Efficacy and Biocompatibility of Neutral Icodextrin Peritoneal Dialysis Fluid

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Neutral icodextrin peritoneal dialysis (PD) fluid (n-ICO) has become available for use in Japan. However, removal of water and solutes remains to be elucidated in detail. The present study was designed to determine removal of water, electrolytes, and small, middle, and large molecules in a period of 16 hours. In addition, biocompatibility with respect to peritoneal mesothelial cells was determined.

Three stable patients undergoing PD at Tohoku University Hospital were administered n-ICO. Water removal was monitored every 2 hours. Sodium, urea nitrogen [molecular weight (MW): 28 Da], uric acid (MW: 168 Da), β_2-microglobulin [β2M (MW: 11,800 Da)], α_1-microglobulin [α1M (MW: 33,000 Da)], albumin (MW: 66,000 Da), and immunoglobulin G (MW: 160,000 Da) were measured in plasma and dialysate.

Primary human peritoneal mesothelial cells were collected from 6 patients. Equal numbers of cells were seeded into 96-well culture plates and cultured for 12 hours. Culture medium was then replaced with dialysate, and 24-hour cell proliferation was determined by WST-1 assay.

Water removal was sustained for 16 hours with n-ICO. The Na concentration in effluent did not change over that time. Small molecules such as urea nitrogen and uric acid were rapidly removed. Thus, their dialysate-to-plasma concentration ratio (D/P) approached 1.0 (equilibrium) in 2 – 4 hours. The D/P values for the larger molecules β2M and α1M were 0.4 and less than 0.1 respectively at 16 hours. However, larger molecules were removed in a time-dependent manner.

Cell proliferation with n-ICO PD fluid was not different from that with lactate-buffered glucose PD fluid, but was increased from that with acidic icodextrin PD fluid (a-ICO).

Water and solute removal with the new n-ICO is not much different from that with a-ICO. However, biocompatibility as reflected by cell proliferation was superior under n-ICO than under a-ICO and equal to proliferation under glucose PD fluid.

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Key words
Icodextrin, neutral PD fluid, volume overload, small pores, peritoneal mesothelial cells

Introduction

In peritoneal dialysis (PD), volume overload, which is associated with mortality, is one of the chief concerns. Conventional PD fluid uses glucose as an osmolyte for filtration of water, electrolytes, and uremic toxins. Because glucose is a relatively small molecule, it can diffuse through the peritoneum to the capillaries, reducing the glucose concentration in the peritoneum. To increase ultrafiltration with conventional glucose-based solution requires a reduction of session time or an increase in the glucose concentration. A shortened dwell time can result in decreased removal of larger molecules. Compared with glucose, icodextrin is a larger molecule and passes through the peritoneal membrane only with difficulty. Thus, icodextrin PD solution (ICO) can achieve better fluid removal over a longer period of time (1).

We previously demonstrated the beneficial role of ICO for body fluid control without alteration of residual renal function in end-stage renal disease patients (2). In patients not using ICO, left ventricular mass index (LVMI) did not change during a period of 12 months, but in patients using ICO, LVMI significantly declined within 6 months and was maintained at that level for up to 12 months. Residual renal function in

those patients, as indicated by urine volume, did not change during the 12 months.

It is now evident that acidic PD solution can induce peritoneal fibrosis (3). Conventional ICO is also acidic (a-ICO) and raises concerns about biocompatibility with respect to the peritoneum (4). Lactate-buffered, neutral ICO PD fluid (n-ICO) became available for use in Japan at the end of 2014; however, the efficacy and safety of n-ICO have not been fully evaluated. The present study therefore aimed to determine removal of water, electrolytes, and small, middle, and large molecules with n-ICO during a 16-hour period. Furthermore, because the biocompatibility of n-ICO is also not known, *in vitro* examination of cell proliferation was performed.

Methods

Water and solute removal

Three stable patients undergoing PD at Tohoku University Hospital were administered n-ICO (Nicopeliq: Terumo, Tokyo, Japan). Table I sets out the characteristics of the patients. All patients had already been using n-ICO once daily for 4 months. The dialysate-to-plasma ratio (D/P) of creatinine and the initial-to-end dialysate glucose concentration in a peritoneal equilibration test indicated high-average transport in all patients. No patient had ever used acidic PD solution.

After a dwell of more than 6 hours with a neutral glucose-based solution, the effluent was fully drained before n-ICO was infused into the peritoneal cavity. Every 2 hours, the dialysate was fully drained, and water removal was monitored. Every 2 hours, 10 mL of effluent was also sampled for Na, urea nitrogen [molecular weight (MW): 28 Da], uric acid (MW: 168 Da), β_2-microglobulin [β2M (MW: 11,800 Da)], α_1-microglobulin [α1M (MW: 33,000 Da), albumin (MW: 66,000 Da), and immunoglobulin G (MW: 160,000 Da) were measured. Blood was sampled once and measured for the foregoing molecules so that their D/P could be measured.

All human studies were performed according to the principles of the Declaration of Helsinki, and all protocols were approved by the institutional ethics committee.

In vitro examination for cell proliferation

Human peritoneal mesothelial cells were collected from the PD effluent of 6 patients (5). Equal numbers of cells were seeded into 96-well culture plates and cultured for 12 hours. The culture medium was then replaced with PD fluid: a-ICO PD fluid (Extraneal: Baxter Healthcare, Tokyo, Japan), n-ICO (Nicopeliq), or neutral biocompatible 2.5% glucose PD fluid (Midpeliq: Terumo). The 24-hour cell proliferation was then determined using the premixed WST-1 Cell Proliferation Assay System (Takara Bio, Shiga, Japan)

TABLE I Patient characteristics

Characteristic	*Patient ID*		
	A	*B*	*C*
Age (years)	47	39	57
Sex	Male	Female	Female
Body weight (kg)	71.8	48.2	38.9
Height (cm)	162.3	148.0	146.0
PD vintage (months)	13	6	16
Time on PD with n-ICO (months)	4	4	4
Primary disease	Diabetes mellitus	Focal segmental glomerulosclerosis	IgA nephropathy
PET category			
D/P creatinine	High average	High average	High average
D/D_0 glucose	High average	High average	High average

PD = peritoneal dialysis; n-ICO = neutral icodextrin dialysate; IgA = immunoglobulin A; PET = peritoneal equilibration test; D/P = dialysate-to-plasma ratio; D/D_0 = end-to-initial dialysate ratio.

according to the standard protocol. Sodium was measured by the electrode method; urea nitrogen and uric acid, by the enzymatic method; β2M, α1M, albumin, and immunoglobulin G, by the modified bromcresol purple method, turbidimetric immunoassay, and latex agglutination turbidimetry respectively.

Statistical analysis

Statistical significance was determined by 1-way or 2-way repeated-measures analysis of variance in the Sigma Plot software application (version 12: Hulinks, Tokyo, Japan), followed by Bonferroni *post hoc* analysis for multiple comparisons versus time 0. For the WST-1 assay, the Tukey *post hoc* analysis was used.

Results

Water and Na removal

With n-ICO, water removal was sustained for 16 hours (Figure 1). During that time, the Na concentration in effluent did not change. Converting the Na concentration to NaCl, more than 4 g salt was removed after 12 hours (Figure 2).

Small-, middle-, and large-molecule removal

Small molecules such as urea nitrogen and uric acid were rapidly removed. Thus, their D/P concentration ratio approached 1.0 (equilibrium) after 2 – 4 hours. The D/P values for the larger molecules β2M and α1M were 0.4 and less than 0.1 respectively at 16 hours. However, larger molecules were removed in a time-dependent manner (Figure 3).

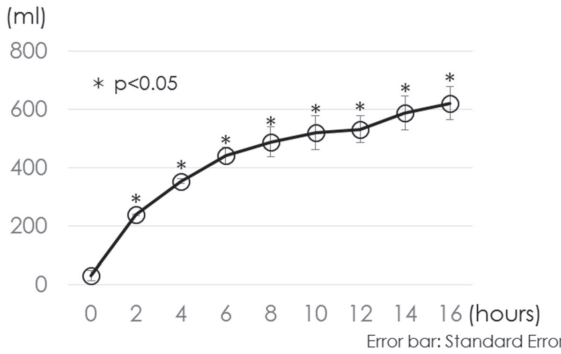

FIGURE 1 Water removal after a neutral icodextrin dwell. Water removal was plotted every 2 hours. Water removal was calculated as the full dwell volume at each time point minus the volume at time 0. Results are presented as mean ± standard error of the mean.

In vitro *examination for cell proliferation*

Figure 4 shows relative absorbance values at 30 minutes after WST-1 administration. Cell proliferation was not different with n-ICO than it was with a neutral glucose PD fluid, but it was increased compared with proliferation under a-ICO.

Discussion

Water and solute removal with n-ICO was almost identical to that with conventional a-ICO. Removal of as much as 4 g salt was achieved during a dwell time of more than 12 hours. Interestingly, biocompatibility

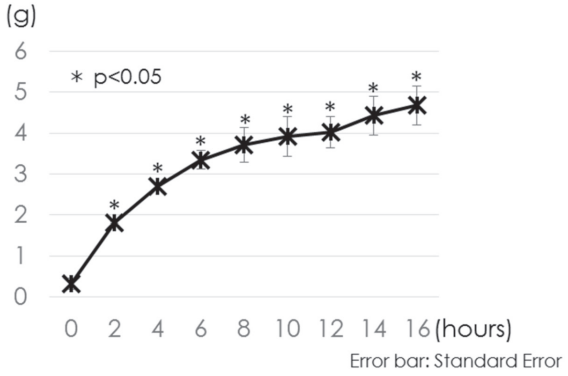

FIGURE 2 Sodium removal with the use of neutral icodextrin. Changes in salt were calculated using the Na concentration every 2 hours (measured in a 10-mL sample of effluent at each time point). Results are presented as mean ± standard error of the mean.

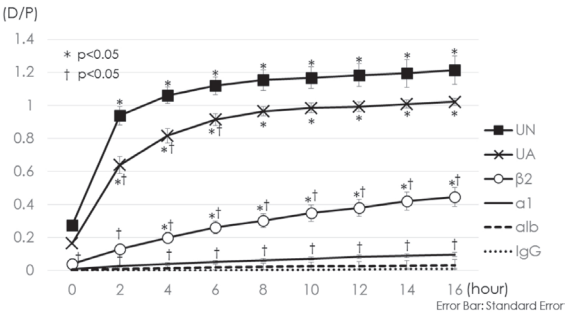

FIGURE 3 Small-, middle-, and large-molecule removal with the use of neutral icodextrin. Changes in the dialysate-to-plasma ratio of various molecules were calculated every 2 hours (measured in a 10-mL sample of effluent at each time point). Results are presented as mean ± standard error of the mean. *$p < 0.05$ versus time 0. †$p < 0.05$ versus urea nitrogen. UN = urea nitrogen; UA = uric acid; β2 = β_2-microglobulin; α1 = α_1-macroglobulin; alb = albumin; IgG = immunoglobulin G.

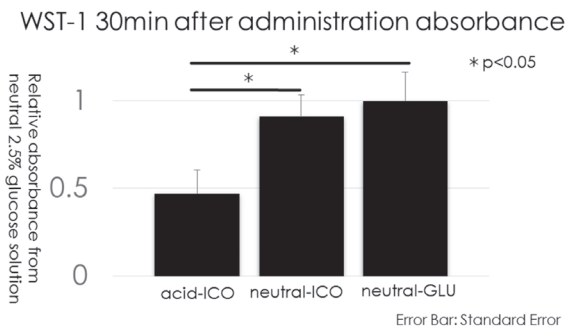

FIGURE 4 Cellular proliferation with the use of peritoneal dialysate. Cellular proliferation was determined by WST-1 assay and reported as relative absorbance of WST-1 after 30 minutes. Results are presented as mean ± standard error of the mean. *$p < 0.05$. Acid-ICO = acidic icodextrin dialysate; neutral-ICO = neutral icodextrin dialysate; neutral-GLU = neutral 2.5% glucose dialysate.

for cell proliferation with n-ICO was superior to that with a-ICO and equal to that with glucose PD fluid. With the new n-ICO now being widely available for use by PD patients, we have demonstrated its efficacy and biocompatibility, which are the novel observations of our study.

Volume overload is among the major concerns in PD, being that it is an independent risk factor for mortality. To decrease volume overload in PD patients, removal of both salt and water is often required. However, with glucose-based solution and a short dwell time, free water is more likely to be removed by Na sieving, and thus little salt will be removed (6). Patients with volume overload and a higher salt consumption, especially those with heart failure, require removal of salt. Although Na-sparing diuretics have often been used to reduce volume in such patients, reduction of residual renal function can be expected because of an accompanying reduction in renal flow and enhancement of the renin–angiotensin system (7). In contrast, maintenance of the renin–angiotensin system and renal circulation by gradual water removal has been shown to be a beneficial role of PD in the treatment of heart failure (8). We previously reported that icodextrin treatment successfully lowered the LVMI without altering urine volume (2). Decrease in the LVMI is significantly correlated with increased ultrafiltration, indicating that ultrafiltration is responsible for the decrease in LVMI and better volume control. Thus, ICO is beneficial for volume control in heart failure patients, without altering residual renal function.

Furthermore, the diuretic tolvaptan is now available for use in heart failure and has been shown to provide a benefit to PD patients while maintaining residual renal function (9). Combined treatment with ICO and tolvaptan could be a good combination for volume control without reduction of residual renal function. However, the results of the present study indicate that more than 4 g salt can be removed during ICO treatment. Patients having volume overload without accumulation of salt might experience intravascular dehydration and hyponatremia, which can also result in a reduction of residual renal function. Serum Na should be carefully monitored in patients using ICO.

Since the introduction of neutral biocompatible PD solution after 2004 in Japan, the number of cases of encapsulating peritoneal sclerosis has been declining (10). Neutral biocompatible PD fluid has also been associated with a reduction in the rate of continuous ambulatory PD peritonitis (11), and a-ICO has been shown to be a potential contributor to the development of peritoneal fibrosis (12). Results from the present study support that association, in that a reduction in cellular proliferation was observed with a-ICO, which was improved with the use of n-ICO. The mechanism by which n-ICO improves cellular proliferation and the question of whether n-ICO protects against peritoneal fibrosis remain to be elucidated. The n-ICO now available in Japan is buffered with lactate. Because bicarbonate-buffered PD fluid has been associated with a reduction in the incidence of continuous ambulatory PD peritonitis (13), further study of such solutions is warranted.

Conclusions

The new n-ICO PD fluid demonstrates efficacy in water and solute removal consistent with that for conventional acidic-ICO. However, the biocompatibility of n-ICO with respect to peritoneal mesothelial cell proliferation was superior to that of a-ICO and equivalent to that of neutral glucose PD fluid, which could protect the peritoneum from injury and might lead to a longer PD vintage.

Disclosures

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