Cerebral ischaemia during haemodialysis - finding the signal in the noise

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ABSTRACT

Haemodialysis patients have multiple risk factors for small vessel cerebrovascular disease and cognitive dysfunction. Haemodialysis itself may cause clinically significant neurological injury through repetitive cerebral ischaemia. However, supporting evidence to date consists of epidemiological associations, expert opinion, and small, single-centre studies of variable methodological quality. Isolating the impact of intra-dialytic haemodynamic instability from underlying renal and vascular disease on clinically relevant functional outcomes would require very large, controlled studies, given the heterogeneity and confounding comorbidities of the population, and the complex relationship between blood pressure and cerebral oxygen delivery. There has been an increase in complementary physiological studies looking directly at intra-dialytic cerebral oxygen balance, which have provided supporting evidence for the occurrence of cerebral ischaemia, often independently of haemodynamics. Data suggesting a relationship between these measures of oxygen balance and functional outcomes is only hypothesis-generating at this stage. We advocate the testing of interventions that aim to reduce intra-dialytic cerebral hypoxia (rather than hypotension) in sufficiently powered studies, followed by correlation with validated, longitudinal assessment of clinically relevant neurological damage.

ARTICLE

Advances in haemodialysis technology, monitoring and prescription over recent decades have enormously increased the safety and availability of the procedure. It currently serves as either destination treatment or a bridge to transplantation for approximately 384 per million population in the UK[1]. Whilst life-sustaining, there is growing awareness that intermittent haemodialysis may carry significant physiological costs. In particular, the initiation of haemodialysis does not necessarily improve quality of life [2] and in other studies has been associated with a decline in cognitive function and performance status[3,4]. Given the impact of cerebral function on quality of life, including functional independence and decision-making, this is a major concern.

There are many plausible mechanisms whereby haemodialysis may result in neurological injury. As an intermittent treatment, it involves fluctuations in fluid balance, electrolytes, uraemic toxins, and water-soluble medications. Osmotic stress, inflammation and microemboli are all recognised complications of the procedure[5]. Subclinical dialysis disequilibrium has been identified even in long term haemodialysis patients[6]. Blood exposure to filter membranes and dialysate impurities induces an inflammatory response, activating complement and coagulation cascades[7]. Levels of inflammatory markers correlate with cognitive performance in renal disease [8]. Much interest has focused on whether

intra-dialytic hypotension causes long term neurological injury through repetitive cerebral ischaemia, partly because it is most amenable to intervention[5].

Elucidating the role of intra-dialytic hypotension is complex, as renal disease itself affects the brain through both metabolic and structural effects. Mechanisms include accumulation of uraemic toxins, endothelial dysfunction, vascular calcification, klotho deficiency and hypertension with associated dramatically accelerated small vessel cerebrovascular disease[9]. Cognitive impairment and white matter abnormalities are independently associated with renal impairment in a dose-related fashion [10, 11,12, 13]. Additionally, albuminuria is associated with cerebral white matter abnormalities and cognitive impairment independently of eGFR[12,14]. Conversely, some investigators have found that haemodialysis can be associated with improved cognitive performance, presumably by virtue of clearing uraemic toxins [15]. Given this background, it is extremely difficult to isolate the impact of ischaemic, osmotic and inflammatory insults derived from haemodialysis itself. How can we find the signal in the noise?

The data supporting haemodialysis-induced brain injury consist of epidemiological associations, expert opinion, and small often methodologically flawed studies[5,16,17]. Injury to the brain can be assessed either by radiological methods, which provide largely structural information, or validated neurocognitive tests, which provide (arguably more important) functional information[18]. Some but not all observational studies have suggested that patients who undergo maintenance peritoneal rather than haemodialysis have a slower decline in cognitive function, or fewer abnormalities on brain magnetic resonance imaging (MRI) [19, 20]. Increasing haemodialysis vintage has been associated with reductions in baseline cerebral blood flow, frontal lobe oxygenation and cognitive performance, as well as a greater burden of white matter abnormalities on MRI, particularly subtle changes on diffuser tensor imaging (DTI) [21, 22, 23]. The potential for confounding in these studies is considerable, not least by time and treatment indication. Reliance on radiological measures of end organ damage is also problematic: many of the abnormalities detected are of uncertain significance. Some investigators have been able to demonstrate an association between DTI detected white matter changes and measures of executive function and processing speed, but most studies provide no clinical correlate [22 24].

Studies looking at intra-dialytic haemodynamics might be expected to have more success. With sufficient patient numbers and haemodynamic data, blood pressure changes could be treated as an "intervention" in a pseudorandomised study. Both quality and quantity of data are vitally important as patients with

cardiovascular disease are likely to be prone to both intradialytic haemodynamic instability and cerebrovascular disease independently[18,25]. Moreover accurate measurement of blood pressure on haemodialysis is challenging, further weakening any signal.   Non-invasive arm-cuff blood pressure (NIBP), either sphygmomanometry or oscillometry, is intermittent and misses significant haemodynamic fluctuations. The popular volume clamp techniques (eg Finometer, Finapres Medical Systems, Enschede, The Netherlands) permit continuous non-invasive data collection, but are not available in routine clinical practice, and have never been validated in the end-stage renal failure population. Unfortunately, most published studies are small with sparse haemodynamic data, which is rarely screened for signal quality[16]. Many derive models and predictions using blood pressure from only one or two treatments, but haemodynamic status varies considerably between sessions and over time[26].

The evidence for an impact of intra-dialytic haemodynamics on brain structure and function can be briefly summarised. Frequent haemodialysis schedules almost certainly reduce haemodynamic and osmotic stress, but have not been found to impact on cognitive function[3,27].   Two very different cross-sectional studies found no association between any domain of cognitive function and intra-dialytic haemodynamics[28,29]. The larger study, in 383 patients, did not gather haemodynamic information, but used receipt of intra-dialytic fluid bolus in the week preceding cognitive testing as a surrogate for propensity to severe hypotension [29]. In contrast, Wolgram et al. averaged NIBP indices from 12 consecutive sessions in a small cohort of 32 patients [28]. The same 32 patients were reassessed after 12 months: there was no relationship between change in cognitive function and typical intra-dialytic haemodynamics, assessed from 15 sample sessions over the year[30].

Two longitudinal prospective studies looked at the association of intra-dialytic haemodynamics and progression of MRI-detected abnormalities, with the caveats regarding radiological endpoints discussed above. One found an association between progression of frontal lobe atrophy over 3 years and the total number of intra-dialytic hypotensive episodes recorded in clinical records over that period[31]. Another small single-centre trial found a relationship between dialysate temperature and white matter changes over 12 months, but this was not mediated by a difference in intra-dialytic hypotension, at least not in the two sessions monitored[16]. The authors found an association between white matter abnormalities and a non-standard and only partially controlled measure of variability in beat-to-beat mean arterial pressure (MAP) measured by a volume-clamp device [16]. Whilst longer term blood pressure variability has been well studied in chronic renal disease patients and appears to have prognostic significance[32], beat-to-beat variability is a complex phenomenon

whose analysis requires rigorous methodological standards, and has not been robustly investigated in this population: it cannot yet be linked to either the haemodialysis procedure or to neurological outcomes[33-37].

The failure to definitively link intra-dialytic haemodynamics to cerebral ischaemia may reflect the fact that blood pressure is only one factor determining cerebral oxygen delivery, which equals the product of cerebral blood flow and arterial oxygen content. Many factors beyond hypotension-induced reductions in cerebral blood flow may alter intra-dialytic cerebral oxygen delivery. Arterial oxygen content may be reduced by blood loss or intra-dialytic ventilation-perfusion mismatch (inflammation and neutrophil sequestration)[38]. Cerebral vascular resistance may be altered by ultrafiltration-induced increases in blood viscosity and rising pCO_2 with bicarbonate loading[38]. Regional autoregulation may preserve cerebral blood flow in the face of changing driving pressure, but this is not predictable[39]. The lower threshold for cerebral autoregulation in haemodialysis patients is highly variable (95% confidence intervals 38.9 mmHg to 109.3 mmHg), and many lack autoregulation altogether[40]. Most, but not all, transcranial Doppler studies report a decrease in middle cerebral artery blood flow velocity during haemodialysis [41,42]. However, ultrafiltration-induced haemoconcentration will alter velocity independently of oxygen carrying capacity[41,42].

Even if there is reduced oxygen delivery due to intradialytic hypotension, anaemia, hypoxia or another cause, this does not necessarily lead to cellular ischaemia. Other factors such as the functional capillary density (distance from vessels to cells), oxygen dissociation curve (affected by pH, pCO_2 and temperature, all relevant to haemodialysis), cellular oxygen demand and mitochondrial health are important[43]. A potentially cleaner method of detecting intra-dialytic cerebral ischaemia might therefore be to look directly at cerebral cellular oxygen balance during treatment, learning lessons from the neurocritical care literature[44].

Brain oxygenation reflects both oxygen delivery and consumption, and there are currently two measurement methods suitable for continuous monitoring at the bedside. Both assess local rather than global oxygen balance. The gold standard is direct, invasive measurement of oxygen tension in the brain parenchyma or CSF using specialised probes, with normal pO_2 ranging from 3.3 to 5.2 kPa[44,45]. There is no scientific consensus on the extracellular pO_2 that first induces ischaemic stress in neurons, but PO_2 <1kPa is associated with neuronal death[44]. This method is clearly not suitable for the haemodialysis outpatient. The alternative is near-infra-red spectroscopy (NIRS), which can

provide a continuous, non-invasive measurement of frontal lobe tissue oxygenation. Cerebral NIRS relies on the fact that infrared light can penetrate the skull: changes in haemoglobin oxygen saturation in the frontal cortex are estimated from the absorption of different wavelengths of near-infrared light by oxygenated and deoxygenated haemoglobin [46]. Changes in cerebral saturations measured by spatially-resolved NIRS have generally, but not always, been shown to correlate well with changes in parenchymal brain tissue oxygenation [47-49]. A small body of literature supports a relationship between NIRS-detected cerebral desaturation and hard patient outcomes in other populations[50-56]. However a number of factors can reduce the accuracy of the signal and there is no consensus on what level of desaturation is harmful[46] .

There are few studies investigating cerebral NIRS during haemodialysis; most have looked at very small numbers of sessions with no evaluation of neurological outcomes[57,58]. However, our own group has found an association between decline in executive cognitive function over 12 months and typical exposure to intra-dialytic cerebral ischaemia, defined by area under the curve below the cut-off of a relative 15% drop in NIRS-measured cerebral saturations[40]. A strength of our study included the large amount of high quality raw physiological data gathered (635 monitored sessions in 58 patients, including continuous volume-clamp blood pressure, belt respiratory rate, ECG, pulse oximetry, relative blood volume and cerebral NIRS, with robust signal processing and quality control). However, the findings can only be considered hypothesis-generating due to small patient numbers. In addition, this definition of ischaemia, though based on previous literature, is arbitrary.

Even assuming that cerebral ischaemia is a consequence of haemodialysis, it is not necessarily preventable. We identified some patients who repeatedly developed asymptomatic cerebral desaturation shortly after initiation of dialysis, in the absence of changes in blood pressure, cardiac output (validated with ultrasound dilution), respiratory rate, peripheral saturations, haematocrit or autonomic balance (estimated by spectral analysis of heart rate variability) – i.e. in the absence of a clear change in cerebral oxygen delivery (unpublished data). If we trust the NIRS signal, it is possible (but entirely speculative) that acute inflammation, changes in pH and ionic environment or changes in temperature are altering the oxygen diffusion gradient or distance, or cellular oxygen demand. This is not easily modulated.

In conclusion, the question of whether the haemodialysis procedure itself has adverse neurological consequences, in particular cerebral ischaemia, is more complex than it first seems. The occurrence of harmful repetitive intra-dialytic cerebral ischaemia is supported by biological plausibility and a growing body of circumstantial evidence from complementary epidemiological and physiological

studies, but finding the true signal in such heterogeneous, imperfect data is not an easy task. We would advocate suitably powered multicentre randomised controlled trials, testing the effects of interventions that aim to reduce intra-dialytic cerebral hypoxia (rather than hypotension), followed by correlation with validated, robust, longitudinal assessment of clinically relevant neurological damage over a period of years.

In the meantime, it is reasonable for clinicians to focus on optimising factors likely to impact on intra-dialytic tissue oxygen delivery. We suggest increased monitoring to detect subclinical hypotension and hypoxia, with consideration of convective treatments, cooling, or supplemental oxygen in high risk patients. There is evidence that blood pressure should generally be maintained above MAP 60 mmHg[40] or systolic blood pressure (SBP) 90 mmHg[59], but targets should be individualised: where present, the lower limit of cerebral autoregulation can be estimated from baseline MAP in haemodialysis patients as in other populations[40,60]. In addition, we believe it is important to screen all haemodialysis patients for cognitive impairment as part of routine care, and address non-dialytic risk factors such as depression, neurotropic medications and lack of physical activity[61].

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