Two Icodextrin Exchanges Per Day in Peritoneal Dialysis Patients

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ABSTRACT

ICO provides better pharmacokinetics biocompatibility than glucose PDFs. It is also associated with a wide range of benefits and some rare side effects. The aim of this literature review is to provide updated evidence and outcomes regarding utilizing 2-ICO exchanges daily. Utilizing 2-ICO exchanges per day has better clinical outcomes and increased ICO benefits more and more, particularly for patients with UF failure, hypervolemia, and high-average or high-transport characteristics. Still, studies documented rare side effects, like skin rash and hyperosmolar hyponatremia. Ultimately, there were limited investigations on this topic. Thus, randomized controlled trials are needed to establish guidelines and recommendations.

Keywords: chronic kidney disease; dialysis; icodextrin; peritoneal;

INTRODUCTION

Peritoneal dialysis (PD) is an established type of renal replacement therapy (RCT) that primarily aims to remove excess water and clear toxins through ultrafiltration (UF) [1,2]. The effectiveness of PD relies on excess fluid removal via the procedure [3]. UF and transport of solutes occurs across the peritoneal membrane, which the PD utilizes as a semi-permeable membrane [4]. PD has many advantages compared to hemodialysis (HD), resulting in a better quality of life (QoL) for PD patients [5]. These advantages include lower cardiovascular consequences, preserved vascular access sites and residual renal function (RRF), flexibility, easier to use, autonomy, accessibility in remote areas, and decreased hospital visits [5-8]. However, long-term use of PD may lose effectiveness primarily due to the alteration in peritoneal membrane structure and function resulting from some PD fluids (PDFs) [9].

Traditional PDFs encompass glucose as an osmotic agent [10,11]. Nevertheless, glucose has many drawbacks. It can result in insufficient UF or UF failure and poor dialysis, particularly in patients with high-average or high-peritoneal membrane transport characteristics [12]. These drawbacks result from alteration in peritoneal membrane structure [12]. Multiple evidence from prior studies indicates that long-term exposure to advanced glycosylation end products (AGEs), lactate, low pH, and glucose (PDF components) contribute to peritoneal damage [13]. Moreover, there is a risk for systemic glucose absorption after utilizing hypertonic glucose fluids, which can cause adverse effects on mortality, worsened diabetic patients' situations, dyslipidemia, metabolic disorders, insulin resistance, and hyperglycemia [14].

Compared with glucose PDFs, utilizing icodextrin (ICO) minimizes metabolic disturbance and reduces exposure to glucose [15]. ICO is an iso-osmolar PDF, a glucose polymer derived from starch [16]. Over more than twenty years, nephrologists have effectively utilized ICO-based PDFs [17]. Besides, the development of ICO-based PDFs represents a significant advancement in controlling fluid volume, particularly in long-term PD patients with UF failure [11]. Numerous prior studies indicate that survival for PD technique and patients may prolonged with long-term use of ICO PDF [18-20]. Although in the past, evidence recommended only 1-ICO exchange daily to improve UF in PD patients with poor UF [21], several recent studies have implied that 2-ICO exchanges daily are more effective [22-25].

A recent review about that 2-ICO exchanges daily is not available. Therefore, the aim of this literature review is to provide updated evidence and outcomes regarding utilizing 2-ICO exchanges daily.

Icodextrin Pharmacokinetics

After intraperitoneal administration, ICO's pharmacokinetics follow a simple single-compartment model [26]. Table 1 summarizes ICO's pharmacokinetics. The pharmacokinetics of ICO start with slow absorption via the peritoneal cavity. A prior study reported that during the 12 hours of ICO administration, about 40% of the dose was absorbed [26]. Besides, the plasma half-life and peak plasma concentration were 14.7 hours and 12.7 hours, respectively. Absorbed ICO is metabolized by plasma amylase to maltotetraose, maltotriose, and maltose, which maltases could also metabolize to glucose without raising blood insulin or sugar [26-28]. Intraperitoneal metabolism of ICO is minimum [15]. Eliminating metabolites is done through PD or urine [26,29]. Finally, ICO metabolism can cause hypochloremia or hyponatremia [26].

Icodextrin Biocompatibility

Multiple investigations established that ICO provides better biocompatibility than glucose PDFs [30]. It preserves the function of the peritoneal membrane and morphology and viability of mesothelial cells, improves blood pressure (BP) control, UF, metabolic control, rates of sodium removal, and PD duration, positively impacts peritoneal host defense, and avoids glucotoxicity [31-39]. Besides, it also enhanced QoL [40]. Furthermore, a prior study highlighted that in comparison to traditional ICO PDF, neutralization of ICO PDF can decrease the release of lactate dehydrogenase (LDH) and is associated with a favorable effect on preserving cell viability. Although the ICO's safety and effectiveness are well documented, side effects can still arise, including local inflammatory defense stimulation, allergic rash, and peritonitis [41,42]. However, these side effects are rare [30].

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Table 1. ICO's pharmacokinetics

Parameter	Detailed	Reference
Absorption	≈40.0% absorbed via peritoneal lymphatics during the 12-hour dwell.	[26]
Plasma kinetics	Peaked at 12.7 hours. Half-life ≈14.7 hours. Returned to baseline within a week.	[26]
Metabolism	Metabolized by amylase to maltotetraose, maltotriose, and maltose, maltases may also metabolize these metabolites to glucose.	[26-28]
Elimination	More than 20% of absorbed ICO is eliminated by PD or via urine (If the RRF exists).	[26,29]
Intraperitoneal metabolism	Not significantly.	[15]
Clinical considerations	ICO does not result in hyperinsulinemia or hyperglycemia but may contribute to hypochloremia or hyponatremia.	[26]

ICO, icodextrin; PD, peritoneal dialysis; RRF, residual renal function.

Table 2. Summary of studies about utilizing 2-ICO exchanges daily in PD patients

Publication year, Ref.	Study design	Aim	Sample size	M/F, mean age	Evidence and Outcomes (2-ICO exchanges daily)
2008, [3]	Prospective cohort study	To investigate the utilization of 2-ICO exchanges daily in patients with high-average or high transport characteristics to reduce exposure to glucose.	9 patients	6/3, 57.1 ± 16	Serum sodium levels and total PD solution volume remained stable. Significant reduction in glucose exposure. Increase in serum ICO-levels. It appears to be safe.
2009, [22]	Prospective randomized study	To study the impacts of 2-ICO exchanges daily on LVH and BP in PD patients with UF failure and hypervolemia.	40 patients (34 patients completed the study) 17 patients in each group	2-ICO exchanges daily: 10/7, 45.80 ± 14.08 1-ICO exchange daily: 12/5, 50.47 ± 15.02	2-ICO exchanges daily: Clinical advantage. Significantly reduce LVMI and mean BP. It could be more effective for those patients.
2010, [23]	Prospective randomized study	To assess and compare the serum BNP levels after 2-ICO exchanges daily and 1-ICO daily in CAPD patients with high-average or high transport characteristics and to evaluate the associations between LV functions and BNP.	28 patients 14 patients in each group Group A (2-ICO exchanges daily) Group B (1-ICO exchange daily)	Group A: 9/5, 46.71 ± 13.65 Group B: 10/4, 49.28 ± 15.34	Group A showed a more significant improvement in ejection fraction along with a decrease in CTI, HR, LV mass, and serum BNP. There was a positive association between a reduction in HR, LV mass, and BP and a reduction in BNP. Monitoring BNP could be practical for follow-up of high-transport CAPD patients with high-average or high-transport characteristics.
2011, [11]	Prospective study	To report their experience with daily 2-ICO exchanges in PD patients with poor UF, specifically on body weight and net UF.	9 patients	7/2, 55 ± 6	Body weight decreased in 66.7% of patients. Decreased in mean BP and serum sodium levels. Hb1Ac levels remained stable. Slightly increase in mean serum creatinine. It appears to be safe.
2011, [24]	Retrospective study	To report the safety of the switch from 1-ICO exchange daily to 2-ICO exchanges daily in PD patients in whom 1-ICO exchange results in inadequate UF.	8 patients	2/6, 70 ± 9	Safe. Significant increase in UF. Asymptomatic serum sodium concentrations decreased. RUO and osmolality remained stable.
2013, [44]	Prospective study	To report the effectiveness and impact of PD initiation using 2-ICO exchanges daily.	7 patients	6/1, 64 ± 9.83	Practical therapy for patients with good RRF. One patient developed a skin rash. Excellent volume control.

2022, [45]	Retrospective study	To report their experience with daily 2-ICO exchanges.	8 patients	6/2, 77.13 ± 7.34	Significant improvement in UF. Permitting better UF failure and fluid overload management. No relevant adverse outcomes were reported.
2023, [46]	Retrospective study	To assess frail ESRD patients who are on a supportive 2-exchange-assisted CAPD program.	49 patients 41 patients had been on as CAPD for >3 months and 8 patients received 2-ICO exchanges.	32/17, 79.6	All symptoms were improved. The 1-year survival was 0.55. Peritonitis rate was decreased. The program may deliver an adequate dialysis method for these patients.
2023, [47]	Case Report	To represent an ERSD patient on off-label use of 2-ICO exchanges daily during CAPD.	1 patient	M, 76	Hyperosmolar hyponatremia was developed. Off-label utilization of ICO should be evaded.
2024, [25]	Retrospective study	To assess the effect of 2-ICO exchanges daily compared to 1-ICO daily on CAPD patients' QoL, laboratory parameters, and UF.	19 patients Group A: 9 patients (1-ICO exchange daily) Group B: 10 patients (2-ICO exchanges daily)	Group A: 7/2, 58.11 ± 8.74 Group B: 7/3, 63.2 ± 11.65	Group A showed a significant UF increase, a RUO decrease, and a significantly higher cost.

Ref., reference; ICO, icodextrin; PD, peritoneal dialysis; LVH, left ventricular hypertrophy; BP, blood pressure; UF, ultrafiltration; LVMI, left ventricular mass index; BNP, brain natriuretic peptide; CAPD, continuous ambulatory peritoneal dialysis; LV, left ventricle; CTI, cardiothoracic index; HR, heart rate; Hb1Ac, hemoglobin A1c; RUO, residual urine output; RRF, residual renal function; ERSD, end-stage renal disease; QoL, quality of life.

Twice-Daily Icodextrin Exchanges

In PD patients with UF failure, 2-ICO exchanges daily introduce an alternative PDF [33]. Firstly, the researcher noticed that UF did not improve significantly after 8 to 10 hours of administering the ICO, then they hypothesized that using 2-ICO exchanges daily would improve UF more than 1-ICO exchange [21]. This new method provides exhaustive benefits, such as enhancing UF and avoiding glucose-related toxicity [33]. Nevertheless, safety data regarding this method is still deficient; it is therefore not recommended [43].

We reviewed ten earlier studies about utilizing 2-ICO exchanges daily in PD patients published from 2008 to 2024. The studies' designs were 50.0% prospective, 40.0% retrospective, and 10.0% case report. The sample size ranged from 1 to 49, and the mean age ranged from 45.8 to 79.6. Moreover, the reviewed studies included 172 patients; 66.9% of patients were male (115 cases). Compared to 1-ICO exchange daily [22-25], 2-ICO exchanges daily showed superior clinical outcomes and increased UF more significantly. Studies also reported more significant improvement in ejection fraction with 2-ICO exchanges daily and reduced left ventricular mass index (LVMI), cardiothoracic index (CTI), heart rate (HR), mean BP, and serum sodium concentrations [22-25]. However, it can increase costs and decrease residual urine output (RUO) [25]. It was safe and effective, especially for patients with UF failure, hypervolemia, and high-average or high-transport characteristics [22,23]. Besides, monitoring brain natriuretic peptide (BNP) may be beneficial for some patients [22]. Other Studies that report the impact of 2-ICO exchanges daily on PD patients also highlight similar beneficial clinical outcomes, such as improved UF, reduced glucose exposure, reduced LVMI, stable metabolic markers, and better fluid overload management [3,11,44-47]. Generally, it appears safe, but there were two reported side effects: one case with skin rash [44] and another with hyperosmolar hyponatremia [47]. Finally, applying a supportive 2-exchange-assisted continuous ambulatory PD (CAPD) program was declared to be helpful for frail end-stage renal disease (ESRD) patients (Table 2).

CONCLUSION

ICO provides better pharmacokinetics biocompatibility than glucose PDFs. It is also associated with a wide range of benefits and some rare side effects. Utilizing 2-ICO exchanges per day has better clinical outcomes and increased ICO benefits more and more, particularly for patients with UF failure, hypervolemia, and high-average or high-transport characteristics. Still, studies documented rare side effects, like skin rash and hyperosmolar hyponatremia. Ultimately, there were limited investigations on this topic. Thus, randomized controlled trials are needed to establish guidelines and recommendations.

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