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Plasma Exchange in the Treatment of Neuromyelitis Optica Spectrum Disorders: A Systematic Review and Meta-Analysis

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Abstract

Objective: We hypthesised that adding plasma exchange to an immunosuppressive drug or plasmaexchange alone helps in cessation of the progression of Neuromyelitis Optica Spectrum Disorders(NMOSD).

Methods: MEDLINE, EMBASE, Trip Database, Cochrane library and clinicaltrial.gov databases were searched for studies evaluating the efficacy of therapeutic plasma exchange in NMOSD. The proportionof patients improved were pooled across studies. The outcome measure studied was Kurtzke's Expandeddisability status scale (EDSS) score.

Results: Nine studies including a total of 239 patients were eligible for meta-analysis. The pooledproportion of patients who improved with plasma exchange was 76% (95% CI 69 to 83%).

Conclusion: We need further large scale randomized trials into the possibility of a beneficial effect ofPlasma Exchange in patients with NMOSD.

Keywords: *Plasma Exchange; Treatment of Neuromyelitis; Optica Spectrum*

Introduction

Neuromyelitis optica (NMO) is an inflammatory demyelinating disorder of the central nervous system disease distinct from Multiple Sclerosis. Most patients have autoantibodies in their serum against the astrocytic water channel – aquaporin 4(AQP4 IgG) which has high specificity in cases clinically suspected to have NMO [1, 2]. AQP4 antibody positivity has now been found in a wider range of clinical and magnetic resonance imaging manifestations, leading to the broader concept of NMO spectrum disorders (NMOSDs) [3]. The core clinical characteristics required for diagnosing patients with NMOSD include optic neuritis, myelitis, area postrema, brainstem, diencephalic, or cerebral presentations [3].

NMOSD is emerging as an important cause of disability in adult population. Before completing 5 years ofdisease onset, half of the patients with NMOSD are wheelchair bound or functionally blind [4] The treatment of NMOSD is primarily immunosuppressive. In the acute phase, high-dose methylprednisolone, plasma exchange, or intravenous immunoglobulin (if no better with steroids) are used to control inflammation for rapid recovery [10]. Plasma exchange is generally the second option when steroid therapy is having unsatisfactory response, but the amount of benefit of adding PLEX to any immunosuppressive therapy for treatment of acute attacks of NMOSD has not been quantified any randomized trial [6]. It is believed that prompt initiation of PLEX could be associated with satisfactory clinical outcome [7-9]. Here we summarize the available evidence for plasma exchange in NMO in the form of proportionsrecovered in published case series.

Methods

Search strategy: A detailed search strategy was performed by two independent authors to identify allstudies on the effect of plasma exchange on NMOSD. We searched electronic databases Medline, Embase, TRIP database and Cochrane CENTRAL with the use of MeSH terms' neuromyelitis optica', 'plasma exchange', 'Devic disease and plasma exchange'. The search was limited to studies in English.The bibliographic references in relevant review articles were also examined for eligible studies.

We included: (a)Randomized control studies using plasma exchange in NMOSD (b) case series and cohort studies using plasma exchange for treatment of NMOSD. Any case series with incomplete data where proportion of patients improved were not clear and case reports were eliminated from the review.

Data extraction: Information drawn from the data included design of the study, baseline characteristics ofpatients, regimens used in the treatment and outcome measures. For all the studies, the baseline characteristics of the patient retrieved were, when available: range of age and mean age, proportion of women, follow-up duration, mean Expanded Disability Status Scale (EDSS) score before and after plasma exchange.

Bias assessment

The studies included in our study were rated for the quality using Newcastle Ottawa criteria [11].

Statistical analysis

Clinical efficacy which is defined as the percentage of NMOSD treated by Plasma Exchange with its 95%confidential intervals (CI) is the outcome used as an example for this study. Pooled prevalence estimates were calculated using random effects and fixed effects models on software Stata version 13 (StataCorp., College Station, TX) Heterogeneity was estimated using I^2 statistic.

Results

When we did a comprehensive search, it was shown that there was no RCT evaluating plasma exchangefor the treatment of NMOSD. However, we found 9 case series studies which satisfied the inclusion criteria and were included in the meta-analysis of proportion improved. The quality of studies analyzed using NewCastle Ottawa scale showed a score of about 5-6/9.

The search strategy is shown as a flow chart in figure 1 and table 1.

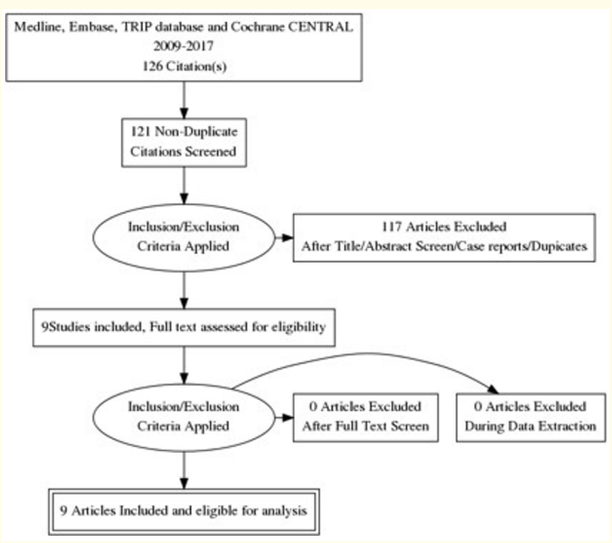

Figure 1: *Flowchart of study selection on the basis of Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) Guidelines.*

	SelecTion				CompArabiLity	OutcOme			Total score(out of 9)
	Representativeness of the exposed cohort	Selection of the non exposed cohort	Ascertainment of exposure	Demonstration that outcomeof interest was not present at start of study(for side effects)	Comparability of cohorts on the basis of the design or analysis	Assessment of outcome	Was follow up long enoughfor outcomes to occur	Adequacy of follow up of cohorts	
Bonnan[9] *et al* 2009	*	*	*	-	*	*	-	-	5/9
H Abboud [16] *et al* 2016	*	*	*	-	*	*	-	-	5/9
Kim [17]*et al* 2013	*	*	*	-	-	*	*	*	6/9
Petrou p [18] *et al* 2016	*	-	*	-	-	*	*	*	5/9
Wang [19]*et al*2011	*	-	*	-	-	*	*	*	5/9
Watanabe [20] *et al* 2007	*	-	*	-	-	*	*	*	5/9
Saharat [21] *et al* 2017	*	-	*	-	-	*	*	*	5/9
Liufriu [23] *et al* 2009	*	-	*	-	-	*	*	*	5/9
Lim [22] *et al* 2012	*	-	*	-	-	*	*	*	5/9
Merle [24]*et al* 2012	*	-	*	-	-	*	*	*	5/9

Table 1: *Quality of studies by using The Newcastle-Ottawa Scale (NOS).*

Pooled results

In our study, the pooled proportion of clinical efficacy using plasma exchange is 76% [95% confidential interval (CI 0.69 to 0.83)] in plasma exchange in NMOSD from 9 studies with a total of 338 cases. Thereis no evidence of heterogeneity (I^2 value) = 21.38%) (p = 0.25) (Figure 2 and Table 2).

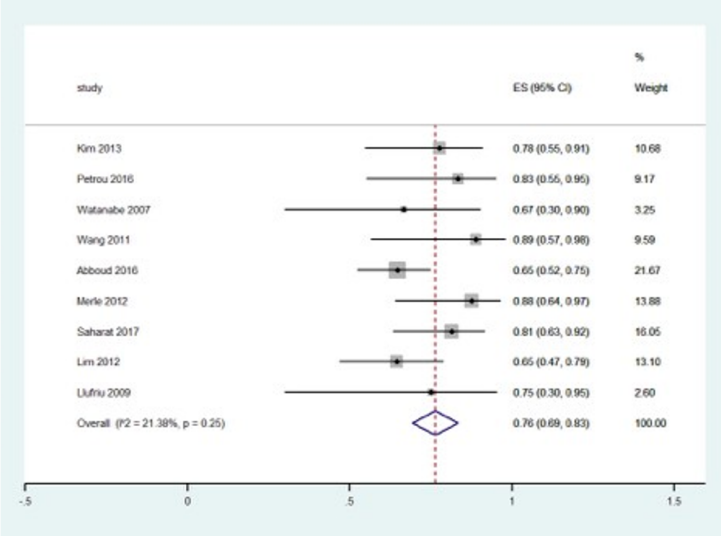

Figure 2: *Forest Plot Showing the proportion of Patients improved after PLEX therapy in Neuromyelitis Optica Spectrum Disorders.*

Study	Study Duration	Sample Size	Study Design	Mean/Median Age (Range)	Male/ Female (% females)	Intervention	Change in EDSS	Proportion Recovered
Bonnan [9] *et al.* 2009	1982-2008	N=43	Retrospective cohort	34+14 (14-82)	3/40 (93%)	PE vs IVMP	EDSS=1. 2+1.6 vs 2.6+2.3 P<0.01	
Su Hyun Kim [17] *et al.* 2013	2010-2011	N=15	Case series	40 (12-53)	13/15 (87%)	PE	7.4+1.0 to 4.6+ 1.8 (at attack to at 6 months)	78% (14/18 attacks)
Petrou p [18] *et al.*2016		N=12	Case series	32+11.2		PE	5.6+1.4 to 4.7+1.5 (at attack to at 12 months)	83% (10/12)
Watanabe [20] *et al.* 2007	2002-2005	N=6	Case series	21-62	6/6 (100%)	PE	5.75 (3.5-8 5) to5.25 (2.5-7.5) (before and after PLEX)	66% (4/6)
KaichenWang [19] *et al.* 2011	2001-2008	N-9	Case series	48.67 ± 10.3 (34-62)	9/9 (100%)	PE	8.38 (6-9) to 7.55 (6-8.5) (before and one week after PLEX)	88% (8/9)

Hesham Abdoud [16] *et al.*	2005-2010	N=59	Retrospective cohort	41.6+18.2	55/59 (93.2%)	IVMP vs PE	0.5 vs 1.25 (Improvement in EDSS) odds ratio=3.36, 95% CI 1.0657 to 10.6004, p = 0.0386	65% (42/65 attacks)
HaroldMerle [24] *et al.* 2012	1995-2010	N=36	Ambispective cohort	35.6+11.8 (13-61)		IVMP vs PE	VA-	87% (14/16)
Llufriu [23] *et al.* 2009	1995-2007	N=4	Case series	39 (34–48)	¾ (75%)	PE	8.0 (6.5–9.0) to 6.0 (6.0–8.0) (At attack and 6 months)	75% (3/4)
Lim [22] *et al.* 2012	2007-2011	N=31	Case series	39 (9-62)		PE	5.5(3.5-9) to 4(1.5-8.5) (at attack and 6 months)	65% (20/31)
Saharat [2] *et al.* 2017		N=24	Case series	41 (34-48)	20/24 (83%)	PE	8.5 (8-9) to 6.25 (5-7.75) (at attack and 6 months) VOS= 6 to 2 (no light perception to 20/30-59)	81% (22/27)

Table 2: *Clinical and demographic characteristics of 239 patients from 9 studies included in the systematic review.*

Discussion

This systematic review and meta-analysis impart an information to support the benefit of plasma exchange to aid reduce the disability in NMOSD patients. The plasma exchange is effective in both seropositive and seronegative NMOSDs [11,12]. NMO relapses are generally more severe and less responsive to high dose steroid therapy in comparison to Multiple Sclerosis [13]. The treatment of relapseand the measures to prevent the relapse is the key for disability reduction in NMO [14].

We included 9 case series. The pooled proportion of patients who improved with plasma exchange was 76% (95% CI 69 to 83%). Among the 9 studies included, the small scale study conducted by Watanabe., *et al.* in 2007 was one of the earliest. He showed that three of the six patients included showed functional improvement which was significant following PE, and the improvement was seen after one or two exchanges, however there was little or no improvement in the other three patients.

Another study published in 2009 by Llufriu., *et al.* who retrospectively reviewed a total of 41 patients of which twenty-three (56%) had multiple sclerosis, 7 (17%) had acute disseminated encephalomyelitis, 4 (10%) had neuromyelitis optica, 2 (5%) had Marburg disease, 2 (5%) had clinically isolated syndrome, 2(5%) had idiopathic ON and 1 (2%) had idiopathic transverse myelitis. He concluded that PLEX improved clinical outcome in 63% of patients at 6 months. Bonnan., *et al.* included 43 patients with 96 spinal attacks showed that change in EDSS and residual EDSS were significantly reduced in PE-treated attacks with no basal impairment (2.1 ± 1.9 vs 5.8 ± 2.0; $P < 0.01$). He also proved that EDSS lowering was also greater in the PE-treated group of patients (−5.5 ± 2.1 vs −1.2 ± 1.3; $P < 0.01$).

A small, uncontrolled, retrospective series published in 2011 by Wang., *et al.* included 9 patients, among which eight of nine patients showed improvement to their baseline condition at the 2-month post PLEX follow-up. Lim., *et al.* published a retrospective case series which included medical records of patients with NMOSD treated over a period of 5 years. He came to a conclusion that steroid refractory attacks in NMO-IgG-positive NMOSD improved with PLEX which is an effective rescue therapy.

Merle., *et al.* proved that, sequential treatment with pulse intravenous corticosteroids and plasma exchangein patients with NMO related optic neuritis is more effective than standard monotherapy with corticosteroids. The outcome considered was visual acuity. Morgan., *et al.* studied 5 patients who were given a total of 17 therapeutic plasma exchange(TPE) series. The average course of therapy was three (ranged 1 - 5) series with five (ranged 3 - 7) TPE per series. The total patients included showed both subjective and objective response to PLEX. Su hyun Kim retrospectively reviewed the medical records of15 patients and found that PLEX which was given after IVMP therapy led to improvement which were significant in 50% of the 18 attacks among 15 patients. This was seen immediately after the procedure was completed. The improvement was seen in 78% (14 attacks) after 6 months. A retrospective review conducted by Hesham., *et al.* included admissions to the Johns Hopkins Hospital comprising of 83 NMO patients. All these patients were treated with IVMP alone versus IVMP+PLEX. On follow up, EDSS improved to the baseline state in sixty-five percent of IVMP + PLEX treated patients. However, only 35%of the patients who received IVMP alone on follow up achieved their baseline EDSS (OR=3.36, 95% CI 1.0657 - 10.6004, $p = 0.0386$). Petrou P studied 12 patients of NMOSD of which 10 patients improved significantly and their mean EDSS score reduced to 4.7 ± 1.5 after treatment from 5.6 ± 1.4 before the treatment. 8 of them were positive for anti aquaporin 4 antibodies. Saharat., *et al.* studied 20 patients who were NMOSD seropositive, 1 patient who was NMOSD seronegative and 3 patients who had LETM. Functional improvement was seen in 81% of included patients after 6 months of plasma exchange.

PLEX or plasmapheresis is the process of filtration of the plasma. The plasma is removed from the patient, replaced by artificial plasma and reinfused - *the plasma exchange*. Basically, filtration step goalis to remove a particular volume of patient's plasma and return an artificial plasma substitute in its place.

[15] The removal of pathological substances from the blood comprising of monoclonal autoantibodies and paraproteins, followed by the replacement of deficient plasma components with healthy plasma is the major therapeutic benefit of TPE [16]. The pathophysiology in most autoimmune diseases is unclear due to alack of correlation between the presumed pathological antibody titres and the clinical severity. The pathophysiology must be more complex and can include the changes in immune cell numbers, function and phenotype, causing alterations in the immune system.16 The efficacy depends on the Plasma Volume (PV) removed, the pathogenic substance to be removed and its distribution between extravascular and intravascular spaces, and synthesis of the substance and its equilibrium rate between the compartments [17]. Plasma exchange is thus beneficial and safe in NMOSD since the pathology is mainly inflammatory, though there can be some adverse effects in a minority of patients. In a retrospective analysis of 509 patients including 4857 exchanges conducted by Basic-Jukic N., *et al.* which was published in 2005, the most common complications of plasma exchange recorded were paresthesias (2.7%). Other complicationsincluded hematoma at the puncture site and mild to moderate allergic reactions. Five procedures had true anaphylactoid reactions. Severe adverse reactions potentially life-threatening constituted 0.12% [18].

Conclusion

The meta analysis we performed in this study showed that the PLEX improved EDSS scores in patients with NMOSDs. This systematic review and meta-analysis has a limitation of the inclusion of only case series and non availability of randomized controlled trials. Multi centre Randomized trials are required toprove the benefits of PLEX in NMOSDs.

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