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# Clinical Improvement with Therapeutic Plasma Exchange in Neuroimmunological Children: A Single Center Experience

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## About this report

This open peer review (OPR) report shows the public comments made on this article during peer review, by the reviewers, the associate editor and the editor-in-chief, for every revision round, together with the authors' replies. Comments appear only with the consent of the people who wrote them. Reviewers who chose to sign their report are named; the others are shown as "Referee". Comments are edited for language only, and confidential remarks to the editors are not included.

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## 1 Original submission

1 comment · 16 May 2023

### Referee 1 Reviewer

MAJOR REVISION 16 May 2023

In the Discussion section:
1. The present study shows that the response to plasma exchange in patients with motor manifestations is more favorable than in patients with ocular manifestations.------> Please clarify the patient group that manifested this result.
2. It was also shown that in the MS and NMOSD group, in patients with a lower MRS score in the follow-up the main complaints were decreased visual acuity and motor problems. ------> Do you mean that PE in this specific group led to any special consequences? Please clarify.
3. Finally, this study shows that TPE is a good treatment with minimal side effects in children with neurodegenerative diseases caused by antibodies, especially in GBS and AE. -----> Given that there is no comparison method, how could you consider PE a good therapeutic method? What about the natural course of the disease?

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# Revision 1

AUTHORS' RESPONSE TO REVIEWERS

Authors' reply to reviewers

The next pages contain the authors' point-by-point reply to the comments of this revision round, as submitted with the revised manuscript. It is published as the authors wrote it.

14 June 2023

Re: Resubmission of manuscript “Clinical improvement with Therapeutic Plasma Exchange in Neuroimmonologic Children; Single Center Experience”

Manuscript Code: 137105

Dear Editor,

We are very excited to have been given the opportunity to revise our manuscript “Clinical improvement with Therapeutic Plasma Exchange in Neuroimmonologic Children; Single Center Experience” for **Iranian Journal of Pediatrics**. We truly appreciate you assigning such qualified Subject Editor and reviewers to our manuscript. Their efforts and insights were a tremendous help to us during this revision. We worked hard to prepare point-by-point responses to each of the comments of the reviewers. The revision has been developed in consultation with all coauthors, and each author has given approval to the final form of this revision. We want to extend our appreciation for taking the time and effort necessary to provide such insightful guidance. We hope that the revisions in the manuscript and our accompanying responses will be sufficient to make our manuscript suitable for publication in Iranian Journal of Pediatrics.

We shall look forward to hearing from you at your earliest convenience.

Yours sincerely,

Somayeh Hajatnia

**Responses to the reviewers' comments:**

**Manuscript Number: 137105**

**Clinical improvement with Therapeutic Plasma Exchange in Neuroimmonologic Children; Single Center Experience**

**Journal**: Iranian Journal of Pediatrics

We would like to thank the “Iranian Journal of Pediatrics” for giving us the opportunity to present in its article “Clinical improvement with Therapeutic Plasma Exchange in Neuroimmonologic Children; Single Center Experience" reconsider. We also thank the reviewer for their high evaluation of the research content. We carefully considered their comments in preparing our review, resulting in a clearer, more compelling, and more comprehensive paper. We hope that the reviewed article can be approved. The following summarizes how we respond to reviewer comments. Below are our one-by-one responses to their comments. Thanks again for all the help.

**********

**Reviewer’s comments:**

**Reviewer #1:**

Thank you for providing this opportunity to review the following paper: "Clinical improvement with Therapeutic Plasma Exchange in Neuroimmonologic Children; Single Center Experience". The authors discussed the therapeutic efficacy of PEX as a treatment option in a small cohort heterogenous group of neuroimmunological disorders in children from a single referral children's hospital. The following are my comments on the paper:

1- English language editing is needed.

**Response:**

Thank you for your attention and valuable comment. Based on the esteemed reviewer's opinion, the entire manuscript has been rewritten and edited by a native expert writer.

2- "Introduction" looks disorganized. It should be focused on the efficacy of PEX in pediatric neuroimmunlogical disorders in detail based on literature review./ The last paragraph can be removed completely.

**Response:**

We appreciate the valuable comment provided by the respected reviewer. The introduction section has undergone a thorough revision to align with the esteemed reviewer's perspective, with a primary emphasis on highlighting the efficacy of the PLEX method through previous research conducted on pediatric neuroimmunlogical disorders. Moreover, as per the esteemed reviewer's recommendation, the final paragraph of the introduction has been excluded. The

substitute text in the document is presented below and is highlighted in green across the manuscript:

Therapeutic plasma exchange (TPE) has become a well-established treatment method for various pediatric neuroimmunological disorders in recent decades. Its effectiveness lies in the removal of circulating autoantibodies, immune complexes, and cytokines from the blood, followed by volume replacement with fluid. In summary, TPE involves drawing venous blood into an external circuit, separating the cellular components from the plasma, and replacing the plasma with fresh frozen plasma and albumin [1]. The first instance of therapeutic plasma exchange dates back to 1960 when Schwab and Fahey performed the procedure to reduce high globulin levels in a patient with macroglobulinemia [2]. The American Apheresis Society strongly advocates for plasma exchange as a primary treatment option in diseases like Guillain-Barré syndrome (GBS) and N-methyl-D-aspartate receptor (NMDAR)-related autoimmune encephalitis, and as a secondary treatment option in diseases like acute disseminated encephalomyelitis (ADEM), multiple sclerosis, neuromyelitis optical spectrum disorder (NMOSD), and pediatric autoimmune neuropsychiatric disorders associated with streptococcal infections (PANDAS) [3]. The efficacy of therapeutic plasma exchange in various pediatric neuroimmunological disorders has been demonstrated in the existing literature [4-7]. Recently, Akcay et al. [8] evaluated the effectiveness of TPE in patients with multiple sclerosis (MS), transverse myelitis (TM), and ADEM, using EDSS and GS scoring criteria. They reported positive outcomes with this treatment method. Similarly, Atay et al. [9] conducted a study on twenty patients with neuroimmunological disorders, including autoimmune encephalitis (AE), GBS, and ADEM, and observed clinical improvement after TPE. In our current study, we present our experience with TPE in children with neurological disorders at a single center and describe the resulting clinical improvements.

3- "Material & Method": inclusion and exclusion criteria are not cleared. In case of a few disorders such as MS, ADEM, and NMOSD, PEX is not the first line treatment. Why did the authors consider PEX as the first line treatment in these patients? / Except for MRS, other improvement criteria are not cleared such mental complaints, they are subjective, not objective; therefore, they are not reliable.

**Response:**

We appreciate your kind consideration and valuable input. The inclusion criteria for this study consisted of neuroimmunological patients who, despite receiving first-line treatments, obtained inadequate treatment response or, due to the severity of the disease and its rapid progression, required plasma exchange for their treatment. As per the suggestion of the respected reviewer and for clarification purposes in the Materials and Methods section of the article, this information was added and highlighted in green:

The inclusion criteria for this study consisted of neuroimmunological patients who, despite receiving first-line treatments, obtained inadequate treatment response or, due to the severity of the disease and its rapid progression, required plasma exchange for their treatment.

Furthermore, patients were excluded from the study if they died during plasma exchange due to reasons unrelated to the procedure itself or if their diagnosed condition changed to non-neuroimmunological disorders after completion of the procedure. Patients with primary autonomic and coagulation disorders were also not included in the research. For further transparency, this section was added to the Materials and Methods part of the article and highlighted in green:

Furthermore, patients were excluded from the study if they died during plasma exchange due to reasons unrelated to the procedure itself or if their diagnosed condition changed to non-neuroimmunological disorders after completion of the procedure. Patients with primary autonomic and coagulation disorders were also not included in the research.

Additionally, regarding the consideration of TPE as a first-line treatment, as mentioned in the manuscript, according to the American Apheresis Society [3], this procedure is considered a first-line treatment for patients with GBS and NMDAR-associated autoimmune encephalitis, while for other neuroimmunological patients, it is considered as a second or third-line treatment. However, this study did not mention whether this method was considered as a first-line treatment for all subgroups. In present research, TPE was used for other neuroimmunological patients such as AE, ADEM, ON, MS, and NMOSD when these patients did not respond adequately to other first-line treatments such as IVIg and steroids.

Regarding the assessment criteria of patient improvement in the initial stage before considering the MRS scoring system, it is necessary to mention that based on clinical conditions and characteristics, specific clinical examinations were performed for each subgroup before and after each cycle, and the effectiveness of the treatment was evaluated during the 3 to 6-month follow-up period based on clinical examination improvement. For example, in the MS patient group, the status of patients in terms of visual acuity, color vision, deep tendon reflexes, muscle force, level of consciousness (GCS), and psychiatric disorders was precisely evaluated before and after TPE, as well as during the three to six-month follow-up period. Similarly, in another subgroup, AE patients, the status of patients in terms of seizure, deep tendon reflexes, level of consciousness (GCS), and psychiatric disorders was thoroughly evaluated before and after TPE, as well as during the three to six-month follow-up period. A summary of the results of these examinations is mentioned in sections 2-1 to 2-6 of the present manuscript.

4- "Results": Again, the treatment approach of enrolled patients is not clear. Treatment approach is very heterogeneous; therefore, the efficacy of PEX is hard to follow in patients./Again improvement criteria in different groups of disorders are not cleared . The authors have mentioned improvement in visual or behavioral symptoms vaguely.

**Response:**

We would like to thank you for your valuable comment. Regarding the therapeutic approach, it is essential to note that the use of TPE procedure is generally not employed as a first-line treatment, as evident in Table 1, where the majority of patients received treatments such as IVIG and steroids. However, the initiation of TPE treatment occurred when patients were in the acute stage of the disease and did not respond adequately to other treatments, making it a

therapeutic option for the acute phase. As for the evaluation and effectiveness of TPE, as mentioned in the previous comment, all specialized assessments were conducted separately for each subgroup. Evaluation indices such as visual acuity, color vision, deep tendon reflexes, muscle strength, level of consciousness (GCS), psychiatric disorders, seizures, and gag reflex were accurately assessed before and after TPE and during the three to six-month follow-up period. It is important to emphasize that the primary objective of the present study was to evaluate the efficacy of TPE treatment in the acute phase of the disease.

5-"Discussion": No reference has been cited for the beginning sentences/ Tables 1 and 2 can be merged as a single table./ Table 3 is very busy and non-informative. It just be summarized to side effects of PEX in patients if there no significant abnormality in lab tests

**Response:**

The valuable comments of the esteemed reviewer were incorporated. The first sentence of the discussion section was revised by incorporating a reference and is as follows (highlighted in green):

In recent years, the TPE method has been increasingly used with promising results in the treatment of children with various diseases [12].

[12] Öztürk, Ahmet Gökcan, Zeynep Erva Küçük, Serhan Özcan, Merve Havan, Emrah Gün, Edin Botan, and Tanıl Kendirli. "Use of Therapeutic Plasma Exchange in the Pediatric Intensive Care Unit." Turkish Archives of Pediatrics 57, no. 2 (2022): 186.

Furthermore, Table 1 and Table 2 were merged based on the valuable comment of the reviewer, and Table 1 was revised and highlighted in green in the manuscript as follows:

Table 1: Demographic data of studied patients in various subgroups

| Diagnosis | Case Num. | Age | Age Ave. | Age SD* | Weight (kg) | Weight Ave. (kg) | Weight SD* | Gender | Initial treatment | Number of TPE procedure |
|---|---|---|---|---|---|---|---|---|---|---|
| MS | 4 | 14 | 12.50 | 1.12 | 73 | 53.25 | 13.46 | Female | Steroid | 8 |
| | 13 | 13 | | | 52 | | | Female | Steroid | 7 |
| | 14 | 12 | | | 53 | | | Male | Steroid | 8 |
| | 18 | 11 | | | 35 | | | Female | Steroid | 5 |
| NMOSD | 5 | 11 | 9.50 | 1.50 | 34 | 30.75 | 8.01 | Female | Steroid | 7 |
| | 6 | 7 | | | 19 | | | Female | IVIG/Steroid | 5 |
| | 11 | 10 | | | 41 | | | Male | Non | 7 |
| | 15 | 10 | | | 29 | | | Female | IVIG/Steroid | 7 |
| AE | 1 | 12 | 12.50 | 1.12 | 60 | 45.25 | 8.53 | Male | IVIG | 10 |
| | 9 | 11 | | | 40 | | | Male | IVIG/Steroid | 5 |
| | 16 | 14 | | | 41 | | | Male | Steroid | 7 |
| | 17 | 13 | | | 40 | | | Female | Steroid | 8 |
| GBS | 3 | 9 | 8.75 | 3.19 | 24 | 27.00 | 13.87 | Male | IVIG | 7 |
| | 7 | 4 | | | 13 | | | Female | IVIG | 5 |
| | 8 | 9 | | | 21 | | | Male | IVIG/Steroid | 5 |
| | 10 | 13 | | | 50 | | | Male | IVIG | 7 |
| ADEM | 2 | 15 | 15 | - | 50 | 50 | - | Male | IVIG/Steroid | 8 |
| ON | 12 | 12 | 12 | - | 47 | 47 | - | Female | Steroid | 5 |

*SD: Standard Deviation

In addition, as per the reviewer's suggestion, Table 3 was removed, and the valuable information from this table regarding the side effects was mentioned in detail in Section 3 - Side Effects. This modification has also been highlighted in green in the manuscript, as shown in the following text:

In a patient within the MS subgroup, the initial platelet count prior to therapeutic plasma exchange was 294,000/µL, which decreased to 110,000/µL after the TPE procedure. Considering the absence of any significant symptoms in the patient and a platelet count above 100000/µL, no specific therapeutic intervention was required during hospitalization. Additionally, the platelet count returned to the normal range (203,000/µL) during the 3-month follow-up period.

**Reviewer #2:**

Thank you for choosing me to review this manuscriptThis is a single-center study with a small sample size. Because of the small sample size, the authors cannot analyze the results to show any correlation or odds ratios. The results of this study are in accord with the previous studies. We all know that PE is effective in almost all immunologic diseases and should be considered in every child with these diseases. The main shortcomings of this procedure are the logistics and availability of the device. To me, this study has nothing to add to the current literature, however, as a single-center study, the results could be encouraging for other local centers to consider this procedure. Before any decision, this manuscript needs precise native English and style revision.

**Response:**

We appreciate your kind consideration and valuable input. The present study investigates the effectiveness of plasmapheresis as an adjunctive therapeutic approach alongside other first-line treatments in children with neuroimmunological disorders. Due to limited resources for plasmapheresis, the number of enrolled patients in this study was restricted. Currently, this research can serve as a starting point for further studies in this field at other centers within the country. In Iran, plasmapheresis is still considered as a last resort therapeutic option in some smaller centers. By locally employing this treatment method, we can demonstrate the effectiveness and low adverse effects of this procedure in the country. This may create an opportunity for other medical centers in different cities to have better access for timely administration and quicker response in patients with severe symptoms. Furthermore, according to the esteemed reviewer's opinion, the manuscript has been revised by a native translator.

**Reviewer #3:**

1. The present study shows that the response to plasma exchange in patients with motor manifestations is more favorable than in patients with ocular manifestations. Please clarify the patient group that manifested this result.

**Response:**

Thank you for your attention and valuable comment. Therapeutic plasma exchange is typically regarded as a primary treatment option for patients suffering from neuroimmunological disorders like CIDP and GBS with motor impairments. This procedure has demonstrated notable advancements in the well-being of these individuals. However, it should be noted that each neuroimmunological disorder may have its own specific conditions and symptoms, and the decision regarding the use of plasma exchange should be made on an individual basis by the treating physician. This decision is typically based on the patient's clinical history, test results, and other relevant factors related to the disease and its status. In the present study, positive changes were observed in the group of patients with neuromyelitis optica spectrum disorder (NMOSD) and multiple sclerosis (MS) at two stages: after plasma exchange and during the follow-up period of 3 to 6 months post-treatment. Particularly, patients with motor manifestations demonstrated a greater degree of improvement compared to those with solely ocular manifestations or ocular-motor manifestations. It is important to note that these findings are reported based on the observations and results obtained in the current study.

Also, the following text has been added to the manuscript and highlighted in green:

In the present study, positive changes were observed in the group of patients with NMOSD and MS at two stages: after plasma exchange and during the follow-up period of 3 to 6 months post-treatment. Particularly, patients with motor manifestations demonstrated a greater degree of improvement compared to those with solely ocular manifestations or ocular-motor manifestations.

2. It was also shown that in the MS and NMOSD group, in patients with a lower MRS score in the follow-up the main complaints were decreased visual acuity and motor problems. Do you mean that PE in this specific group led to any special consequences? Please clarify it.

**Response:**

We appreciate the valuable comment provided by the respected reviewer. An error occurred in expressing the intended meaning here, and the reason for that was a problem in translating the text of the manuscript. In fact, the severity of the disease and the presence of concurrent ocular and motor symptoms in patients of these two groups prior to undergoing therapeutic plasma exchange were associated with a decrease in their MRS scores. The previous text has been removed as a correction, and the following text has been added as the revised text in the manuscript:

The least changes in the MRS score in the follow-up were observed in two groups of patients with Multiple Sclerosis and Neuromyelitis Optica Spectrum Disorder who presented with concurrent visual and motor impairments as their initial complaint.

3. Finally, this study shows that TPE is a good treatment with minimal side effects in children with neurodegenerative diseases caused by antibodies, especially in GBS and AE. By

considering there is no comparison method, how could you consider the PE as good therapeutic method? What about the natural course of the disease?

**Response:**

we appreciate your focus and insightful comment. Previous research and clinical experiences have demonstrated that therapeutic plasma exchange is utilized as a valid and approved method by the medical community. The use of this therapeutic approach and the positive experiences reported by many healthcare professionals and neuroimmunological patients indicate its effectiveness and efficacy. The present study also showed that in cases where patients did not respond adequately to initial treatments such as IVIG and corticosteroids, this procedure led to clinical symptom improvement. Furthermore, the current research demonstrates that approximately 95% of patients have shown a favorable initial response to this treatment modality. Therefore, this method can be utilized as a therapeutic approach in the pediatric population affected by neuroimmunological diseases. Additionally, in this study, the MRS scoring method was employed to evaluate patients' clinical response to this treatment modality. As mentioned in the manuscript, a decrease in the MRS score (indicating an improvement in patients' symptoms) was observed after therapeutic plasma exchange in the majority of patients.
The effectiveness of therapeutic plasma exchange depends on the type and severity of the disease, as well as the patient's response to treatment. In some cases, TPE can lead to temporary improvement in symptoms and patient function, but additional treatments may still be necessary. Therefore, TPE can assist in reducing symptoms during the acute phase of the disease and enhancing the patient's quality of life, although it cannot completely eradicate the disease. For instance, in the case of patients diagnosed with MS and NMOSD in this study, maintenance therapies such as rituximab have been utilized. However, in monophasic diseases like ADEM and GBS, there has been no requirement for additional maintenance treatment following plasma exchange.

Finally, we are very grateful to the honorable referees. We appreciate your positive feedback about the paper, and we thank you for the time you have spent reviewing and scrutinizing our manuscript. We have improved the quality of the paper according to your comments.

Sincerely,
Somayeh Hajatnia

## 2 Revision 1

1 comment · 2 Jul 2023

**Zahra Rezaei** Reviewer

ACCEPT 2 Jul 2023

Dear author/s,
Thank you for your meticulous revision and comprehensive attitude.