Clinical effects of icodextrin in peritoneal dialysis

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Abstract

Objective. This study reviews the relevant publications on the clinical effects of icodextrin in peritoneal dialysis (PD).

Design. The study provides a systematic review of the literature (MEDLINE search with icodextrin as the keyword).

Results. Icodextrin induces sustained transcapillary ultrafiltration during long dwell periods. It also stimulates increased removal of sodium by the peritoneal membrane, reduction of extracellular water (ECW) and total body water (TBW). Effects of icodextrin on blood pressure control and residual renal function are discrepant. Icodextrin induces a reduction in the formation of advanced glycation end-products, while the longitudinal changes in the peritoneal membrane transport are less prominent.

Conclusions. Use of icodextrin in PD improves the sodium and fluid balance. Icodextrin is potentially more biocompatible, when compared with the conventional glucose solutions. The side effects are rare.

Keywords: icodextrin; fluid status; sodium balance; residual renal function; side effects

Introduction

Icodextrin is an alternative to the hyperosmolar glucose containing solutions in peritoneal dialysis (PD). Icodextrin is an iso-osmolar dialysis solution that consists of a mixture of high molecular weight water-soluble polymers of glucose, isolated by the fractionation of hydrolyzed cornstarch [1], which induces sustained transcapillary ultrafiltration through colloid osmosis during dwells of >12 h. Peritoneal ultrafiltration with icodextrin is ideal than the 1.36% and 2.27% glucose solutions, and in general, comparable with the 3.86% glucose solution [2].

This review focuses on the clinical effects of icodextrin on the sodium and fluid balance in PD. Furthermore, the discrepant effects of icodextrin on blood pressure control and residual renal function (RRF) are also discussed. The effects of icodextrin on the peritoneal membrane, biocompatibility and its side effects are also discussed.

Effects of icodextrin on extracellular and total body water

Among the several studies on icodextrin, two randomized controlled trials have been studied on the effects of icodextrin on fluid status [3–7]. The two randomized controlled trials [3,6] showed a reduction in extracellular water (ECW) or total body water (TBW) with the use of icodextrin. In the study by Konings et al. [6], the left ventricular mass decreased in the group randomized to icodextrin.

Woodrow et al. [4] inferred that the ECW and TBW decline with the use of icodextrin in automated peritoneal dialysis (APD) patients. In the cross-sectional study by Boudville et al. [7], the APD patients on icodextrin had a significantly lower ratio between the ECW and intracellular water, compared with patients treated with conventional glucose solutions. Ultimately, there appears to be an overall agreement between the studies concerned with the effects of icodextrin on volume status. The use of icodextrin may also reduce the dropout from PD treatment—in a recent retrospective study from Japan, the treatment dropout rate and even mortality were significantly reduced in patients treated with icodextrin [8].

Effects of icodextrin and hypertonic glucose on RRF

Despite the fact that continuous fluid removal can be achieved with PD, chronic fluid overload is a common problem, particularly in anuric PD patients, leading to the high prevalence of hypertension and left ventricular hypertrophy in them [9,10]. One of the contributing factors to chronic fluid overload in PD patients is the decline in the peritoneal ultrafiltration capacity, caused by diabetiform alterations of the peritoneal capillaries, due to the long-term effects of high glucose concentrations in the peritoneal cavity [11]. This leads to an increased uptake of the glucose from the PD solution into the peritoneal capillaries, and a subsequent loss of the osmotic gradient and ultrafiltration...
capacity. To increase the peritoneal ultrafiltration, higher glucose concentrations are prescribed, resulting in greater exposure of the peritoneal membrane to glucose and increasing peritoneal damage [9]. Predominantly, in patients with high transport ultrafiltration failure of the peritoneal membrane, the use of conventional glucose solutions may result in insufficient peritoneal fluid removal, owing to the rapid uptake of glucose through the peritoneal membrane. In addition to the loss of peritoneal ultrafiltration capacity, a progressive decline in RRF and a subsequent loss of urine production have an adverse impact on the balance between the fluid intake and removal in PD patients [3].

In the study by Gunal et al. [12], a significant decrease in the blood pressure and cardiothoracic index was observed when the peritoneal ultrafiltration was increased with the use of hypertonic glucose solutions. However, in our research, the RRF and urine volume declined to a highly significant degree.

In contrast, according to both Davies et al. and Plum et al., despite an increase in the peritoneal ultrafiltration, no adverse effects were observed on the RRF [3,5]. Davies et al. showed that the RRF was better preserved with the use of icodextrin than with the standard glucose solutions [3]. As discussed earlier, it has been suggested that a relative preservation of the intravascular volume, due to the oncotic effect of the icodextrin metabolites, might be an important factor concerned with the preservation of renal function, despite the reduction in ECW [13]. Also, the results from the NEPP study [14] did not suggest any adverse effects of the use of icodextrin on RRF.

In contrast, the findings of Konings et al. revealed a much higher baseline RRF and a greater decline in the RRF with the use of icodextrin compared with the results of Davies et al. and Plum et al. [3,5,6]. Probably, the patients in Konings’ study may have been less overfilled at the baseline [15], although a direct comparison between the fluid status in the various studies cannot be made. However, it is quite likely that the arterial underfilling played a role in the decline of RRF in Konings’ study. Four patients were found to be severely underfilled (according to the normalized ECW values) [16]. When the underfilled patients after icodextrin treatment were excluded from the analysis, the decline in RRF did not differ much between the patients treated with icodextrin and the control subjects (−1.0 ± 1.6 versus −0.6 ± 0.8 ml/min; P = 0.6), whereas the fall in RRF in the underfilled patients was higher than the other subjects (−3.2 ± 2.4 ml/min versus −1.0 ± 1.6 ml/min; P = 0.055) [17].

Patients with a more advanced decline in RRF, as documented in the studies by Davies and Plum [3,5], may have been more overfilled at the start of the study, and therefore, it is less likely that the use of icodextrin would have resulted in underfilling.

### Effects of icodextrin on sodium balance and blood pressure

The net sodium balance in PD depends on the sodium intake, urinary sodium excretion and peritoneal sodium removal. Peritoneal sodium removal appears to be increased with the use of icodextrin [3], which may be due to both the enhanced ultrafiltration and the reduction in sodium sieving, due to the induction of ultrafiltration by colloid osmosis during the use of icodextrin, with a lesser role for aquaporin-mediated water transport [18].

With a strict sodium restriction and an increased use of 3.86% glucose solutions, Gunal et al. observed a reduction in blood pressure in the overfilled continuous ambulatory peritoneal dialysis (CAPD) patients [12]. In contrast, despite an improvement in the fluid status, the use of icodextrin did not result in the decrease in blood pressure in the studies by Davies et al. and Konings et al., and even appeared to result in a small increase in blood pressure in the study by Plum et al. [3,5,6]. In contrast, according to the study by Woodrow et al., the systolic blood pressure declined in the APD patients, who switched over to icodextrin for the long dwell [4]. There are three potential explanations for these conclusions. First, the improvement in fluid status (mean decline in ECW, which was 1.7 L and 1.0 L, according to Konings et al. [6] and Davies et al. [5], respectively) might have been too small to bring about a significant improvement in the blood pressure control. Indeed, the decline in the body weight, with the approach of Gunal et al. [12], using hypertonic glucose solutions, was much larger (−4 kg). Second, owing to the oncotic effect of icodextrin metabolites that enter the systemic circulation [19,20], the blood volume might have remained relatively stable in icodextrin-treated patients, despite a decrease in ECW. Third, in some of the studies, the observational period might be too short to monitor the changes in the blood pressure owing to the ‘lag’ phenomenon [21], although this holds true for the long-term studies, such as those by Konings et al. [6] and Davies et al. [5].

Moreover, dietary sodium intake was not strictly controlled in all the studies. As sodium balance is dependent on the relation between the intake and output, especially in anuric PD patients, a reduction in sodium intake, along with the use of icodextrin is vital to maintain the sodium balance with less increase in the extracellular volume and blood pressure, compared with the conventional glucose-containing solutions [22]. The maintenance of sodium balance is also important for volume-dependent effects. In this aspect, a reduction in the tissue renin–angiotensin–aldosterone system activity, due to sodium restriction, could have additional beneficial effects on the blood pressure control and cardiovascular structure. Also, the recent concept of non-osmotic storage of sodium in the body, especially in the skin [23], may be significant, although its relevance is still unknown.

### Effects of icodextrin on intravascular volume and water balance

Because of the oncotic effect of icodextrin metabolites that enter the systemic circulation [19,20], resulting in thirst, increased fluid intake and subsequently to pseudohyponatraemia, the blood volume might have remained relatively stable in icodextrin-treated patients, in spite of the decrease...
in ECW. Some icodextrin metabolites might enter the systemic circulation, after being degraded to oligosaccharides (maltose, maltotriose and maltotetraose) and eventually to glucose [19,20]. This may be supported by the fact, as reported by Davies et al., that the atrial natriuretic peptide, a surrogate marker of the intravascular fluid status, did not decline in the icodextrin-treated patients [13], whereas it decreased in patients treated with standard glucose solutions. In another study, the atrial natriuretic peptide was found to increase after the treatment with icodextrin [24]. In contrast, the fact that the left ventricular mass decreased in the study by Konings et al. [6] suggests that the intravascular volume also declines. Thus, the effects of icodextrin on surrogate markers of intravascular fluid volume remain to be elucidated. Available indirect evidence would suggest that with a small decline in ECW, the intravascular fluid volume remains stable or even increases with the use of icodextrin, potentially due to the oncotic effects of the icodextrin metabolites, whereas with larger declines in ECW, the intravascular volume also decreases [4,6]. Future studies, assessing changes in the plasma volume after icodextrin prescription, are required to confirm this hypothesis.

Effects of icodextrin on the peritoneal membrane

Icodextrin has a pH of 5.8, uses lactate as a buffer and contains relatively low levels of glucose degradation products (GDP), such as glyoxal (GO), methylglyoxal (MGO) and 3-deoxyglucosone (3-DG), compared with the 1.36% glucose solutions [25]. The GDPs are reactive carbonyl compounds, which may, among others, induce the production of advanced glycation end products (AGE). Although their relevance with PD is not completely elucidated, AGE compounds may have adverse effects on the peritoneal membrane and cardiovascular status [26].

Owing to the reduction in GDPs, the icodextrin may seek to reduce AGE formation, becoming more biocompatible than the conventional glucose-containing dialysis solutions [25]. Indeed, Ueda et al. showed a significantly lower generation of N-carboxymethyllysine (CML), as compared with the standard 1.36% glucose solutions [25]. A significant reduction in the carbonyl stress and lower CML generation was observed during a single dwell of icodextrin, when compared with the standard 1.36% glucose solutions [25]. Posthuma et al. also observed lower formation of AGE products after in vitro incubation of albumin with icodextrin, when compared with the conventional glucose solutions [27].

On the other hand, Konings et al. found an increase in plasma and dialysate levels of CML after treatment with icodextrin [28], whereas Gottloib et al. observed an increase in thiobarbituric acid reactive substances (suggesting an increase in lipid peroxidation) in the peritoneal effluent, and dysplastic changes of mesothelial cells in rats, after exposure to icodextrin [29]. When compared with the bicarbonate/lactatebuffered solutions, in vivo studies after long-term exposure to standard lactate-buffered solutions showed greater loss in ultrafiltration capacity, increased vascular endothelial growth factor (VEGF) expression and vascular density, higher AGE concentrations, upregulation of tumour growth factor β (TGF-β) expression and development of fibrosis [30]. Effects of icodextrin on in vitro studies are discrepant. After exposure to icodextrin, in vitro studies showed an improved phagocytic and respiratory burst activity in polymorphonuclear cells and monocytes, when compared with glucose-based solutions [31]. Improved proliferation of mesothelial cells was observed after incubation with icodextrin, when compared with glucose-based solutions [32]. In contrast, exposure of mesothelial cells to undiluted icodextrin showed a reduction in cell viability and proliferation, and damage of DNA, similar to glucose-based solutions [33]. However, the clinical significance of these findings is still unclear.

Cancer antigen 125 (CA125) is produced in the peritoneal cavity by the mesothelial cells and can be detected in dialysis effluents. In the NEPP study, levels of CA125 in a standard PD regimen (SPD; 4 dwells glucose lactate based) were compared with a low glucose-GDP regimen (NEPP; 1 dwell amino acids, 1 dwell icodextrin and 2 dwells bicarbonate/lactatebuffered glucose-based solution). The CA125 levels declined more after initiating CAPD with the SPD regimen and remained lower than that resulting from the treatment with NEPP, suggesting that non-glucose solutions may have less detrimental effects on mesothelial cell mass and probably on the peritoneal membrane [14]. On the other hand, the NEPP regimen was associated with an increase in IL-6, IL-8 and VEGF [34]. Besides, according to a recent study by Katsutani et al., a reduction in plasminogen activator inhibitor-1 and tissue-type plasminogen activator may be implicated to the fibrogenesis in human peritoneal mesothelial cells [35].

Also, in the EAPoL study, longitudinal changes in the peritoneal membrane function (increase in solute transport and reduction in ultrafiltration capacity) were more pronounced in anuric patients, treated with conventional glucose solutions, than the icodextrin-treated patients. This suggests a beneficial effect of the use of icodextrin in the preservation of the peritoneal membrane [36]. Still, we believe that until now, the clinical effects of icodextrin on the preservation of peritoneal membrane integrity are still not completely elucidated and should be the focus for future studies.

Side effects of icodextrin

Despite the beneficial effects of icodextrin in increased peritoneal sodium removal, improved fluid status, lipid profiles and possible diabetic control [37,38], there are also a few important clinical side effects, which deserve mention. The side effects of icodextrin have been largely concerned with skin rashes [39]. However, reports of severe cutaneous hypersensitivity reactions to icodextrin remain rare and may have different presentations. Three patients developed a vesicular rash on their palms after starting treatment with icodextrin, but they were able to continue their treatment [40]. The vesicular rash resolved spontaneously. In another case report, a woman with a generalized exfoliative dermatitis, secondary to an allergic reaction to icodextrin, was reported, and she had to discontinue taking icodextrin [41].
At the moment, the overall incidences of allergic reactions are unknown. Primarily in the years 2001 and 2002, reports regarding sterile peritonitis in patients treated with icodextrin increased. This complication has been attributed to peptidoglycan contamination of the dialysate by the gram-positive bacteria, *Alcyclobacillus acidocaldarius*. Since the implementation of corrective actions, the incidence of aseptic peritonitis due to icodextrin has declined [42].

Icodextrin is metabolized to maltose and is used once daily to avoid systemic accumulation. The concentration of icodextrin metabolites reaches steady-state levels within 2 weeks and remains stable throughout the duration of the polymer use. In the long-term study, exposure to these levels of maltose and oligosaccharides over 3½ years represent the longest exposure of these substances in the uraemic patients, without any clinical or metabolic adverse effects, providing an important evidence of safety [43]. But the clinical effects of icodextrin are still unknown.

Icodextrin and its metabolites may, to a small degree, be transported from the peritoneum to the systemic circulation by lymphatic transport. After 6 weeks of treatment with icodextrin, the total serum icodextrin and metabolite concentration was found to be ~5.2 mg/ml [3]. This was observed to have implications on the blood glucose measurement methods [44,45], based on glucose dehydrogenase pyrroloquinolinequione-based methods (GDH-PQQ), which could lead to an overestimation of blood glucose and undetected hypoglycaemia. Recently, in a Norwegian study, the serum glucose was measured simultaneously in the venous blood, using the laboratory reference method (hexokinase), and compared with eight glucometers [46]. Two assays, the Ascensia Contour (Bayer HealthCare Diagnostic Division, New York, USA) and the Accu-Chek (Roche Diagnostics, Indianapolis, USA), showed >60% higher glucose values than the reference method. Both glucometers were based on the GDH-PQQ method and thus should not be used in diabetic PD patients treated with icodextrin.

In patients using icodextrin, the serum amylase activity is significantly lower than in those treated only with glucose-based solutions, which may have implications on the diagnosis of pancreatitis. In patients treated with icodextrin and suspected of pancreatitis, lipase should be measured to confirm the diagnosis [47].

**Conclusion**

Icodextrin is an attractive alternative in PD. Improvement in fluid status due to its sustained transcapillary ultrafiltration during the long dwell period may lead to more peritoneal sodium removal and maintenance of sodium balance. Icodextrin induces less production of AGE, which has the potential positive long-term effects on cardiovascular status and peritoneal membrane function. Despite many similarities in the results of various clinical studies on icodextrin, the few discrepancies, mainly concerning the effects of icodextrin on blood pressure control and RRF, should be the focus of further studies. Severe side effects of icodextrin are rare. Furthermore, studies concerning the long-term effects of icodextrin on peritoneal membrane function are anticipated with great interest.

**Conflict of interest statement.** None declared.

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