Commentary for A randomized controlled trial of alanyl-glutamine in peritoneal dialysis fluids to assess impact on biomarkers of peritoneal health and systemic inflammation

Journal:	*Kidney International*
Manuscript ID	Draft
Article Type:	COMMENTARY
Date Submitted by the Author:	n/a
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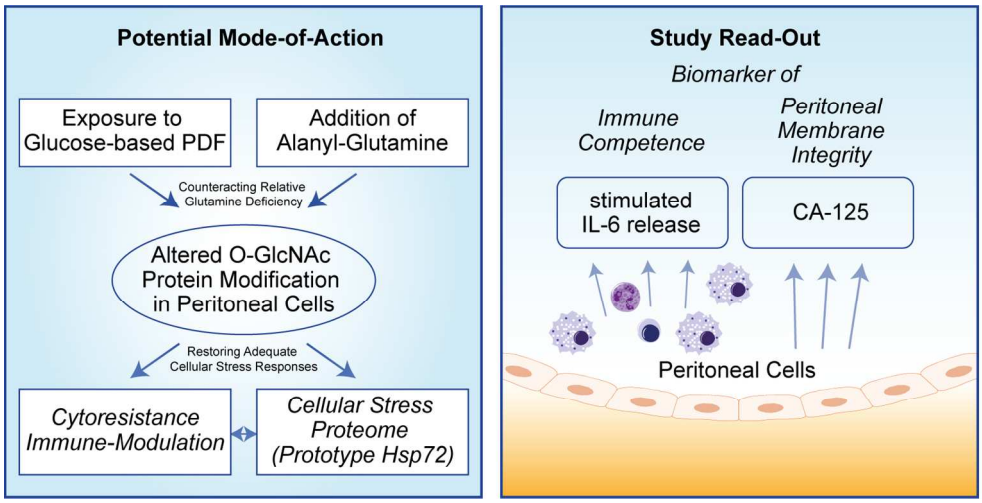
Keywords:	peritoneal dialysis, peritoneal membrane, peritonitis, inflammation
Subject Area:	Dialysis



Left panel - potential mode-of-action of the cytoprotective effect of alanyl-glutamine supplementation of peritoneal dialysis solutions. Right panel – biomarkers selected as primary outcome measures selected in the proof-of-concept study reported in this issue of Kidney International.
HSP 72 Heat Shock Protein 72; PDF peritoneal dialysis fluid; CA-125 Cancer Antigen 125.
The figure is courtesy of Klaus Kratochwill, Christoph Aufricht, and Andreas Vychytil, from the Medical University of Vienna.

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Abstract

Peritoneal dialysis technique survival remains challenging due to peritonitis and long-term alterations to peritoneal membrane function and integrity. Up to now, the development of less bio-incompatible dialysis solutions have not had a major impact on these aspects of the therapy. A novel approach, supplementing dialysis solutions with a cytoprotective additive, alanyl-glutamine, has shown benefits to surrogate biomarkers of cell function in a randomised controlled study.

Key words

Peritoneal dialysis, peritoneal membrane, peritonitis, inflammation

Peritoneal dialysis technique failure as a therapeutic goal

PD technique failure (TF) rates remain too high and at least part of that is due to the impact of the peritoneal dialysis solutions on peritoneal membrane physiology – both in terms of cell integrity and immune defences. In a recent study from ANZDATA, peritonitis was the most common cause of technique failure, accounting for 27% of PD patients switching to HD(1). As an indicator of its importance to the therapy, TF has been selected as the primary outcome measure for the international Peritoneal Dialysis Outcomes and Practice Patterns Study (2). Efforts to reduce TF have included developments in dialysis bag connection systems to reduce infection, flexible catheters to improve peritoneal access, improvements in clinical practice(1) as well as the impact of automated PD and icodextrin on prescription and volume management.

Over the last two decades there has been emphasis on improving the biocompatibility of peritoneal dialysis solutions to reduce damage that occurs to the membrane with time on therapy while benefiting host defences. The strategy has been to minimise the generation of glucose degradation products during solution preparation as well as altering the buffer to achieve a more physiological pH. These changes have required significant alterations in the preparation and presentation of solutions increasing the cost of the therapy. Although biocompatible solutions result in better preservation of residual kidney function and possibly more a stable peritoneal membrane(3), clinical benefits such as prevention of peritonitis and membrane failure has been difficult to demonstrate, in part because the latter takes several years on therapy to demonstrate.

The potential benefits of Alanyl-Glutamine supplementation

In this issue of Kidney International Vychytil and colleagues investigate the addition of alanyl-glutamine (AlaGln) to biocompatible peritoneal dialysis fluids with the objective of improving markers of mesothelial cell health(4). This approach extends the existing concept of biocompatibility by replacing deficient glutamine in order to restore dysfunctional mesothelial cellular stress responses (Figure left panel). The rationale for the approach comes from clinical evidence of the benefit of glutamine supplementation in critically ill adults(5), and from experimental models of PD demonstrating that supplementing glucose-based peritoneal dialysis solutions with pharmacological doses of AlaGln protected mesothelial cells in-vitro and preserved peritoneal integrity in-vivo(6). The cellular mechanisms are complex, but include enhancement of expression of one of the best described cytoprotective human stress proteins, Heat-shock protein 72, thereby strengthening resistance of mesothelial cells against toxicity from peritoneal dialysis fluids (6).

The current study

In a proof of concept study, published in this issue of Kidney International, the two pre-defined primary outcome measures were biomarkers of cellular integrity (Figure right panel): (1) the dialysate appearance rate of cancer-antigen 125, which can be used to assess mesothelial mass in stable PD patients without acute peritonitis; and (2), ex-vivo stimulated dialysis effluent cell interleukin-6 release, which is a marker of peritoneal immune competence and associates with outcome in critically ill patients. The study was a randomised cross-over design of 8 weeks of AlaGln supplementation at a concentration of 8mM or matching placebo to freshly mixed double chamber Physioneal bags in 50 prevalent patients who had been on PD treatment for a mean of 18 months. AlaGln supplementation significantly improved the primary outcome measures as well as impacting on secondary outcome markers, including stimulated tumor necrosis factor-alpha release by dialysis effluent cells and improvement in systemic inflammation with reductions in blood levels of IL-8 and high sensitivity C-reactive protein. Although there was no impact on peritoneal ultrafiltration or transport of creatinine, urea and glucose, there were increases in peritoneal transport of uric acid, phosphate and potassium; peritoneal protein loss was significantly lower after treatment with AlaGln. The latter is potentially important since it correlates to mortality in patients on PD.

Challenges to the study

Despite these positive findings, they must be treated with caution given that the selected primary outcome measures are surrogates and not of themselves clinically meaningful to patients. They are reminiscent of the early work with conventional biocompatible dialysis solutions, with similar research design, for example using a relatively short duration cross-over study to evaluate the effect on biomarkers of "peritoneal integrity" as well as short-term clinical measures(7), and hopefully they will feed into the design of a subsequent phase 3 randomised controlled trial (3). Biomarker exploration has been central to understanding peritoneal pathophysiology, however cytokines have complex profiles – and it is not yet clear whether increased local production is good or bad. IL-6 has a role in multiple inflammatory pathways - increased systemic IL-6 associates with poorer outcomes in patients on PD, and has a role in peritoneal fibrosis in unresolved inflammation (8). Thus the finding of restored simulated IL-6 release in peritoneal dialysis effluent following Ala-Gln supplementation requires to be translated into clinically relevant outcomes such as frequency of peritonitis. Equally the interpretation of dialysate CA 125 is subject to debate.

The challenge in proving therapeutic utility should not be underestimated. For this innovation to have merit it clearly needs to impact on clinically meaningful outcomes such as peritoneal integrity, frequency of infection, residual renal function and technique survival. Occurrence of peritonitis is a key outcome measure which has been prioritised by patients and health care professionals through the SONG-PD initiative (9). All four peritonitis episodes in the study reported here occurred in the control group with none occurring during the intervention, however too much significance should not be placed on this because of the small sample size. The history of studies of biocompatible peritoneal dialysis solutions testifies to just how difficult it can be to translate science from the bench to the bedside.

A further problem is the high withdrawal rate during this short study (13 of 50 patients). This is a common criticism of studies of peritoneal dialysis, reflecting the problem that drives the research in the first place. Paradoxically, the study of more sustainable treatment is subjected to problematic attrition rates that justify that study in the first place. Finally, there are the practicalities of adding the AlaGln supplement to the dialysate. In this study research nurses were required to undertake that task while taking great care to minimise the risk of infection. However, for this innovation to be sustainable AlaGln would require to be added to dialysate solutions at manufacture, requiring significant developmental investment.

Conclusion

Reducing TF in PD is an important goal and any step towards this must be applauded. However there is much more to TF than membrane function and integrity, especially given the considerable variation between centres and their practices (1), so the beneficial effect of a novel approach will have to be large to be visible over the background noise. The supplementation of dialysate with AlaGln as a cytoprotective agent in innovative and this study suggest that it will restore mesothelial integrity and inflammatory responses providing a potential step change for PD. A sufficiently powered phase three study that impacts on clinically meaningful endpoints, however challenging, is now required.

Caption for figure

Left panel - potential mode-of-action of the cytoprotective effect of alanyl-glutamine supplementation of peritoneal dialysis solutions.

Right panel – biomarkers selected as primary outcome measures selected in the proof-of-concept study reported in this issue of Kidney International.

HSP 72 Heat-shock Protein 72; PDF peritoneal dialysis fluid; CA-125 cancer antigen 125

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