Title

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Journal

Neurology Clinical Practice, 8(4)

ISSN

2163-0402

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Publication Date

2018-08-01

DOI

10.1212/cpj.0000000000000480

Peer reviewed

RESEARCH CLASS OF EVIDENCE

Safety and efficacy of plasma exchange in pediatric transverse myelitis

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Neurology: Clinical Practice August 2018 vol. 8 no. 4 327-330 doi:10.1212/CPJ.0000000000000480

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Abstract

Background

We sought to review safety and efficacy of therapeutic plasma exchange (TPE) in a cohort of pediatric patients with transverse myelitis.

Methods

Billing data of all plasma exchanges performed at our tertiary care pediatric hospital between August 2010 and August 2016 were compared to electronic medical records to find all patients whose indication for apheresis was transverse myelitis. Patient outcomes were quantified on the modified Rankin Scale.

Results

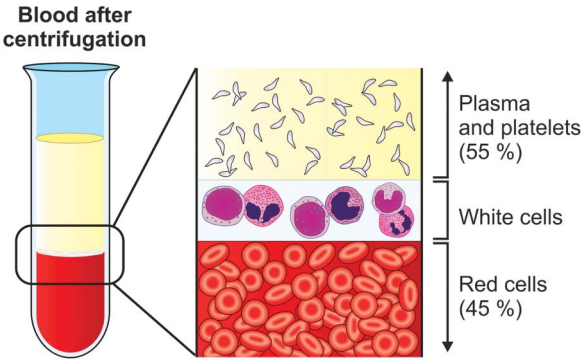
Fifteen of 19 patients (79%) had major improvement in symptoms after a course of 4–7 therapeutic plasma exchanges. The majority required further inpatient (6, 32%) or outpatient (8, 42%) physical therapy. Four (21%) patients returned to baseline and over 75% regained their ability to ambulate as of last follow-up. Four adverse events were noted over 114 treatments.

Conclusions

TPE can be a useful treatment for pediatric transverse myelitis. The retrospective nature of this study without a comparator group limits conclusions about efficacy. However, controlled trials would help to validate our results.

Classification of evidence

This study provides Class IV evidence that plasma exchange is safe and effective in pediatric transverse myelitis.



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Transverse myelitis (TM) is a disorder of the spinal cord where inflammation can cause sensory, autonomic, and motor dysfunction.[1] The pathophysiology is thought to be immune mediated[2] but identified autoantibodies (that might be causative) have not been identified in idiopathic cases. A majority of TM cases are initially categorized as idiopathic,[2] but many (15%–36%) are never further classified despite multi-year follow-up.[3] Up to 66% of cases are associated with an infectious prodrome within a month of TM diagnosis.[4]

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Funding information and disclosures are provided at the end of the article. Full disclosure form information provided by the authors is available with the full text of this article at Neurology.org/cp.

In 108 of 114 treatments, TPE was well-tolerated. Symptoms were noted in 4 patients during a total of 6 treatments.

TM in children, regardless of cause, can result in long-term disability.[4] Corticosteroid treatment is currently considered standard of care.[4] Other interventions that have been utilized in both children and adults include therapeutic plasma exchange (TPE), IV immunoglobulin (IVIg), and cyclophosphamide.[2,4] One study from 2015 noted outcomes in 12 children treated with TPE for CNS demyelination conditions, but only 6 were diagnosed with acute TM.[5] This study analyzes our experience with TPE in pediatric TM.

Methods

Institutional review board (IRB) approval was granted to conduct a retrospective chart review of pediatric patients billed for TPE at Children's Health Children's Medical Center Dallas between August 2010 and August 2016. Charts were reviewed for indication for TPE and those patients with TM were included in this analysis. Data about treatments, adverse events, and outcomes were extracted. One patient was excluded based on diagnosis of leukemia complicating diagnostic evaluations and data interpretation. One patient included in the analysis was subsequently diagnosed with neuromyelitis optica (seropositive). All other patients remained in the idiopathic TM diagnostic category during follow-up.

Standard protocol approvals, registrations, and patient consents

Data collected for this study were done so under an IRB-approved protocol. Parents of patients or legal guardians signed informed consent as dictated per protocol.

Data availability

Anonymized data not published within this article will be made available by request from any qualified investigator.

Results

A total of 19 patients were identified whose indication for TPE was TM. Patients ranged in age from 7 months to 17 years (mean 9.4 years). The cohort showed a slight female predominance (11 female and 8 male) (table). Patients received 4–7 TPEs (mean 5.9) performed every other day using a COBE Spectra or Spectra Optia Apheresis System (TerumoBCT, Lakewood, CO). Target treatment goal was, in almost all cases, 1.1 patient plasma volumes. This goal was reached in 112 of 114 treatments (98%) and exceeded in 8 treatments (7%). Most commonly (7 of 8), 1.2 plasma volumes was reached because the final albumin bottle was finished rather than wasted.

A 5% albumin solution (with IV calcium supplementation) was the only replacement used in 93 treatments (81%). A total of 19 treatments in 11 patients required 1 unit per 5 kg of cryoprecipitated antihemophilic factor (AHF). A total of 3 TPEs in 2 different patients required two-thirds 5% albumin and one-third thawed plasma replacement. Institutional practice is to add cryoprecipitated AHF if the pretreatment fibrinogen is below normal (130–140 mg/dL). Thawed plasma is generally used if the prothrombin time and activated partial thromboplastin time are also elevated (greater than 1.5 times upper limit of normal), because cryoprecipitated AHF does not contain a full dose of the labile clotting factors.

Six of 19 (32%) patients were less than 30 kg at the time of TPE. Therefore, the 225 mL volume of the apheresis circuit (including blood warmer) would have exceeded 12% of their total blood volume. In order to prevent risk of cardiovascular collapse, a reconstituted whole blood unit ±10% of patient hematocrit was used to prime the circuit after initial saline prime.

In 108 of 114 treatments, TPE was well-tolerated. Symptoms were noted in 4 patients during a total of 6 treatments. The first instance was a patient noting new onset numbness and tingling of 2 fingers in her right hand. Ionized calcium was normal. Symptoms resolved spontaneously within 30 minutes (adverse event [AE] grade 1). TPE was completed without incident. The second and third incidents were more serious, possibly because they occurred in a more critically ill patient. During TPE 5 of 7, the patient experienced bradycardia during a fit of coughing (a 6-second pause on telemetry). The patient had had similar incidents before, but this was the most severe to date. Apheresis was paused, ionized calcium was checked (normal), heart rate stabilized, and TPE was completed without further incident (AE grade 2). The same patient also experienced hypotension during the next treatment (mean arterial pressure of 30–40s), despite running at 105% fluid balance during the procedure. TPE was paused and ionized calcium was checked (normal). Epinephrine drip was started by the pediatric intensive care team and slowly weaned after completion of apheresis (AE grade 3). The patient had further incidents after TPE course was complete and eventually had a pacemaker placed. Side effect 4 was moderate hypotension (blood pressure 90/40), which resolved with 100 mL normal saline bolus (AE grade 2). This patient had no further blood pressure issues, but did complain of her legs falling asleep during the next plasma exchange (2 out of 4 total). Symptoms were determined to mimic her TM and there was no other evidence of citrate toxicity, so TPE was completed without further incident. The final complaint was of sharp, sternal chest pain.

Table Demographics, treatment, and outcomes

Patient no.	Sex	Age	Days to TPE 1	Total no. of TPEs	Other treatments	Physical therapy	Nadir mRS	Time to last follow-up, mo	Follow-up mRS
1	F	13 y	2	7	Sol ×5, 2 before TPE, IVIg after TPE	Inpatient	5	39	2
2	F	8 y	6	5	Sol ×5, 2 before TPE	None	5	12	1
3	F	11 y	7	5	Sol ×5, all before TPE	Outpatient	4	3	1
4	F	12 y	6	7	Sol ×5, all before TPE	Outpatient	3	44	2
5	F	13 y	36	7	Sol ×6, all before TPE OH, Cytoxan after	Outpatient	3	36	2
6	M	10 mo	4	7	1 g IVIg 3 days before TPE, 2 g/kg IVIg over 5 days after TPE	None	NA	9	NA
7	M	17 y	33	5	Sol ×5, all before TPE	Outpatient	3	6	1
8	F	10 y	8	4	Sol ×5, all before TPE	Outpatient	2	60	0
9	M	8 y	1	7	Sol ×5, 1 before TPE, Cytoxan ×2 after	Inpatient	5	36	5
10	M	11y	69	5	Sol ×5, all before TPE	None	2	4	1
11	M	16 y	23	7	Sol ×5, all before TPE	Outpatient	4	3	2
12	F	17 y	6	5	Sol ×5, 3 before; 1 rituximab dose after	None	4	12	2
13	M	15 y	8	7	Sol ×5, 1 before TPE	Inpatient	5	4	2
14	F	1 y	18	7	Decadron/sol unknown doses OH	Outpatient	5	22	2
15	F	7 mo	17	5	IV steroids and IVIg ×2 at OH before	None	NA	0	NA
16	F	1 y	2	5	Sol, 1 dose before TPE	Outpatient	NA	6	NA
17	M	11 y	4	6	Sol ×5, 1 before TPE	Inpatient	5	27	5
18	M	13 y	11	7	Sol ×5, all before TPE OH	Inpatient	5	39	4
19	F	7 mo	4	5	Sol ×5, 2 before TPE	Inpatient	NA	76	NA
Mean		9.9 y	13.75	5.9					

Abbreviations: IVIg = IV immunoglobulin; mRS = modified Rankin Scale; NA = not applicable; Sol = Solu-Medrol; TPE = therapeutic plasma exchange.

Electrolytes were normal, cardiac monitor showed no abnormality, and pain was not close to catheter skin insertion site or location of distal tip according to most recent chest radiography. Symptoms resolved with pain medication; TPE was completed without incident.

Other treatments

All patients received corticosteroids prior to TPE. In 18 cases, the method of delivery was confirmed to be IV. In 17 cases, the number of doses was recorded. Most patients (14 of 17) received 5 doses of IV Solu-Medrol. On average, they received 3.2 doses (range 1 to 6) prior to initiation of plasma exchange.

Two patients received IVIg at other hospitals prior to TPE being initiated here. Much (between 63% and 78%)[6] of those doses would have been removed. After completing their course of apheresis, 5 patients received additional chemotherapy: 2 with cyclophosphamide, 1 with rituximab, and 2 with IVIg. While the rituximab treatment was given after a subsequent neuromyelitis optica immunoglobulin G returned positive, the other 4 treatments were given due to lingering deficits after plasma exchange therapy.

Outcome results

Fifteen of 19 patients (79%) had substantial improvement in symptoms at hospital discharge. Post hospital follow-up was available on 18 of 19 (95%) patients for a mean of 25 months (range 0 months to 6 years). Of those 18, 14 (78%), were ambulatory at time of last follow-up. A modified Rankin Scale (mRS) score was assigned to each patient at nadir and at last follow-up (table). Excluding the patients with infantile onset (for which mRS would not be an appropriate scale), there were 15 patients assessed. Of these 15, 12 (80%) had mRS of 2 or less (meaning they were independent of all activities). It is worth noting that for the patient with infantile onset and available follow-up data, the patient was able to start ambulating around 24 months of age after being quadriplegic

There is no uniformity in the literature as to whether the treatment regimen for TM should include TPE.

at nadir. This is notable given the relatively poor prognosis of TM in infancy.

Discussion

The largest limitation of these data is the retrospective nature of its collection. That said, this is a larger cohort of pediatric TM treated with TPE than we found in literature review. Previous reported outcomes noted only 57% of patients being able to walk 30 feet after 3.2 years.[7] Assuming the patient lost to follow-up was not walking, there is still a 75%–80% success rate by this measure for our TPE-treated patients. Similarly, a smaller recent case series looked at TPE in multiple acute inflammatory disorders.[5] The authors included 6 patients with TM, 3 of whom were walking without assistance (Expanded Disability Status Scale score 4 or less) at last follow-up (50%).

There is no uniformity in the literature as to whether the treatment regimen for TM should include TPE. Some centers add TPE only after corticosteroids fail, while others choose to perform TPE concurrently with the patient's course of steroids in severe cases.[4] TM remains uncategorized by the American Society for Apheresis as an indication for TPE.[8]

The majority of our case series of 19 pediatric patients with acute TM treated with TPE (4–7 treatments of 1.1 plasma volumes every other day) showed recovery (75% with major subjective symptom improvement at hospital discharge and at least 78% were ambulatory at last follow-up). TPE can be an effective and safe treatment for pediatric acute TM. Further studies are indicated to prospectively and on a larger scale characterize which patients may benefit from plasma exchange as part of their TM treatment.

Author contributions

D.K. Noland contributed to the data collection and analysis as well as the drafting of the article. B.M. Greenberg contributed to the data collection and analysis as well as the editing of the article.

Study funding

No targeted funding reported.

Disclosure

D.K. Noland estimates 50% effort spent performing clinical apheresis. B.M. Greenberg has received funding for travel from Transverse Myelitis Association; has filed patents on the use of antibody suppression in multiple sclerosis; serves as a consultant for Novartis, Alexion, and EMD Serono; and receives research support from Genentech, Medimmune, Chugai, Medday, NIH, University of Texas Southwestern, Transverse Myelitis Association, the Guthy Jackson Charitable Foundation, the National MS Society, and PCORI. Full disclosure form information provided by the authors is available with the full text of this article at Neurology.org/cp.

Received April 9, 2017. Accepted in final form April 2, 2018.

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