Extending the role of peritoneal dialysis: can we win hearts and minds?

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ABSTRACT

Background. The ability of peritoneal dialysis (PD) to achieve low-molecular weight solute clearance and ultrafiltration at low haemodynamic cost makes it an attractive therapy in situations where more aggressive therapy may be undesirable due to sudden reductions in cerebral, coronary or renal blood flow.

Methods. We undertook a review of the literature to examine the recent evidence for this in two specific examples: the removal of glutamate following acute stroke and ultrafiltration for the treatment of diuretic resistant heart failure.

Results. In acute stroke, glutamate, when released into the extracellular tissues, causes neuronal cell death due to its excitotoxic properties. Experimental evidence from animal models indicates that its removal, including via PD, can reduce infarct size and restore functional brain tissue. PD is effective in removing glutamate in patients treated for renal failure. In heart failure, PD has a number of both theoretical and practical advantages for extending treatment, especially as an established home therapy. Several recent cohort studies describing its use in approaching 300 patients with diuretic resistance show consistent benefits in hospitalization and severity.

Conclusion. Both these applications require substantial further clinical evaluation before they can justify wider adoption but their potential to alleviate morbidity on a large and potentially highly cost-effective scale demands further study.

Keywords: excitotoxicity, glutamate, heart failure, stroke, ultrafiltration

INTRODUCTION

Although there is undeniably a worldwide chronic kidney disease (CKD) epidemic [1] the numbers of people seriously affected (i.e. requiring renal replacement) is still small compared with other cardiovascular conditions such as stroke and heart failure. Whilst acute stroke has dropped to third or fourth in the league table of leading causes of death in most developed Western economies [2] it remains one of, if not the main cause of disability, especially when this is severe and complex [3]. For many of these countries heart failure is now the dominant cause of acute hospital admission, especially in the elderly [4]. In the USA, heart failure was responsible for 1 million hospital admissions per year amongst an estimated 5.8 million sufferers between 2000 and 2010 [5, 6]. Taken together the morbidity associated with these conditions presents a major health and economic challenge which is predicted to increase dramatically in coming years—especially in the developing countries—as the population ages [7]. This short review examines current evidence that peritoneal dialysis (PD) might have an extended role to play in stroke and heart failure, either by reducing morbidity or improving the quality of life associated with these conditions in a way that is also cost-effective.

PD FOR ACUTE STROKE: REMOVING GLUTAMATE

Glutamate in the brain

Glutamate is the most abundant excitatory neurotransmitter, present in all parts of the brain [8]. It is stored intra-cellularly in comparatively high (mmol/L) concentrations in the synapse from which it can be released rapidly under physiological and patho-physiological conditions. Within the neurovascular unit glutamate is highly compartmentalized, and despite the overall concentration in the brain of between 10 and 12 mmol/L, <2 µmol/L is present in the extracellular fluid (ECF) that surrounds neurons (Figure 1). The plasma concentration of glutamate (40–100 µmol/L) is greater than that of the ECF but in normal circumstances there can be no net influx of glutamate from the vasculature
due to the presence of the blood brain barrier (BBB). This compartmentalization requires a variety of specialist energy-dependent glutamate receptors on different membranes.

In normal physiological circumstances glutamate is stored in neuronal vesicles close to the presynaptic membrane of nerve cells. Action potentials result in coalescence of the vesicles with the presynaptic membrane and concomitant discharge of glutamate into the synaptic cleft (Figure 2). Specific glutamate receptors, N-methyl-D-aspartate (NMDA) and α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) are located on the postsynaptic membrane. On activation of these receptors, there is an influx of Ca$^{2+}$ ions resulting in an action potential, thus propagating the signal. Residual glutamate in the synaptic cleft is rapidly removed by astrocytes, pre- and postsynaptic neurones and by endothelial cells (ECs) of the BBB. Removal is facilitated by excitatory amino acid transporters (EAAT) that are Na$^+$ dependent and are able to internalize glutamate against a high electrochemical gradient. Glutamate may be recycled as a molecule, converted to glutamine or broken down in any of these compartments. Glutamate may be formed de novo in neurons or from glutamine before being internalized in vesicles. Following an action potential and associated membrane depolarization, various ions are selectively pumped in and out of the cells to re-establish normal resting membrane potential (about −70 mV inside the neuron) and this process requires energy mainly in the form of adenosine triphosphate (ATP).

Another pathway for glutamate is internalization into EC via EAATs on the abluminal membrane and transportation across the luminal membrane into capillaries and eventually the peripheral circulation. This pathway can activate in circumstances when the concentration of glutamate in the ECF increases beyond normal limits. Since the concentration of glutamate within ECs can then be greater than that of the circulation it will flow down a concentration gradient via energy-independent carriers.

**Excitotoxicity**

In the presence of ischaemia, such as in acute stroke, neurovascular cells in the immediate area of the insult are deprived of oxygen and glucose leading to depletion of its energy source, ATP, within minutes. ATP is essential in maintaining the Na$^+$/K$^+$ pump that fails to operate. The pump is crucial in maintaining the resting membrane potential of neurons, and failure of the pump leads to a rapid fall in potential. When it reaches about −50 mV, voltage-dependent ion channels automatically open causing an unrestricted influx of ions, including Na$^+$ and Ca$^{2+}$ to flow down their concentration gradients. The effects of this are complex but initially lead to a massive release of glutamate into the extracellular space that activates NMDA and AMPA receptors of any neurons in the immediate vicinity leading to firing of neurons and further energy expenditure thus excitotoxicity. Ultimately, the influx of Ca$^{2+}$ initiates several cascades including the activation of caspase leading to apoptotic death of neurones [9]. Other cascades include the production of reactive oxygen species and osmotic changes brought about by the influx of Na$^+$ leading to cell damage and necrosis [10, 11]. The complexity of the processes that occur following an ischaemic attack makes treatment with drugs that might inhibit the process difficult; the alternative strategy—a treatment that removes glutamate from the site of injury is therefore attractive.

**The principle of using dialysis to ameliorate excitotoxicity**

If dialysis were to be effective in ameliorating ischaemic injury following stroke then a number of conditions would need to be fulfilled: first, there should be evidence that a diffusive gradient exists between the site of injury (i.e. the intra-cerebral extra-cellular space and the blood compartment); secondly, that dialysis is able to remove glutamate with sufficient efficiency to influence the concentrations of glutamate at the site of damage and thirdly that this can be achieved without exacerbating the brain injury due to the dialysis procedure itself. There is growing evidence that these three criteria might be fulfilled. Previously, it was shown that the severity of injury associated with ischaemic stroke is proportional to the elevation of glutamate levels in the cerebrospinal fluid—and more importantly the blood—implying that a diffusion gradient does exist across the BBB at least in the context of acute ischaemic stroke [12]. Indeed the normal physiological mechanism for removing glutamate via the endothelial route shown in Figure 2 [13, 14] can be enhanced by reducing the blood glutamate concentrations as has been demonstrated with the use of blood glutamine scavenging strategies. For example, infusion of glutamate oxaloacetate transaminase into experimental animal models of stroke has positive effects on infarct size and neurological recovery associated with reduced extracellular glutamine concentrations on in vivo magnetic resonance spectroscopy [15].

The stroke penumbra would be a critical area to target. The penumbra is an area of the brain surrounding the ischaemic focus that is still viable, albeit it with reduced blood flow, and as such can be considered transitional. The aim would be to save as much penumbra tissue as possible and to slow down or halt cortical spreading depression (CSD), which is essentially an expansion of the damaged neuronal tissue at the foci of the ischaemic attack [16, 17] The propagation of CSD is partly as a result of excitotoxicity.
**PD reduces infarct size**

PD is well suited to reduce blood glutamine concentrations as recently demonstrated [18] given its low-molecular weight (147 D, less than glucose) combined with its potential to avoid treatment associated injury due to its relatively good haemodynamic profile. PD is not associated with the cardiac stunning observed in haemodialysis treatments, and although acute infusion of dialysate does lead to an increase in systolic blood pressure, this is relatively modest (<5 mm Hg) [19–21]. The recent study of del Carmen Godino *et al.* [22] is the first to put these principles to the test. First in a rat model of acute ischaemic stroke they demonstrated that PD commenced 2.5 h after injury reduces the infarct size, an effect that was in direct proportion to the degree of reduction in blood glutamate levels and not seen when glutamate was added to the dialysate to prevent its removal or in sham-operated animals. Beneficial effects were even seen if started up to 5 h after injury and reduction in the size of the infarct was associated with maintained functionality of the rescued brain tissue. Secondly, in parallel human studies they were able to demonstrate that in patients with renal failure that PD was effective in reducing blood glutamate levels, with near equilibration occurring by 4 h commensurate with its molecular weight, confirming recent observations [18].

A burgeoning literature, however, tells us that caution needs to be taken when attempting to extrapolate work from animal models of stroke to the clinical setting. Virtually, all clinical
trials of neuroprotective mechanisms and interventions in stroke have so far failed. The reasons for these failures are complex but may include the homogeneous nature of animal models versus the heterogeneity found in humans and methodological shortfalls bridging pre-clinical and clinical studies [23]. More specific to this review are trials on NMDA receptor antagonists in acute stroke. There have been many trials using this intervention and all have failed, most remain unpublished since they ended early and no efficacy has been demonstrated [24]. As already described above, glutamate is a major excitatory neurotransmitter and it has been suggested that the complexity of its actions has been overlooked in clinical trials [25]. For example, it is thought that glutamate may activate pro-survival pathways in response to neurovascular insult and so blocking NMDA receptors in a non-specific manner may be causing more damage than no intervention at all.

It is still a significant step to confirm that acute PD will have value for humans with acute stroke, but there is now a strong argument for progressing with feasibility studies. Unlike trials that have used NMDA blocking mechanisms, in this review we suggest that lowering the concentration of blood glutamate may help to decrease the excitatory burden on neurons within the stroke penumbra but not affect the de novo syntheses of glutamate for use in intra-cellular pro-survival pathways. This could be achieved by the removal of glutamate from synaptic clefts of affected neurons via the EC-mediated mechanism described above.

If PD can be shown to reduce neuronal damage after cerebral ischaemia such treatment could prevent the development of malignant cerebral oedema in patients with large cortical infarcts and thus reduce the need for major invasive treatment such as decompressive craniotomy [26].

### PD FOR HEART FAILURE: HOME-BASED ULTRAFILTRATION

**General principles and comparison with extracorporeal ultrafiltration**

Although the concept of using PD for severe chronic heart failure (CHF) has been reported and debated in the scientific literature for some years, its precise role remains unclear, mainly due to the lack of appropriately designed, prospective clinical studies and clarity over the precise indications. As in the case for acute stroke, its principal attraction is its relatively benign haemodynamic profile [19–21], although there are in fact a number of theoretical and practical reasons why it might be preferred to other extracorporeal methods of ultrafiltration (see Table 1) [27]. Given that the primary mechanism of cardiorenal failure is a reduction in renal perfusion which in turn activates the sympathetic nervous and renin–angiotensin systems, then a treatment that is gentle, continuous and less likely to give rise to sudden reductions in renal perfusion might be expected to preserve residual kidney function effectively—and in particular reduce diuretic resistance. The key practical advantage of PD is that it enables the patient to be treated at home. Therapeutically, the ability to maintain and optimize medications that are contraindicated as kidney function declines, for example those

| Table 1. Comparison of potential advantages and disadvantages of PD and extracorporeal ultrafiltration |
|---------------------------------------------------------|------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------|
| **PD**                                                   | Intermittent haemodiafiltration                       | Isolated ultrafiltration, e.g. ‘aquapheresis’                                                                                      |
| Access                                                  | Peritoneal catheter helpful in reducing ascites mechanical problems | Central or peripheral venous may require repeated cannulation                                                                    |
| Duration/sessions                                       | Continuous                                            | Intermittent—up to 8 h; sessions may extend over days followed by break; continuous requires admission                               |
| Location                                                | Home; suitable for assisted PD potential to reduce hospitalization | Outpatient dialysis facility                                                                                                       |
| Anticoagulation                                         | None                                                  | Standard                                                                                                                         |
| Blood flow rate                                         | –                                                     | Central or peripheral venous may require repeated cannulation                                                                   |
| Ultrafiltration rate                                     | 0–3000 mL/day, typically 1500 mL but dependent on membrane function | Intermittent—up to 8 h; sessions may extend over days followed by break; continuous requires admission                               |
| Biochemical control                                     | Yes—allows optimization of co-prescription of heart failure treatment, e.g. ACR/ARB, spironolactone | Outpatient cardiology clinic may require hospitalization, e.g. UNLOAD trial                                                       |
| Improves residual diuresis                              | Some evidence (see Table 2)                           | Might be complex for prolonged treatments                                                                                         |
| Haemodynamic                                            | Theoretically independent of BP                       | Not suitable if acidotic, hyperkalaemic, eGFR less than ∼20 mL/min or other metabolic concerns                                    |
| Activation of sympathetic nervous and renin angiotensin systems | Less likely                                         | Short-term studies show no difference in comparison with diuretics                                                              |

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that cause hyperkalaemia such as spironolactone as demonstrated in a recent randomized trial are likely to be the main benefit [28]. It has been suggested that one of the potential benefits of PD would be the enhanced clearance of inflammatory cytokines [27]. This seems unlikely, however, in view of the increasing evidence that systemic and intraperitoneal cytokine profiles are independent of each other, reflecting their local production within the peritoneal cavity which might even contribute to the systemic inflammatory state [29].

Generally, it is agreed that the role of supplementary ultrafiltration (PD or extracorporeal) is for patients with diuretic resistant cardiorenal syndrome type 2 as defined by Ronco et al. [30], i.e. worsening kidney function in the context of CHF where the main clinical problem is fluid retention. Even this definition is not so sharp and potentially can change over time. For example with the growth of walk-in or home delivered intravenous diuretic infusion services, some patients who may have been considered diuretic resistant as defined as requiring regular admissions for intravenous diuretic therapy could now be considered diuretic ‘managable’. Also, as judged by several case reports [31–33] and the clinical experience of many nephrologists, instigation of PD in patients with severe heart failure can lead to impressive short-term improvements in residual diuresis implying that there was a reversible component of cardiac de-compensation and at least a mixture of cardiorenal syndrome 1 and 2. Given these relatively complex scenarios, the role of PD is as much, or indeed more, about the life-style choices and patient empowerment as it is about the relative merits of the treatments to control symptoms. The availability of assisted PD services to address the frequent barriers to home therapies seen in this patient population is key to making this treatment approach viable for those who might benefit [34].

**Treatment goals and outcomes for PD treatment of heart failure**

So what are the goals for instigating PD for CHF and what is the evidence that they can be achieved? In the context of the generally poor survival of patients with diuretic resistant heart failure, frequently associated with multi-morbidity, the focus should be on improved symptom control, quality of life and in particular reducing the need for hospital admissions. Important symptoms include the discomfort associated with excessive oedema, including ascites which PD is particularly well suited to controlling provided initial care is taken to reduce this gradually, breathlessness and ability to undertake activities of daily living as for example assessed by the Minnesota Living with Heart Failure Questionnaire. Additional therapeutic goals would include preserving or even improving residual diuresis and diuretic sensitivity, regaining any reversibility in the functional severity of the heart failure as evidenced by the improvement in the New York Heart Association classification and the ability to maximize pharmacological treatment of heart failure. The tools available to the clinician are various and include incremental introduction of PD, for example a single icodextrin exchange [31, 35], various APD regimes, two daily ‘back-to-back’ icodextrin exchanges only given high clearances may not be required [36], use of high-dose diuretics and RAAS blockade (which have already been shown to preserve urine volume in PD [37, 38]) and perhaps in the future low sodium dialysates that improve diffusive sodium removal and reduce thirst [39].

The last 2–3 years has seen publication of an increasing number of cohort studies describing the use of PD for CHF. Summarized in Table 2, these have included almost 300 patients since 2010 [40–49]. Although the synthesis of data reported from these studies can be qualitative at best, given the different approaches to patient selection, methods of describing survival and hospitalization and the likely retrospective study design in many of the cohorts described, it is possible to draw common patterns from the information presented. In all cases the primary reason for starting PD was the CHF and kidney function was quite variable varying from dialysis dependency to CKD stage 3. Generally survival was poor, as would be anticipated for this population, although there were exceptions, for example the recent study from Italy [49] where

<table>
<thead>
<tr>
<th>Authors</th>
<th>Number</th>
<th>Survival</th>
<th>Hospitalizations</th>
<th>Functional benefits</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nakayama et al. [40]</td>
<td>12 (PD)</td>
<td>75% median follow-up 26 m</td>
<td>&gt;3 per year prior to PD, none for heart failure afterwards</td>
<td>NYHA class improved in all from Class III, n = 9; IV, n = 3 to Class 1, n = 9; II n = 3 Average ejection fraction improved from 28–36%; 5 kg weight loss</td>
</tr>
<tr>
<td>Sotirakopoulos et al.</td>
<td>19 (PD)</td>
<td>68% at 1 year 42% at 2 years</td>
<td>Prior to PD 5–20 d/m/p for fluid-related problems to ‘none’ after Cardiac related admissions reduced from 1.4 to 0.4 d/p/m; all cause admissions not changed</td>
<td>NYHA class improved 3.8 to 2.7, QOL improved but technical complications high. PD = HD</td>
</tr>
<tr>
<td>Cnossen et al. [43]</td>
<td>12 (PD)</td>
<td>Median 16 m</td>
<td></td>
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<td>and [35]</td>
<td></td>
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<tr>
<td>Nunez et al. 2012</td>
<td>28 (PD)</td>
<td>Reduced death risk: 0.4 (0.21–0.75)</td>
<td>84% reduction in hospital admissions in first 6 months</td>
<td>Comparison used propensity scoring. Overall mortality was 63% by 16 months. In 25 patients there was improvement in NYHA class (mean 1.04), the MLWHF questionnaire and 6-min walk test 'Long-term’ survivors required fewer diuretics and experienced on average a one class reduction in NYHF classification</td>
</tr>
<tr>
<td>Kunin et al. [46]</td>
<td>37 (PD)</td>
<td>Median 14 m</td>
<td>Reduced by 55% in 'long-term’ survivors</td>
<td></td>
</tr>
<tr>
<td>Rizkallah et al. [47]</td>
<td>10 (PD)</td>
<td>?</td>
<td>Reduced from 3.2 to 0.1 d/p/m and length of stay (37 to 0.78 days)</td>
<td>Transplant ineligible. NYHA class IIB improved, improved diuretic response, 7 kg weight loss</td>
</tr>
<tr>
<td>Courivaud et al. [48]</td>
<td>126 (PD)</td>
<td>58% at 1 year 85% at 1 year 56% at 2 years</td>
<td>Reduced from 3.3 to 0.3 d/p/m</td>
<td>Improvement of left ventricular ejection fraction observed Prior to PD had at least three admissions during the previous year requiring extracorporeal ultrafiltration</td>
</tr>
<tr>
<td>Bertoli et al. [49]</td>
<td>48 (PD)</td>
<td></td>
<td>Reduced from 43 to 11 admissions per year</td>
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</tr>
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NYHA, New York heart association; MLWHF, Minnesota living with heart failure questionnaire; d/m/p = days/month/patient
first year survival was high at 85%, although this did drop significantly in the second year. This variability points to significant heterogeneity in the cohorts; several authors observed that following initiation of PD, events (including deaths) directly related to heart failure were reduced but other causes of mortality were common as might be anticipated in this complex group of patients. There was, however, much less heterogeneity in the key benefits observed. In particular, all the cohorts reported impressive reductions in heart failure-related hospital admissions; a crude calculation of the average reductions is 83% (range 55–100). Improvement in heart failure was also observed and typically reported as a ‘1’ class change in the NYHA classification. Studies variably reported improvement in the ejection fraction (but noted often that the clinical improvements were not predicted by this measurement), weight loss, better quality of life and reduced resistance to diuretic therapy. Complications of the PD itself, e.g. infection rates, were not reported systematically but equally not raised as a barrier to treatment.

**Why is the use of PD for heart failure not more widespread?**

It is perhaps surprising that PD is not used more frequently for heart failure and indeed it may well be under-reported. However, the most likely explanation is the lack of sufficient prospectively designed, conducted and preferably randomized controlled trials in which the inclusion criteria are clearly defined, especially in light of the negative findings of the CARESS trial in which the use of extracorporeal ultrafiltration was associated with a greater number of adverse events [50]. There are plans in place to undertake such a study in the UK which will be funded by the British Heart Foundation (research grant PG/13/27/29864) led by the UK Renal Research Consortium’s cardiorenal clinical study group (Chief Investigator Prof. C. McIntyre) which will go some way to addressing this deficit. Hopefully, this will stimulate other investigators to undertake similar trials which will undoubtedly be needed.

The other main barrier to the use of PD for heart failure is likely to be the fact that these patients are looked after by different specialist teams who are unaware of the possibilities this modality can offer, are unskilled in PD use or frankly sceptical of the successes reported by enthusiasts in highly selected cases. There are good reasons for this scepticism. The large reductions in hospital admissions may simply reflect the better support from a team expert in managing complex patients in the community rather than the PD treatment per se, something that could be provided equally effectively by skilled community-based heart failure teams. It is also the case that whereas PD is generally associated with good outcomes, especially in the early years of treatment when residual renal function is well preserved, this advantage is greatest in patients with minimal comorbidity and some analyses of registry data have found that patients with heart failure have marginally better outcomes when treated with haemodialysis [51, 52]. These differences translate into no more than a few weeks difference in survival at worst are confounded by age and diabetic status and predate the wider use of icodextrin, but emphasize the need for trials in evaluating this use for PD.

**CONCLUSIONS**

There are strong grounds for pursuing the use of PD beyond its role in CKD, based on these theoretical and experimental observations in acute ischaemic stroke and the uncontrolled, selective but relatively consistent experience in heart failure. The challenges are, however, significant and include not just controlled evidence of efficacy but also recognition that working across speciality boundaries brings its own problems that will include skills and attitudes. Given that these patients often have complex multi-morbidity, focussing on morbidity and cost-effectiveness as much as mortality will be an important aspect of further research.

**CONFICT OF INTEREST STATEMENT**

None declared.

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