al.

2 There is excessive use of Finally, However, Unfortunately, Nevertheless, Hence. It is not always necessary to 'Introduce@ a sentence. There are numerous spelling mistakes and typho's.

Response: 9 sentences have been rewritten, one sentence remains unidentified.

Before: PE has emerged as an effective modality in rapidly reducing serum TG levels and has been used for HLAP clinically. However, the exact role of PE on the disease course is unclear and remains poorly evaluated.

After: Although TPE has emerged as an effective modality in rapidly reducing serum TG levels and has been used for HLAP clinically, the exact role of TPE in the disease course is unclear and remains poorly evaluated.

Before: Conservative treatment, including fasting, lipid lowering drugs, insulin or fluid restoration might decrease TG level, however slowly from time span of days to weeks. In contrast, PE might decrease TG level rapidly in hours

After: Conservative treatment, including fasting, lipid lowering drugs, insulin or fluid restoration might decrease TG level in a time span of days to weeks, whereas TPE might decrease TG level rapidly in hours

Before: However, conflicting results have been reported. Gubensek et al. [26] analyzed 103 patients of HLAP treated with PE,

After: In consistent with reports as mentioned above, Gubensek et al. [26] analyzed 103 patients of HLAP treated with TPE:

Before: it is wildly believed that TG concentrations are associated with a more complicated hospital course, including a need for admission to intensive care units, persistent multi-organ failure and systemic inflammatory response syndrome (SIRS). Hence, it is desirable to lower the TG concentrations acutely in HLAP

After: It is wildly believed that TG concentrations are associated with a more complicated hospital course, including a need for admission to intensive care units, persistent multi-organ failure and systemic inflammatory response syndrome (SIRS), indicating that it is desirable to lower the TG concentrations acutely in HLAP

Before: However, it is difficult to conclude that TPE has a higher TG-lowering effect than treatment without TPE.

After: Although TPE results in a rapid lowering of TG, it is difficult to conclude that TPE has a higher TG-lowering effect than treatment without TPE.

Before: Although many studies have showed the efficacy of PE in reducing TG levels, the impact of TPE on reducing the severity of HLAP or other endpoints like mortality has not been established. Case reports revealing its role in severe HLAP

have been published in literature. Dehai and Adashek [39] reported a case of HLAP

After: The impact of TPE on disease severity has been demonstrated in a few cases reports. Dehai and Adashek [39] reported a case of HLAP

Before: However, if and how much benefit TPE imparted on reducing the severity of AP hence ameliorating the outcome is difficult to determine.

After: There is limited data from well designed comparative studies regarding the impact of TPE on disease course.

Before: PE was initiated after which the TG level stabilized at 980 mg/dl, however, appropriate insulin treatment was not conducted initially.

After: TPE was initiated with no insulin treatment after which the TG level stabilized at 980 mg/dl.

Before: A review by Garg and Rustagi [52] suggested TPE should be initiated preferably within 36 hours provided patient is able to tolerate the treatment. However, another large retrospective study including 111 HLAP patients treated with TPE showed no difference in mortality in the early (>36 hours) and late (within 36 hours) PE group

After: A review by Garg and Rustagi [52] suggested TPE should be initiated preferably within 36 hours provided patient is able to tolerate the treatment. This time frame requires further investigation, since another large retrospective study including 111 HLAP patients treated with TPE showed no difference in mortality in the early (>36 hours) and late (within 36 hours) TPE group

3 Relationship between Serum TG LELEL should be Level...retrospectively

Response: Since we cannot identify in which paragraph the sentence is referred, so, it has not been modified. We are grateful if the reviewer can be kindly enough to help us to point out the sentence remained modified

Response to Reviewer #2

1 There are a few minor points which may further improve the manuscript and readability: PE, TPE, Plasmapheresis and Plasma Exchange have been used by the authors on different points within the manuscript which may confuse the lay reader. It is better to adopt uniformity.

Response: We have added sentences describing what apheresis broadly describes as follow in the paper (Apheresis broadly describes the removal of blood components. A variety of techniques including plasmapheresis, plasma exchange (PE), low-density lipoprotein apheresis has been used with a goal of reducing disease severity. TPE is a procedure that removes plasma from the blood and replaces it with colloid or

crystalloid solutions), the apheresis related techniques were replaced by phrase “TPE”.

2 The manuscript will improve if the authors can add a table to summarize the results from the studies that they have mentioned in the study.

Response: A table has been added in the paper

Table 1. Reports comparing TG clearance rate and mortality between TPE and non-TPE groups

First author	Date	Study design	Study size	TPE vs Non-TPE	24-hTG clearance rate	Mortality
Yu S	2020	retrospective study	132	43 with TPE	TPE: 71%	TPE: 6.89%
				46 with IIT	IIT: 68%	IIT: 6.52%
				43 with NIIT	NIIT: 62%	NIIT: 2%
Fei F	2020	retrospective study	8	all with TPE	60.30%	/
Gubensek J	2014	retrospective cohort study	103	74 with early TPE	early TPE: 59%	early TPE: 7%
				29 with late TPE (conservative treatment followed by TPE)	conservative treatment: 27%	late TPE: 6%
Simsir I Y	2019	retrospective study	31	all with TPE	69.70%	0
Kandemir A	2018	retrospective study	33	all with TPE	54.40%	3%
Miyamoto	2017	post hoc analysis	30	10 with TPE	no difference between groups	TPE: 0%
				20 without TPE		non-TPE: 10%
Keskin E	2019	retrospective study	41	12 with TPE	TPE: 44%	TPE: 25%
				29 without TPE	non-TPE: /	non-TPE: 0

TPE, therapeutic plasma exchange; IIT, insulin intensive therapy; NIIT, non-intensive insulin therapy

3 Some of the abbreviations have been used without definition at their first use in the text. There are minor linguistic and grammatical errors which should be corrected.

Response: abbreviation, linguistic and grammatical errors have been corrected as stated above in response to Reviewer #1

Enclosed please find the responses to the referees. We sincerely hope this manuscript will be finally acceptable to be published on Word Journal of Clinical Cases. Thank you very much for all your help and looking forward to hearing from you soon.

Best regards

Sincerely yours

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