Opinion Piece

Out with the old, in with the new: could plasma exchange be used to fill a therapeutic gap in neurology?

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Abbreviations

AD – Alzheimer's disease

BBB – Blood-brain barrier

CNS – Central nervous system

MS – Multiple sclerosis

ROS – Radical oxygen species

Abstract

The global tally of neurological disorders is exponentially rising and yet effective therapies for most remain evasive. There is a great deal of research into novel small molecules, immunotherapies and gene therapies to fill this therapeutic gap. We believe greater focus on plasma exchange as a research and clinical tool may provide useful insight into pathological mechanisms and effective treatment strategies. Plasma exchange has been traditionally used to treat antibody-mediated neurological diseases, such as myasthenia gravis and neuromyelitis optica, but there could be much wider future potential uses in neurology. Plasma exchange is not antibody specific, as it also removes a variety of other plasma-soluble factors, including age-related and disease-associated neurotoxic proteins, such as fibrinogen and amyloid. As research develops into the role of blood-brain barrier and immunological alterations in diseases not typically regarded as immune-driven, interest in neurotoxic plasma proteins grows. Here, we highlight that plasma exchange may have uses outside of antibody-mediated neurological diseases, by removing neurotoxic proteins from the systemic circulation.

Key words

Neurodegeneration
Blood-brain barrier
Alzheimer's disease
Stroke
Multiple sclerosis

1) Introduction

Neurological disorders are the leading cause of disability and the second highest cause of death worldwide, and affect an exponentially large number of people[1]. Systemic inflammation is increasingly recognized as a pathological component of a wide variety of neurological diseases[2], and as such there is increasing interest in circulating proteins as biomarkers, mediators and therapeutic targets in neurology. Here we suggest that a greater focus on plasma exchange could provide new insights to better treat and understand neurological disease.

Plasmapheresis was first described in the early 20th century[3,4]. Though the terms are often used interchangeably, plasmapheresis refers directly to the separation of cells from plasma after having been removed from a subject, whilst in plasma exchange the removed plasma is replaced with donor plasma or synthetic colloid. During its early stages as a technology, plasmapheresis was used to enable more efficient blood donation in World War II[5]. Now its primary therapeutic use is in autoimmune disorders, with a presumptive underlying mechanism of autoantibody removal[3]. Evidence levels for the use of plasma exchange vary, and in many cases the choice of plasma exchange as a therapeutic is a specialist decision in refractory diseases. Usefully, the American Society For Apheresis (ASFA) publishes clear guidelines on the current evidence base and recommended protocols for individual diseases, including those where plasma exchange is recommended as a first line therapy[6]. These ASFA guidelines have shaped the UK approach[7].

In neurology, current use of therapeutic plasma exchange is focussed on diseases with proven autoantibody-mediated pathology, such as neuromyelitis optica and myasthenia gravis (see a review guided by the ASFA[8] and a practical review including reference to current guidelines, recommendations and service provisions in the UK[4]). However, plasma consists of more than just immunoglobulins; glucose, electrolytes, and thousands of proteins are also removed by plasma exchange. As research into circulating plasma in diseases spanning the breadth of neurological disorders evolves, we learn more about fundamental aspects of their pathogenesis. Blood-brain barrier (BBB) and immunological alterations, both consequences of ageing and common elements in neuroinflammatory and neurodegenerative diseases[9,10] could alter the constituents and flux of plasma components into the central nervous system (CNS) to propagate disease. Removing CNS-toxic proteins, such as fibrinogen, clotting factors or other inflammatory mediators through plasma exchange could thus provide benefit throughout a wide spectrum of neurological diseases, including but not limited to multiple sclerosis (MS), Alzheimer's disease (AD), stroke, and traumatic brain injury **(Figure 1)**. Further research into the mechanisms

and benefits of plasma exchange in these diseases could provide new insights into disease mechanisms and beneficial treatment strategies.

2) Plasma exchange in MS

Despite an explosion in the number of disease-modifying therapies that reduce the frequency of acute MS relapses, the mainstay of progressive MS treatment remains symptom management. Treatment effects of ocrelizumab in primary progressive MS and siponimod in secondary progressive MS are modest[11–13], and approaches repurposing neuroprotective drugs used in other diseases have been unsuccessful[14]. New therapeutic approaches targeting the root cause of disability and neurodegeneration in progressive MS are needed.

Use of plasma exchange in acute MS exacerbations has long been thought to be beneficial through removal of humoral factors[8,15], consistent with classical EAE models of MS pathophysiology. In contrast, use in progressive MS, where age-dependent neurodegeneration drives irreversible disability, is limited. Guidelines discourage the use of plasma exchange in progressive MS based on small studies performed mostly in the 1990s[15]. Some of these studies used acute relapses rather than disability as an endpoint[16,17], but others intriguingly show some mild benefits in improving disability[18–21]. Our knowledge of plasma factors in both acute and progressive MS has advanced significantly since these studies were performed, but there have been no significant pre-clinical or clinical studies into plasma exchange in progressive MS since then.

BBB disruption early in MS pathogenesis allows circulating factors easy access to the CNS[22]. There is particular interest in fibrinogen[23], which is pro-inflammatory in early lesion formation[24] and progressive MS[25]. As such, depletion of fibrinogen is thought to represent an important therapeutic candidate in MS[23,26,27]. Plasma exchange is already known to reduce circulating levels effectively[28]. As new roles of plasma components like hormones[29], clotting factors[30], members of the complement system[31] and other biomarkers[32] are elucidated in MS, there is increasing interest into the roles and dynamics of individual plasma components in disease pathogenesis.

The impact of plasma exchange in MS outside of removing auto-antibodies, and outside of the acute relapse, warrants further research. In clinical terms, well-powered, blinded, randomized control trials could be designed evaluating effects of plasma exchange (with 5% albumin and/or fresh frozen plasma replacement) on disability accumulation in progressive MS, including study of secondary outcome measures of neurodegeneration, though

a treatment protocol would need to be optimized. Alternatively, and perhaps more interestingly, plasma exchange could represent a relatively safe *in vivo* human model to investigate the effects of circulating plasma factors, and their removal, on progressive MS. This approach could uniquely overcome problems with therapy development based on mouse models that poorly recapitulate progressive human disease[33], and could allow the subsequent development of novel, more specific, treatments, or identify biomarkers that finely tune which patients with progressive disease best respond to plasma exchange.

3) **Plasma exchange in Alzheimer's disease**

Plasma exchange could play a key role in neurology outside of classically immune-mediated diseases in the future. Alzheimer's disease (AD) is a public health crisis on an epidemic scale[34], and yet only symptomatic treatments, such as acetylcholinesterase inhibitors or NMDA receptor antagonists, are available. The FDA has just controversially granted approval for the use of aducanumab, an anti-amyloid monoclonal antibody, in AD[35,36] despite early termination of clinical trials, but the true impact of this drug is as yet unknown. Plasma exchange may represent one interesting research and therapeutic avenue – for a detailed recent perspective see[37].

In AD, there are a few more unusual lines of enquiry into the potential role of plasma and the aging systemic milieu, on the background of increasing research generally into the systemic effects of aging in Alzheimer's disease[38]. Parabiotic studies where the circulations of young and old mice were surgically joined showed that young-mouse brain degenerated whilst old-mouse brain was rejuvenated, with genetic, neuronal and cognitive effects replicated by plasma administration[39,40]. A subsequent human feasibility study by the same team has shown that infusing plasma from 18-30 year-olds into AD patients is safe and tolerable – though they are yet to show any clinical efficacy[41]. Whilst we believe this is an interesting line of research, this limited evidence by no means supports clinical use of young plasma, and further mechanistic and clinical research is needed – indeed misinterpretation and exploitation of similar research has prompted warnings from the FDA over the commercial use of young people's plasma[42].

Other studies are investigating the effectiveness of plasma exchange with 5% human albumin solution in AD[43]. However, phase II trial results showed only mild clinical impact[44]. A recently published multicentre Phase IIb/III trial on 347 patients showed reduction in decline in an activities of daily living scale over 14 months, with improvements in cognitive decline in moderate but not mild AD[45]. The predominant motivation of these studies is to reduce brain amyloid-β (Aβ) levels, based on the 'peripheral sink' hypothesis – the idea that Aβ peptides in

the brain and periphery are in equilibrium, and that removal of Aβ in the periphery leads to passive diffusion down a concentration gradient to reduce monomeric Aβ in the brain[46,47]. In healthy human plasma, soluble low-density lipoprotein receptor-related protein 1 (sLRP1) has been shown to bind 70-90% of plasma amyloid[48]. In AD, sLRP1 is oxidised, increasing free levels of amyloid[49] and altering amyloid flux across the BBB through binding to the receptor for advanced glycation end products (RAGE)[50,51]. It is unclear how plasma exchange with synthetic or donor colloid impacts amyloid flux across the BBB, but this an area of great therapeutic interest, and other pre-clinical studies have used recombinant domains of sLRP1[52] or targeted the sLRP1/RAGE pathway[53] and have shown benefits. However, the role of plasma amyloid (and other plasma AD biomarkers) is uncertain[54,55]. Moreover, whether targeting and/or reducing levels of brain amyloid is effective at treating AD is controversial – highlighted by the recent developments in aducanumab[35], and previous studies of amyloid-targeting therapies such as verubecestat[56] and crenezumab[57]. Interestingly, there were no clear effects of plasma exchange on CSF amyloid in the AMBAR trial[45]. However, it is important to note that plasma exchange could have other beneficial effects outside of amyloid removal – the group behind the AMBAR trial suggest potential antioxidant effects of replacement albumin[45], or there may be removal of other pathogenic plasma constituents.

Whether plasma exchange is truly effective long-term in AD and, if so, through which mechanism or plasma factor, remains to be seen. Further questions arise when considering the choice between plasma exchange with synthetic colloid or donor plasma – and are complicated by the newer use of plasma fraction products such as GRF6019, which may allow more targeted treatments[58]. Regardless of the outcome of these pre-clinical and clinical studies of plasma exchange in AD, interest in this area has led to developments in understanding of a wide range areas within AD research – spanning from the role of aging and inflammation to amyloid dynamics across the BBB.

4) Plasma exchange in other neurological disorders

Elsewhere in neurology, research into plasma factors could translate into use of plasma exchange in the future. In stroke, raised fibrinogen levels are associated with neurological deterioration[59] and severity of white matter lesions[60], whilst another prothrombotic plasma factor, L5, is elevated in patients with acute ischaemic strokes[61]. Fibrinogen deposition, with associated microglial activation, is seen in traumatic brain injury, with increased deposition in acute injury compared to those with long-term survival[62]. There is an even larger group of neurological diseases where interest is growing into the role of the BBB, and the neurovascular unit[9], which

therefore may benefit from plasma exchange. The positive impact of plasma exchange in antibody-negative neurological disorders, such as antibody-negative transverse myelitis[63], new-onset refractory status epilepticus[64], and seronegative autoimmune encephalitis[65,66] lend support to this conceptual framework, though better quality evidence is needed. As knowledge progresses past examining dysfunction of the BBB and moves to age-related flux of plasma components across it, plasma exchange may become increasingly relevant. We foresee uses in *in vivo* human research models but also eventually as a therapy.

5) Limitations of plasma exchange

Plasma exchange is not risk-free. There are procedure-related risks relating to use of central venous access, anticoagulation, and replacement fluids – which are higher in potentially older patients suffering from neurological disorders. Indeed, in the recent highlighted AMBAR AD trial, 10.6% of patients suffered procedure-related adverse events, compared to 0.7% of patients treated with placebo[45].

There are also cost and resource-related implications – with consideration needed for equipment, training, staff, monitoring and exchange fluid provision and storage. In the UK, therapeutic plasma exchange for neurology patients is generally performed in one of 8 specialist centres[4]. If plasma exchange were to become more widespread, this could place significant burden on the health service – particularly if donor or fractionated donor plasma is required. It is also difficult to imagine how plasma exchange could be readily performed in resource-limited settings. However, such costs and resources are arguably comparable to other emerging treatments, such as sophisticated immunotherapies.

6) Conclusions

The escalating prevalence and devastating consequences of neurological disorders without effective treatments pose a major threat to the sustainability of health care systems worldwide. Plasma exchange may not provide an immediate solution – with further clinical and mechanistic research needed before it can be used to treat a wider range of neurodegenerative diseases. In particular, further clarity on plasma exchange fluid and treatment regimens are needed. However, as systemic inflammation and vascular dysfunction are increasingly recognized pathogenic features of a range of neurological diseases, research into neurotoxic plasma proteins and their removal is increasingly relevant. Greater focus on plasma exchange as a clinical and research tool may provide valuable

insights into pathological mechanisms and useful treatment strategies, leading to more sophisticated small molecule therapies in the future.

Author contributions

GD designed the hypothesis. JS, MC, and MP performed the literature search and data collection. AW constructed the figure. JS, MC, MP, and GD contributed to data interpretation and writing. All authors approved the final version of the manuscript.

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Figure Legend

Figure 1: Plasma exchange could be used to fill a therapeutic gap in neurology. Through removing neurotoxic proteins, such as fibrinogen or amyloid, or through other immunomodulatory or anti-oxidative effects, plasma exchange may have therapeutic benefits in neurological diseases where vascular dysfunction and inflammation play a role. Reduced neurotoxic plasma protein egress from the vasculature may reduce neuroinflammation and neurodegeneration in the CNS. Created with BioRender.com.