

Utility and safety of plasma exchange in paediatric neuroimmune disorders

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Abbreviations:

ADEM, acute disseminated encephalomyelitis. AE, autoimmune encephalitis. ANCA, antineutrophil cytoplasmic antibody. ASFA, American Society for Apheresis. ATM+, acute transverse myelitis plus syndrome. CIDP, chronic inflammatory demyelinating polyneuropathy. CMT, Charcot-Marie-Tooth. CNS, central nervous system. CTCAE, Common Terminology Criteria for Adverse Events. CVC, central venous catheter. FFP, fresh frozen plasma. FIRES, febrile infection-related epilepsy syndrome. GBS, Guillain-Barré syndrome. IVIG, intravenous immunoglobulin. mRS, modified Rankin scale. NMDAR-ab, N-methyl-D-aspartate receptor antibody. NMOSD, neuromyelitis optica spectrum disorder. PNS, peripheral nervous system. TPE, therapeutic plasma exchange. TPV, total plasma volume. UK-CID, UK Childhood Inflammatory Demyelination Group.

Abstract

Introduction: Therapeutic plasma exchange (TPE) is increasingly used in a range of neuroimmune disorders in children. Our aim was to ascertain the indications, side effects and outcomes in children receiving TPE for neurological disorders.

Methods: Medical records were retrospectively reviewed for 58 consecutive children (age ≤ 16 years) undergoing 67 courses of TPE across four tertiary centres. Patient characteristics, treatment schedules, complications and outcomes were analysed.

Results: Median age at initiation of TPE was nine years (range 1-15). Indications included peripheral nervous system (PNS, n=18) and central nervous system (CNS, n=40) disorders. Courses comprised a median six exchanges (range 2-179) over eight days (range 3-466). 42/58 (73%) children were severely disabled (bedridden) at initiation and 24/58 (41%) were admitted to intensive care units. Treating clinicians' impression of response was positive in 16/18 (89%) of those with PNS disorders vs. 22/40 (55%) in CNS disorders ($p=0.016$). Improvements in disability (modified Rankin scale) occurred in 13/58 (22%) children by completion of TPE ($p=0.003$). Complications occurred in 40/67 (60%) courses, of which 16/67 (24%) were line-related. Potentially life-threatening complications occurred in 2/67 (3%) courses.

Conclusion: This cohort study provides safety and efficacy information for clinicians and families and a basis for future prospective studies.

What this paper adds:

- **Therapeutic plasma exchange was used as rescue therapy for severely-disabling neurological disorders.**
- **Disability scores remained stable or improved during treatment.**
- **Complications occurred frequently but were typically mild and correctable.**

Introduction

Therapeutic plasma exchange (TPE) is the removal and replacement of patient plasma with the aim of removing pathogenic substances from the body. It is used in a range of neurological illnesses in children in which removal of autoantibodies or other inflammatory mediators from the systemic circulation may be of benefit.

The American Society for Apheresis (ASFA) produces guidelines on the use of TPE, in which disorders are categorised by evidence quality into those in which apheresis is accepted as first-line therapy (category I) or second-line therapy (II), and those in which the role of apheresis is not established (III) or demonstrated to be ineffective or harmful (IV) (1). However, these and similar guidelines issued by the American Academy of Neurology (2) do not distinguish between adults and children in their recommendations. Children are at increased risk of haemodynamic instability and other complications of TPE due to differences in weight, vascular access, management of anticoagulation and other factors, as recently reviewed (3). Additionally, there is a lack of quality data regarding the efficacy of TPE for many disorders in children (4, 5).

The aim of this study was to ascertain the indications, efficacy, treatment schedules and safety profile of TPE administered to children with neurological disorders in four UK tertiary children's hospitals.

Patients and methods

Over the period 2007-2013, 58 consecutive children (age ≤ 16 years) underwent a total of 67 courses of TPE at four paediatric neurology centres in the UK Childhood Inflammatory Demyelination Group (UK-CID): Great Ormond Street Hospital for Children (London), Evelina London Children's Hospital (London), Birmingham Children's Hospital (Birmingham) and Alder Hey Children's Hospital (Liverpool). Patient management, including all investigations, treatments and monitoring, was determined by the primary paediatric neurologists, utilising protocols heavily influenced by their regional centres, and guided by the severity and persistence of symptoms. A standardised data capture form (Supplemental Form 1), completed by the participating physicians at the respective centres, was used to retrieve study data from the patient's contemporaneous medical records or, if unavailable, directly from the patient's primary paediatric neurologist. Patient demographics, clinical history, indication for TPE, treatment schedule, treatment complications and outcome were reviewed, including the results of laboratory, neurophysiological and imaging investigations. Either 1, 1.5 or 2 times the total plasma volume (TPV) were exchanged per procedure; this was multiplied by the number of procedures and divided by the course duration in days to calculate an indicative rate of exchange 'per day' over each course of treatment. Complications were scored for severity using the Common Terminology Criteria for Adverse Events (6).

Assessment of treatment efficacy

The treating paediatric neurologist's evaluation of treatment response was defined as positive if a clinical benefit was observed and documented in the contemporaneous notes during the period of TPE. Full recovery was defined by the absence of medical, educational and social concerns reported from parents, school and the primary paediatric neurologist at the most recent follow up appointment. The modified Rankin Scale (mRS) for children (7) was applied by the participating physicians at the respective centres to quantify the degree of disability at three time points: (a) the day of initiation of TPE, (b) the day of completion of TPE, and (c) final follow up.

Standard protocol approvals, registrations, and patient consents

Service evaluations (clinical audits) were registered at the respective centres. As the data analysis was retrospective and no additional data were collected beyond that required for standard medical care of the patient, a full ethics review under the terms of the Governance Arrangements of Research Ethics Committees in the UK was deemed not necessary by the study team. The study team additionally sought the review of the R&D office of Great Ormond Street Hospital, who confirmed individual patient consent was not required.

Statistical analysis

To compare the demographic, clinical, radiological and serological characteristics between groups, parametric or non-parametric statistical tests (Mann–Whitney U and Kruskal Wallis tests) were used for continuous distributions as appropriate, and χ^2 tests for nominal data. Paired t-tests were used to compare mRS before and after TPE. All results associated with a two-tailed p-value <0.05 were considered significant. Data were analysed using GraphPad Prism 7.

Results

Patient characteristics

The indications for TPE, patient demographics and clinical features at baseline are summarised in Table I. Of the 58 patients, 21/58 (36%) were treated for category I, 16/58 (27%) for category II, and 7/58 (12%) for category III indications as per the ASFA guidelines (1). Prior to TPE patients had received a median of two previous immunosuppressive/immunomodulatory therapies (range 1-4), including steroids (n=52, 90%) and intravenous immunoglobulin (IVIg, n=45, 78%). The median duration of neurological illness at initiation of TPE was 25.5 days (range 1 day to 12.5 years); breakdown by diagnosis is detailed in Table I. Previous therapies are detailed in full in Supplemental Table I. 19/58 (33%) patients had a diagnosis of relapsing disease at first initiation of TPE (8 myasthenia gravis, 4 presumed autoimmune encephalitis, 3 chronic inflammatory demyelinating polyneuropathy, 2 neuromyelitis optica, 1 opsoclonus myoclonus, 1 systemic lupus erythematosus).

Plasma exchange treatment schedules

693 TPE procedures were carried out over 67 courses, each course comprising a median of six exchange procedures (range 2-179) administered over a median of eight days (range 3-466). 51/58 (88%) children had one course, 5/58 (9%) had two courses and 2/58 (3%) had three courses of treatment. Treatment was administered by the local nephrology team (33/67, 49%), NHS Blood and Transplant service (23/67, 34%) or local paediatric intensive care team (11/67, 16%). In 2/67 (3%) courses, children were transferred to another tertiary centre for treatment. Table II details the treatment schedules by indication. Vascular access was by dual-lumen central venous catheter (CVC) via femoral or neck veins. In 37/67 (55%) courses these were non-tunnelled lines (Vascath, Gamcath), in 25/67 (37%) they were tunnelled (Permacath, Haemocath), and in 5/67 (8%) the CVC type was not clearly documented. During exchange albumin (58/66, 88%), Gelofusine (7/66, 11%) or a combination of the two (1/66, 2%) were used as the main component of the replacement fluid (not documented in one course). Fresh frozen plasma (FFP) or Octaplas were also routinely included in the replacement fluid in 30/66 (45%) courses.

Treatment response and outcome

Treating clinicians documented a positive impression of response to TPE during the course of treatment in 38/58 (66%) children (detailed by diagnosis in Table II). Response varied by diagnosis ($p=0.019$, Kruskal Wallis test); positive response was reported more frequently in peripheral nervous system (PNS) vs. central nervous system (CNS) disorders (16/18 vs. 22/40, $p=0.016$, χ^2 test). Improvement in mRS score between initiation and completion of TPE (stratified by diagnosis in Figure 1) was observed in 13/58 (22%) children (mean reduction 0.24, $p=0.003$, paired t-test). There were no instances of deterioration in mRS score over the period of TPE. Change in mRS score at completion of TPE did not vary by diagnosis ($p=0.340$, Kruskal Wallis test) or for PNS vs. CNS disorders ($p=0.596$, Mann-Whitney U test). Neither improvement in mRS score, nor clinician's impression of response, varied by time interval from symptom onset to initiation of TPE ($p=0.928$ and $p=0.298$ respectively, Mann-Whitney U test), and nor did either vary by administration of IV steroid ($p=0.952$ and $p=0.062$ respectively, χ^2 test) or IVIG ($p=0.231$ and $p=0.991$ respectively, χ^2 test) prior to TPE.

Follow-up data after initiation of TPE were available for a median duration of 12.6 months (range 1-70.6). A median of 1.5 (range 0-5) anti-inflammatory/immune-modifying therapies were administered subsequent to TPE, including steroids in 38/58 (66%) children and IVIG in 16/58 (28%). Three children acquired a diagnosis of relapsing disease during the period of follow up (1 CIDP, 1 NMDAR-ab encephalitis, 1 relapse of transverse myelitis). Post-TPE therapies and follow-up duration are detailed by diagnosis in Supplemental Table II. Improvement in mRS score between initiation of TPE and final follow up (Figure 1) was observed in 47/58 (81%) children (mean reduction 2.14, $p<0.0001$, paired t-

test). Final change in mRS score varied by diagnosis ($p=0.008$, Kruskal Wallis test), but not by categorization of PNS vs. CNS disorders ($p=0.093$, Mann-Whitney U test), time interval from symptom onset to initiation of TPE ($p=0.830$, Kruskal Wallis test), or administration of IV steroid ($p=0.192$, Mann-Whitney U test) or IVIG ($p=0.190$, Mann-Whitney U test) prior to TPE.

Complications of treatment

Complications of TPE (Table III) were reported in 31/67 (46%) courses of treatment (31/58 children, 53%). In 19/67 (28%) courses there was one complication, in 8/67 (12%) there were two complications, and in 4/67 (6%) there were three co-occurring complications. Incidence of complications was not affected by the number of TPVs exchanged per procedure (Table III), or by routine addition of FFP or Octaplas to the replacement fluid (Supplemental Table III).

Complications of central venous access were reported in 16/67 (24%) courses of treatment (16/58 children, 28%), either one complication ($n=14$, 21%) or two co-occurring complications ($n=2$, 3%). These were: suspected line infection ($n=11$), line obstruction ($n=3$), line displacement ($n=2$), excessive bleeding ($n=1$) and complications of anaesthesia ($n=1$). No significant differences in complication rate were observed between tunnelled and non-tunnelled central venous catheters (Supplemental Table IV).

Considering complications of TPE and venous access together, grade 1 complications (mild; requiring observation only) occurred in 14/67 (21%) courses; grade 2 complications (moderate; requiring minimal or noninvasive intervention) occurred in 23/67 (34%) courses; and grade 3 complications (severe or medically significant but not immediately life-threatening) occurred in 18/67 (27%) courses. There also occurred two grade 4 complications (life-threatening consequences; urgent intervention required), both of which were septic shock secondary to presumed line infection. No mortality or long term morbidity was incurred. Early cessation of treatment occurred in 5/58 (9%) children, due to: anaemia ($n=2$), recurrent hypotension ($n=1$), recurrent hypocalcaemia ($n=1$) and mechanical problems with the exchange filter ($n=1$). Variation in overall complication rate by diagnosis is detailed in Table II. Courses of treatment initiated on the intensive care unit vs. the ward differed in neither the rate of complications of TPE (12/25 vs. 19/42, $p=1.000$, χ^2 test) nor line-related complications (7/25 vs. 9/42, $p=0.566$). Children who did vs. did not suffer complications of TPE did not differ in age (median 9.3 years vs. 9.3 years, $p=0.928$, Mann-Whitney U), and neither did those who did vs. did not suffer line-related complications (7.2 years vs. 10.4 years, $p=0.516$).

Discussion

In this multicentre evaluation of the utility and safety profile of TPE in children with neurological disorders, an immediate beneficial response to TPE was reported by 66% of treating clinicians. This was more frequently reported in PNS (89%) compared to CNS (55%) disorders. This is in keeping with

known mechanisms of therapeutic effect for TPE in neuroimmune disorders, as recently reviewed (3), in which removal of systemic autoantibodies and other humoral disease mediators can produce a near-instant effect on peripheral nerve and neuromuscular junction disorders, but a reduced and/or delayed effect on CNS disorders in which there is intrathecal production of antibodies. While the delay likely reflects the time required for equilibration between the CNS and systemic vascular component across the complex blood-brain barrier (8), the heterogeneity of clinical response is likely to reflect differences in immunopathology. In an intriguing recent study, responsiveness to TPE in patients with MS relapse was superior in those with a neuropathological pattern of humoral involvement (immunoglobulin and complement deposition) on brain biopsy (9). Furthermore, the presence of ring-enhancing lesions on imaging predicts beneficial response to TPE across a range of CNS inflammatory demyelinating disorders (10).

Where present, the immediate benefits of TPE in our cohort were generally mild or stabilising, as reflected by the relatively modest improvements in mRS score between initiation and completion of TPE, demonstrated in 22% of children only. Assessment of treatment response in the acute setting is challenging, with subtle indications of improvement such as increasing power, reducing encephalopathy and lessening medication burden not reflected in the mRS as a coarse measure of overall disability. Children in the present study were typically severely and acutely unwell at initiation of TPE, with 91% unable to walk unassisted and 41% admitted to the intensive care unit; in all cases TPE was initiated only after failure of one or more other immunotherapies. As such it is reassuring to see there were no instances of further deterioration in mRS score over the period of TPE, which in children suffering a fulminant disease process may in fact represent arrest of an otherwise more morbid or even fatal natural disease trajectory (although in the treated patient this counterfactual is never known). Although in the present study we did not find any significant relationship between time to initiation of TPE and clinical response, there is an emerging consensus favouring earlier escalation of immunotherapy in neuroimmune disorders (11, 12), including recent evidence strongly supporting early initiation of TPE in severe attacks of NMOSD (13). Long-term improvement in mRS score between initiation of TPE and final follow up (median interval 12.6 months) was demonstrated in 81% of children, most likely reflecting the natural history of the various disorders and combined effects of any subsequent immunotherapies.

Complications of treatment occurred in 66% of children (60% of courses), including complications of vascular access in 24% of courses and complications of TPE itself in 46% of courses. This high rate of reported complications is due to several factors. Firstly, the physiological vulnerability of a severely disabled cohort at baseline, including those with dysautonomia and those receiving other immunosuppressive therapies such as steroids. Secondly, the acute context in which TPE was typically initiated. Thirdly, the intensive level of bedside and laboratory monitoring employed to identify and treat complications such as hypotension and anaemia early, often pre-symptomatically or pre-emptively.

Finally, the multiple effects of TPE and its ancillary anticoagulants and blood products on the patient, including fairly predictable derangements of electrolytes and depletion of haemoglobin, platelets, clotting factors and immunoglobulins, and less predictable allergic reactions, perturbations of haemodynamic stability, and complications of vascular access. Complications of TPE in children occur in 28-82% of patients (14, 15) or 14-55% of exchange procedures (15-18), occurring more commonly than in adults (19-22) due to numerous factors predominantly related to reduced reporting of early symptoms, smaller size and smaller circulating volume, as recently reviewed (3). In the present study the commonest complication was hypocalcaemia, occurring in 19% of courses. This occurs as a predictable side effect of citrate, which is typically added to the exchange circuit as an anticoagulant; it occurs in up to 64% of children (15) but can be mitigated or prevented by the addition of calcium to the return line (18, 23, 24). The potentially life-threatening complication of septic shock occurred in two children, both treated without sequelae and without need for early cessation of treatment. In a separate 9% of children TPE was stopped early, due mostly to recurrent but less serious complications. This represents a better-than-expected tolerability profile for what remains a significantly invasive therapy.

In our analysis, course length, procedure frequency and total plasma volumes (TPV) exchanged per procedure were combined to determine TPV exchanged 'per day', a composite measure indicative of the intensity of the exchange course, which varied by indication from 0.7 to 1.7 in our cohort. The most intense exchange schedules were used to treat ADEM (1.7 TPV 'per day') and GBS (1.6). In ADEM (n=12) this can be understood as an urgent response to fulminant and/or life-threatening disease; 67% of children with ADEM were admitted to the intensive care unit and all were maximally disabled on mRS scoring. In peripheral demyelination, exchange intensity was due to the use of a predominantly daily schedule of exchanges, contrary to the alternate-day regimen typically employed for disorders caused by antibodies of predominantly intrathecal origin, such as NMDAR-ab encephalitis (1). We found it interesting that the occurrence of complications in our cohort did not appear to associate with exchange intensity, nor with admission to the intensive care unit, type of central venous access, or age; while accepting that we may have been underpowered to detect such associations in this retrospective study. Course duration varied widely, ranging from two to 179 procedures (median six), depending on clinical response and tolerability for the individual patient. In cases with suboptimal clinical response, the lack of reliable and readily-available biomarkers to determine the immunopathological response to TPE makes the decision of when to stop treatment especially challenging in neuroimmune disorders compared to those with established pathogenic biomarkers, e.g. systemic lupus erythematosus or antineutrophil cytoplasmic antibody (ANCA)-associated vasculitis.

The major limitations of this study were the retrospective ascertainment of cases, and the fact that TPE was administered across a heterogeneous group of disorders, differing in both their immunological disease mechanisms and natural disease course. We were not able to measure and control for the

effects of other treatments and their interactions, such as the potential removal of IVIG by TPE. This cohort was therefore not optimal for a direct evaluation of TPE treatment effect, which is better suited to a prospectively-controlled study design. In conclusion, despite these limitations, this post hoc evaluation demonstrates that TPE can be effective when used in conjunction with other first-line therapies in the acute setting. Importantly, careful anticipation of potential complications and the adoption of appropriate preventative strategies will allow for safer implementation of TPE in the complex management of central and peripheral neuroinflammation.

Contributions

CH and ML devised the study. ME, KL and CH designed the data capture form. ME, KL, MA, SA, JG, RG, RK, DM, SP, KR, MS, SS and EW collected the data. ME and YH analysed the data. ME wrote the first draft of the manuscript with significant contributions from YH, ML and CH. All authors reviewed and contributed to the final manuscript.

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Table I: Characteristics of patients at initiation of plasma exchange

Indication for TPE	ASFA* category	N	Age	Gender	Duration of neurological illness at initiation of TPE	Baseline neurological disability	PICU admission
			Years, median (range)	M/F	Days, median (range)	mRS, median (range)	n/N (%)
All	-	58	9 (1-15)	25/33	25.5 (1-4575)	5 (3-5)	24/58 (41%)
Transverse myelitis**	-	14	8 (1-13)	8/6	12 (3-83)	5 (3-5)	1/14 (7%)
ADEM	II	12	5.5 (1-14)	8/4	8.5 (1-66)	5 (5-5)	8/12 (67%)
Myasthenia gravis	I	8	12 (9-15)	4/4	32 (11-248)	4.5 (3-5)	4/8 (50%)
NMDAR-ab encephalitis	I	7	4 (2-13)	3/4	37 (24-92)	5 (5-5)	3/7 (43%)
GBS***	III	6	8 (1-15)	1/5	6 (3-49)	5 (5-5)	5/5 (100%)
CIDP	I	4	13 (3-14)	0/4	2100 (48-4575)	4 (4-4)	1/4 (25%)
Presumed AE	II	4	14 (10-15)	0/4	46 (45-350)	4 (4-5)	0/4 (0%)
FIRES	-	2	5 (3-7)	1/1	16.5 (8-25)	5 (5-5)	2/2 (100%)
Opsoclonus myoclonus	III	1	2	0/1	286	4	0/1 (0%)

*American Society for Apheresis guidelines (1).

**One child had ATM+; two children had NMOSD.

***One child had known CMT1 mutation; all were treated with IVIG prior to TPE (hence ASFA category III).

Table II: Characteristics of plasma exchange treatment

Indication for TPE	N	Courses per patient	Elective courses	Procedures per course	TPV exchanged per procedure	Course duration	TPV exchanged 'per day'	Complications of TPE*	Complications of vascular access*	Grade 3-4 complications* (by CTCAE criteria)	Positive impression of response (by treating clinician)
		Median (range)	n/N (%)	Median (range)	x1/x1.5/x2	Days, median (range)	Median (range)	n/N (%)	n/N (%)	n/N (%)	n/N (%)
All	58	1 (1-3)	13/67 (19%)	6 (2-179)	15/34/17	8 (3-467)	1 (0.2-2)	31/67 (46%)	16/67 (24%)	20/67 (30%)	38/58 (66%)
Transverse myelitis	14	1 (1-3)	5/18 (28%)	5 (3-179)**	5/11/1***	8 (3-467)	1 (0.4-1.5)	8/18 (44%)	3/18 (17%)	3/18 (17%)	12/14 (86%)
ADEM	12	1 (1-1)	0/12 (0%)	5.5 (3-14)	0/4/8	6 (3-22)	1.7 (0.8-2)	5/12 (42%)	3/12 (25%)	5/12 (42%)	6/12 (50%)
Myasthenia gravis	8	1 (1-2)	2/10 (20%)	7.5 (2-17)	3/6/1	9.5 (3-32)	0.7 (0.5-1.3)	3/10 (30%)	4/10 (40%)	5/10 (50%)	7/8 (88%)
NMDAR-ab encephalitis	7	1 (1-1)	0/7 (0%)	10 (7-19)	3/2/2	23 (8-45)	0.7 (0.3-1.8)	4/7 (57%)	3/7 (43%)	5/7 (71%)	3/7 (43%)
Guillain-Barré syndrome	6	1 (1-1)	0/6 (0%)	5 (3-12)	1/2/3	7.5 (3-60)	1.6 (0.2-2)	4/6 (67%)	1/6 (17%)	1/6 (17%)	6/6 (100%)
CIDP	4	1 (1-3)	5/6 (83%)	5 (4-28)	1/5/0	5 (4-82)	1.4 (0.5-1.9)	3/6 (50%)	1/6 (17%)	0/6 (0%)	3/4 (75%)
Presumed AE	4	1 (1-2)	1/5 (20%)	10 (5-20)	2/2/1	24 (5-70)	0.8 (0.3-1.0)	3/5 (60%)	0/5 (0%)	0/5 (0%)	0/4 (0%)
FIRES	2	1 (1-1)	0/2 (0%)	5.5 (5-6)	0/1/1	6.5 (5-8)	1.5 (1.5-1.5)	1/2 (50%)	1/2 (50%)	1/2 (50%)	1/2 (50%)
Opsoclonus myoclonus	1	1	0/1 (0%)	6	0/1/0	9	1	0/1 (0%)	0/1 (0%)	0/1 (0%)	0/1 (0%)

*Per course of treatment.

**Prolonged course of 179 procedures given as a maintenance treatment strategy to stabilise disease in a frequently relapsing NMO patient. Good effect was observed during the course of treatment without further relapses; however, after TPE the patient resumed a relapsing course, requiring further treatment with steroid, IVIG, azathioprine, cyclophosphamide, and ofatumumab.

***Data missing for one patient.

CTCAE, Common Terminology Criteria for Adverse Events (6).

Table III: Relationship between exchange complications and total plasma volume (TPV) exchanged per procedure

Complication, n/N (%)	Complication severity*		TPV exchanged per procedure			χ^2 for slope**	p
	All grades	Grades 3-4	x1	x1.5	x2		
Hypocalcaemia	13/67 (19%)	0/67 (0%)	5/15 (33%)	5/34 (15%)	3/17 (18%)	1.134	.2868
Anaemia	10/67 (15%)	8/67 (12%)	1/15 (7%)	5/34 (15%)	4/17 (24%)	1.771	.1832
Hypotension	6/67 (9%)	4/67(6%)	3/15 (20%)	2/34 (6%)	1/17 (6%)	1.803	.1793
Coagulopathy	5/67 (8%)	0/67 (0%)	3/15 (20%)	1/34 (3%)	1/17 (6%)	2.070	.1502
Hypokalaemia	3/67 (5%)	0/67 (0%)	1/15 (7%)	0/34 (0%)	2/17 (12%)	.5964	.4400
Thrombocytopenia	3/67 (5%)	1/67 (2%)	1/15 (7%)	0/34 (0%)	2/17 (12%)	.5964	.4400
Bradycardia	2/67 (3%)	2/67 (3%)	1/15 (7%)	0/34 (0%)	1/17 (6%)	.0039	.9501
Hypertension	1/67 (2%)	0/67 (0%)	0/15 (0%)	0/34 (0%)	1/17 (6%)	1.973	.1601
Hypophosphataemia	1/67 (2%)	0/67 (0%)	1/15 (7%)	0/34 (0%)	0/17 (0%)	2.227	.1356
Hyperkalaemia	1/67 (2%)	1/67 (2%)	0/15 (0%)	1/34 (3%)	0/17 (0%)	.0019	.9650
Rash	1/67 (2%)	0/67 (0%)	0/15 (0%)	1/34 (3%)	0/17 (0%)	1.134	.2868

*Scored according to the Common Terminology Criteria for Adverse Events (6).

** χ^2 test for linear trend.

Figure 1: Change in modified Rankin scale score between initiation of plasma exchange, completion of plasma exchange and final follow up

0 - No symptoms. 1 - No significant disability; able to carry out all usual activities, despite some symptoms. 2 - Slight disability; able to look after own affairs without assistance, but unable to carry out all previous activities. 3 - Moderate disability; requires some help, but able to walk unassisted. 4 - Moderately severe disability; unable to attend to own bodily needs without assistance, and unable to walk unassisted. 5 - Severe disability; requires constant nursing care and attention, bedridden, incontinent. 6 - Dead.

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