REVIEW

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Comparison of clinical effects between icodextrin and glucose solutions on outcomes of peritoneal dialysis: systematic review and meta-analysis of randomized controlled trials

Atsuhiro Kanno^{1*}, Yasushi Tsujimoto², Takayuki Fujii³, Emi Fujikura⁴, Kimio Watanabe⁵, Hidemichi Yuasa⁶, Munekazu Ryuzaki⁷, Yasuhiko Ito⁸ and Hidetomo Nakamoto⁹

Abstract

Background: Icodextrin enhances peritoneal filtration for patients on peritoneal dialysis (PD). However, clinically important outcomes have not yet been analyzed using authentic, objective statistical methods. The present systematic review aimed to determine the risks and benefits of icodextrin compared with a glucose-based solution with respect to clinically important and patient-centered outcomes.

Methods: We systematically investigated only randomized controlled trials (RCTs) by adopting the Cochrane Database of Systematic Review (2014) and searched the CENTRAL, MEDLINE, and EMBASE databases for eligible studies reported in the literature. The quality of the evidence was assessed using the GRADE approach.

Results: We finally evaluated important outcomes in 13 RCTs. Icodextrin significantly decreased the number of reported episodes of uncontrolled fluid overload in four RCTs that involved 236 patients (relative risk [RR], 0.31; 95% confidence interval [CI], 0.12 to 0.82; moderate certainty evidence). However, the inclusion of icodextrin for peritoneal ultrafiltration did not significantly differ in six RCTs involving 252 patients (mean difference [MD], 186.76 mL; 95% CI, -47.08 to 420.59; low certainty evidence). Regarding other clinically important outcomes, all-cause mortality in 10 RCTs involving 1106 patients (RR, 0.75; 95% CI, 0.33 to 1.71; low certainty evidence) and technical survival in five RCTs involving 470 patients (RR, 0.57; 95% CI, 0.29 to 1.12; low certainty evidence) were not significant. Urine volume in four RCTs involving 136 patients, residual renal function in five RCTs involving 181 patients and peritoneal function measured as the ratio of solute concentration in dialysate and plasma (D/P ratio) in two RCTs involving 105 patients were not specifically affected by icodextrin, and the results for adverse events were similar between icodextrin and glucose PD solutions.

Conclusion: Icodextrin could relieve uncontrolled fluid overload without adding risk. However, a significant effect on clinically relevant outcomes such as technical survival and overall patient survival was not suggested. More trials are required to increase the statistical power and to verify the value of icodextrin in clinical practice.

Trial registration: PROSPERO, [CRD42018104360](https://doi.org/10.1186/1745-6215-4-360)

Keywords: Chronic kidney disease, Fluid overload, Peritoneal filtration, All-cause mortality, Clinical practice guideline

* Correspondence: thinkdifferent818@gmail.com

¹Division of Community Medicine, Tohoku Medical and Pharmaceutical University, 1-15-1 Fukumuro, Miyagino, Sendai, Miyagi 983-8536, Japan
Full list of author information is available at the end of the article

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Background

Guidelines need to be updated to reflect the current status of patients on peritoneal dialysis (PD) in Japan. Therefore, reliable revised guidelines should be formulated that contain graded evaluations and recommendations to improve patient prognosis. To ensure the reliability of medical information, the Japan Society for Dialysis Therapy (JSDT) revised the clinical practice guideline (CPG) in 2016 based on the GRADE (Grading of Recommendations Assessment, Development and Evaluation) system [1], which is the current global standard method of creating guidelines. In the meantime, icodextrin has become prevalent in Japanese routine clinical practice during the past two decades, and it now occupies an extremely important position based on distinctive characteristics. Ultrafiltration of the peritoneal membrane is essentially important as it is associated with the management of fluid status and it is a determinant of whether or not to continue with PD therapy [2, 3]. Icodextrin is a high-molecular-weight, water-soluble glucose polymer in a sustained colloid osmotic gradient that helps to control excess fluid in patients treated by PD [4]. Icodextrin facilitates prolonged and stable peritoneal filtration regardless of the peritoneal function of patients and has thus improved the global quality of clinical peritoneal dialysis. Considerable evidence has recently accumulated about the role of icodextrin in clinical practice [5, 6]. However, icodextrin as a peritoneal solution has not been fully evaluated at the level of patient-centered outcomes. Furthermore, patient values have not been adopted to evaluate its effect. Thus, the risks of benefits of icodextrin remain obscure. A systematic review should compare clinical effects between icodextrin and glucose solutions.

Methods

Inclusion and exclusion criteria

We included RCTs that compared icodextrin with glucose solutions among patients on PD. The exclusion criteria comprised PD with a neutral-buffered solution, peritonitis associated with PD, and studies other than RCTs. Patients who received PD and HD combination therapy were not included in the RCTs adopted in the present systematic review (SR).

Searches

We created a SR that complied with Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) guidelines [7] (Additional file 1). Before starting the present SR, we registered the review protocol (PROSPERO: CRD42018104360) and adopted the extant a reliable SR, the Cochrane Database of Systematic

Reviews (2014) for an initial systematic review [8]. That search was in accordance with the Cochrane Renal Group's Specialized Register that comprises studies identified from the CENTRAL, MEDLINE, and EMBASE databases. We then searched MEDLINE and Ichushi-Web to identify further investigation to date. Four reviewers (AK, TF, EF, and KW) independently screened all titles, abstracts and the full texts of articles.

Data extraction

Four reviewers (AK, TF, EF, and KW) independently extracted data using a pre-specified format in advance and integrated the results. Disagreements about data collection were resolved by consultation with YT. One reviewer (TF) verified the results, and another (KW) stored the data extracted from each study in a specific format suitable for analysis.

Risk of bias (quality) assessment

Two independent reviewers (AK, TF) used the standard Cochrane Collaboration risk of bias tool to assess bias in all eligible studies evaluate it in the present SR. Discrepancies were resolved by group discussion to reach a consensus. The following sources of bias were assessed: random sequence generation (selection bias), allocation concealment (selection bias), blinding of participants and personnel (performance bias), blinding of outcome assessment (detection bias), incomplete outcome data (attrition bias), selective outcome reporting (reporting bias), and other sources. We evaluated the certainty of evidence for the main outcomes using the GRADE approach [9].

Strategy for data synthesis

Data were integrated using a random-effects model. Results are expressed as RRs with 95% CIs for dichotomous outcomes, and the MD was used for continuous outcomes. Heterogeneity was examined using χ^2 on N-1 degrees of freedom with an alpha level of 0.05 for statistical significance, and I^2 tests. Data were analyzed using Review Manager (RevMan Version 5.3. Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2014). *P* values of < 0.05 were defined as statistically significant.

Results

Study selection

Figure 1 shows a PRISMA flow diagram of the present SR. We extracted and assessed 106 studies of SRs and meta-analysis published between 1968 and 2017. Among them, four SRs and one CPG met the eligibility criteria and the antecedent Cochrane review was adopted. We subsequently selected 10 RCTs that compared icodextrin and glucose solutions. While searching RCTs published after the initial SR, we added three RCTs that satisfied

our inclusion conditions among 260 studies, and finally, used 13 RCTs as core studies.

Characteristics of included studies

We analyzed data of 1275 patients that included 677 who were treated by PD using icodextrin [10–31]. Among 13 studies, five, three, and one were of patients treated with continuous ambulatory peritoneal dialysis (CAPD) [1011–12], automated peritoneal dialysis (APD) [11, 13, 14], and continuous cycling peritoneal dialysis (CCPD) [15], respectively, and the remainder comprised combinations of the modalities. Two studies involved

patients only with diabetes [16, 17] and one of the other studies was limited to non-diabetic patients [18]. Three studies allowed a choice of dialysates with appropriate glucose concentrations to achieve desirable control of edema or blood pressure [10, 14, 19]. Three studies were restricted to patients with high or high-average peritoneal solute transport as the principal inclusion criterion [13, 17, 20]. Two studies excluded patients with uncontrolled volume status at the time of entry [10, 21]. Table 1 shows the characteristics and outcomes of the included studies. We also evaluated each outcomes according to the GRADE approach (Table 2).

Table 1 Details of included studies

Study	Methods	Participants and sample size	Interventions	Outcomes	Notes
Chang TI et al. [10]	<ul style="list-style-type: none"> • Study design: RCT • Study follow-up period: 12 months 	Adult PD patients (aged ≥ 20 years) with ESRD who were maintained on PD and had a measured urine volume ≥ 750 mL/day ($n = 100$)	Treatment group <ul style="list-style-type: none"> • PD solution containing 7.5% icodextrin and 2 exchanges of 1.5% glucose-based solutions Control group <ul style="list-style-type: none"> • 1 exchange of $\geq 2.5\%$ and 2 exchanges of 1.5% glucose-based solution 	All-cause mortality Technical survival Adverse effects (peritonitis, rash) Peritoneal function Ultrafiltration	Daily urine volume decreased faster in the glucose solution group than in the icodextrin group. However, there were no differences in other outcomes.
de Moraes TP et al. [18]	<ul style="list-style-type: none"> • Study design: RCT • Study follow-up period: 90 days 	Adult non-diabetic patients on treatment with APD for at least 90 days and with a recent PET showing a D/P creatinine of > 0.50 ($n = 60$)	Treatment group <ul style="list-style-type: none"> • 2 L of 7.5% icodextrin during the long dwell Control group <ul style="list-style-type: none"> • 2 L of 2.5% glucose during the long dwell 	All-cause mortality Adverse effects (peritonitis) Ultrafiltration Episodes of uncontrolled fluid overload	Ultrafiltration was significantly greater in the icodextrin group compared to control group (800 mL versus 586 mL).
Davies SJ et al. [20]	<ul style="list-style-type: none"> • Study design: RCT • Study follow-up period: 6 months 	Prevalent adult CAPD or APD patients aged ≥ 18 years; controlled or uncontrolled hypertension; high or high -average peritoneal solute transport, urine output ≤ 750 mL/day; dialysate prescription with a glucose concentration of 2.27% or greater ($n = 50$)	Treatment group <ul style="list-style-type: none"> • 7.5% icodextrin for the long dwell Control group <ul style="list-style-type: none"> • 2.27% glucose for the long dwell 	All-cause mortality Episodes of uncontrolled fluid overload	There were significantly differences in ultrafiltration and total fluid loss at 3 months among the icodextrin group (399.0 mL, 373.8 mL, respectively) compared to the control group.
Finkelstein F et al. [13]	<ul style="list-style-type: none"> • Study design: RCT • Study follow-up period: 2 weeks 	APD patients aged ≥ 18 years with a long-dwell change and fill volume of 2.0–2.5 L of a 4.25% dextrose solution and of whom the results of PET were classified into high-average or high category ($n = 92$)	Treatment group <ul style="list-style-type: none"> • 7.5% icodextrin for the long dwell Control group <ul style="list-style-type: none"> • 4.25% glucose solution for the long dwell 	Ultrafiltration Adverse effects (rash)	Net ultrafiltration was significantly greater with icodextrin than with 4.25% glucose at week 2 (-239.7 versus 373.8 mL; $p < 0.001$). Rash occurred more often in the icodextrin group (11 patients) compared with the control group (zero patient).
Konings CJ et al. [21, 24]	<ul style="list-style-type: none"> • Study design: RCT • Study follow-up period: 4 months 	Prevalent adult patients on CAPD or CCPD ($n = 40$)	Treatment group <ul style="list-style-type: none"> • 7.5% icodextrin in place of glucose-containing fluid for the overnight dwell (patients on CAPD) or the daytime dwell (patients on APD) Control group <ul style="list-style-type: none"> • Standard glucose-containing PD solutions 	All-cause mortality Technical survival RRF (urine volume) Ultrafiltration	In contrast to the control group, ECW declined significantly in the icodextrin group. GFR decreased slightly, but significantly in the icodextrin group, but not in the control group.
Lin A et al. [11]	<ul style="list-style-type: none"> • Study design: RCT • Study follow-up period: 4 weeks 	Prevalent CAPD patients stable at least 90 days, aged ≥ 18 years, were treated with a maximum of 6 L of daily 2.5% glucose dialysate with a night dwell above 8 h and a night dwell volume of 2 L for a minimum of 30 days before inclusion ($n = 201$)	Treatment group <ul style="list-style-type: none"> • 7.5% icodextrin in night dwell Control group <ul style="list-style-type: none"> • 2.5% glucose dialysate in night dwell 	All-cause mortality Adverse effects (peritonitis, rash)	Following 2 and 4 weeks, Ccr and ultrafiltration were significantly higher in the icodextrin group versus the glucose group ($p < 0.001$).
MIDAS Study [12, 25]	<ul style="list-style-type: none"> • Study design: RCT • Study follow-up period: 6 months 	Adult CAPD patients aged ≥ 18 years and established on CAPD for at least 3 months using standard 3 to 4 exchanges with no more than one hypertonic glucose bag ($n = 209$)	Treatment group <ul style="list-style-type: none"> • 7.5% icodextrin as overnight dwell Control group <ul style="list-style-type: none"> • Standard glucose-containing PD dialysate as overnight dwell 	All-cause mortality Ultrafiltration Technical survival	The mean overnight ultrafiltration in the icodextrin group was 3.5 times greater than 1.36% glucose at eight hours and 5.5 times greater at 12 h and no different from that of 3.86% glucose group at eight hours and 12 h.
Takatori Y et al. [16]	<ul style="list-style-type: none"> • Study design: RCT • Study follow-up 	Patients with ESRD because of diabetic nephropathy and were newly started on PD (CAPD and APD) as a first RRT ($n = 41$)	Treatment group <ul style="list-style-type: none"> • a maximum of 6 L of daily 1.5% or 2.5% of glucose PD dialysate in association with an overnight or daytime dwell of 2 	All-cause mortality Technical survival RRF (urine	The technical survival rate was 71.4% in the icodextrin group and 45.0% in the glucose group. The icodextrin group showed

Table 1 Details of included studies (Continued)

Study	Methods	Participants and sample size	Interventions	Outcomes	Notes
	period: 24 months		or 1.5 L of 7.5% icodextrin Control group • a maximum of 8 L of daily 1.5% or 2.5% of glucose PD dialysate	volume, GFR/CrCl), Peritoneal function Ultrafiltration Episodes of uncontrolled fluid overload	better cumulative technical survival (log-rank test, $p = 0.0365$). The net ultrafiltration in the icodextrin group was significantly higher during study period than the glucose group.
Paniagua R et al. [26–28]	• Study design: open label, RCT • Study follow-up period: 12 months	Adult prevalent PD patients with non-insulin-dependent diabetes mellitus; high-average and high peritoneal transport status in a simplified PET ($n = 59$)	Treatment group • 7.5% icodextrin in the long dwell Control group • At least 1 bag with 2.5% glucose dialysate in the long dwell Liberal use of 2.5% or 4.25% glucose solution was allowed in both groups	Adverse effects (peritonitis)	Ultrafiltration remained higher in the icodextrin group than in the glucose group throughout the study. Adverse events related to fluid overload were more frequent in the glucose group compared to the icodextrin group. However, infectious peritonitis was similar in both groups.
Plum J et al. [14]	• Study design: open label, RCT • Study follow-up period: 14 weeks	Adult prevalent APD patients who were treated with APD during at least 90 days before the screening visit and whose PD prescription included a long-dwell daytime exchange ($n = 39$)	Treatment group • 7.5% icodextrin as daytime dwell Control group • Daytime dwell of glucose-containing dialysate	RRF (average of creatinine and urea clearance)	After 12 weeks of treatment, RRF in the icodextrin group was 2.9 ± 0.8 ml/min/ 1.73m^2 , and this value did not differ from the control group, which was 1.7 ml/min/ 1.73m^2 .
Posthuma N et al. [15, 29–33]	• Study design: open label, RCT • Study follow-up period: 24 months	Adult prevalent CCPD patients aged ≥ 18 years, consisting of a 2-year treatment period on either icodextrin or glucose-containing solutions for the daytime dwell ($n = 38$)	Treatment group • icodextrin for the daytime dwell Control group • Daytime dwell of glucose-containing dialysate	All-cause mortality RRF (urine volume, GFR/CrCl) Adverse effect (peritonitis) Ultrafiltration	Daytime ultrafiltration volume and 24-h ultrafiltration volume increased significantly in icodextrin-treated patients at 3 and 6 months. However, while ultrafiltration at 9 and 12 months also increased, it did not reach statistical significance.
Wolfson M et al. [23, 34]	• Study design: open RCT • Study follow-up period: Efficacy study (4 weeks) Safety study (52 weeks)	Adult prevalent PD patients aged ≥ 18 years (CAPD only in the efficacy study, APD/CAPD in the safety study) for at least 90 days before the screening visit and were treated with a standard dialysis for at least 30 days before the screening in a long dwell using a solution containing 2.5% glucose at a full volume (Efficacy study: $n = 175$, Safety study: $n = 287$)	Treatment group • PD solution containing 7.5% icodextrin for the long dwell Control group • 2.5% glucose for the long dwell Dialysate volume was either 2 L or 2.5 L, depending on the patient's usual prescriptions	All-cause mortality Adverse events (peritonitis, rash)	During the 1-year period, there were no significant differences in mortality rate between the icodextrin group and the control group. Overall period, 44 patients (16.6%) in the icodextrin group and 14 patients (7.1%) in the control group reported rash.
Yoon HE et al. [19]	• Study design: RCT • Study follow-up period: 12 months	ESRD patients starting CAPD ($n = 80$)	Treatment group • 2 L of 7.5% icodextrin during the long dwell Control group • Four exchanges of glucose-containing dialysates Liberal use of 1.5%, 2.5%, 4.25% glucose-based dialysate was allowed in both groups	All-cause mortality Technical survival RRF (urine volume, GFR/CrCl) Peritoneal function Adverse effect (peritonitis) Ultrafiltration	The Glucose group showed a significant decline in urine volume at 6 and 12 months from 0 month, but the icodextrin group did not.

Table 2 Summary of findings

Icodextrin versus glucose-based solution for patients receiving peritoneal dialysis

Patient or population: patients receiving peritoneal dialysis**Setting:** community**Intervention:** icodextrin**Comparison:** glucose-based solution

Outcomes	Nº of participants (studies)	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with glucose-based solution	Risk difference with icodextrin
All-cause mortality	1106 (10 RCTs)	⊕⊕⊕⊕ LOW	RR 0.75 (0.33 to 1.71)	27 per 1000	7 fewer per 1000 (18 fewer to 19 more)
Technical survival	470 (5 RCTs)	⊕⊕⊕⊕ LOW	RR 0.57 (0.29 to 1.12)	74 per 1000	32 fewer per 1000 (52 fewer to 9 more)
Episodes of uncontrolled fluid overload	236 (4 RCTs)	⊕⊕⊕⊕ MODERATE	RR 0.31 (0.12 to 0.82)	108 per 1000	73 fewer per 1000 (93 fewer to 19 fewer)
Peritoneal ultrafiltration	252 (6 RCTs)	⊕⊕⊕⊕ LOW	–		MD 186.76 higher (47.08 lower to 420.59 higher)
Urine volume	136 (4 RCTs)	⊕⊕⊕⊕ LOW	–		MD 106.08 higher (173.29 lower to 385.45 higher)
Residual renal function	181 (5 RCTs)	⊕⊕⊕⊕ MODERATE	–		MD 0.56 higher (0.37 lower to 1.49 higher)
Peritoneal function	105 (2 RCTs)	⊕⊕⊕⊕ VERY LOW	–		MD 0.001 higher (0.07 lower to 0.07 higher)
Peritonitis	1034 (8 RCTs)	⊕⊕⊕⊕ LOW	RR 0.95 (0.79 to 1.15)	224 per 1000	11 fewer per 1000 (47 fewer to 34 more)
Rash	855 (4 RCTs)	⊕⊕⊕⊕ LOW	RR 1.84 (0.48 to 7.09)	51 per 1000	43 more per 1000 (26 fewer to 310 more)

*The risk in the intervention group (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI). *CI* Confidence interval, *RR* Risk ratio, *MD* Mean difference

Risk of bias in included studies

Figure 2 shows the risk of bias in the included studies. Risk of bias was generally low for random sequence generation and allocation concealment, but most studies were considered unclear regarding blinding of outcome assessments and outcome data were incomplete in five studies.

All-cause mortality

The effects of icodextrin and glucose solutions on patient survival did not significant differ in 10 RCTs of 1106 patients (RR, 0.75; 95% CI, 0.33 to 1.71; $P = 0.49$, $I^2 = 0\%$; low certainty evidence; Fig. 3). However, the point estimate was better for icodextrin than glucose solutions by 7 patients' reductions among 1000 patients.

	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding of participants and personnel (performance bias)	Blinding of outcome assessment (detection bias)	Incomplete outcome data (attrition bias)	Selective reporting (reporting bias)	Other bias
Chang 2016	+	+	-	+	-	+	?
Davies 2003	+	+	+	?	-	+	?
de Moraes TP 2015	+	+	-	?	-	+	?
Finkelstein 2005	+	+	+	?	+	?	?
Konings 2003	?	+	+	?	?	+	?
Lin 2009a	+	+	+	+	?	+	?
MIDAS Study 1994	+	+	?	?	?	-	?
Paniagua 2008	+	?	+	?	-	-	?
Plum 2002	?	?	-	?	?	-	?
Posthuma 1997	?	?	+	?	+	+	?
Takatori 2011	?	?	-	?	?	+	?
Wolfson 2002	+	+	+	+	-	-	?
Yoon 2014	+	+	?	?	?	+	?

Fig. 2 Summary of risk of risk in included studies

Technical survival

An overall effect of icodextrin on technical survival was not significant in five RCTs of 470 patients (RR, 0.57; 95% CI, 0.29 to 1.12; $P = 0.10$, $I^2 = 0\%$; low certainty evidence; Fig. 4).

Episodes of uncontrolled peritoneal fluid overload

Icodextrin significantly decreased the frequency of reported episodic uncontrolled peritoneal fluid overload in four RCTs of 236 patients (RR, 0.31; 95% CI,

0.12 to 0.82; $P = 0.02$, $I^2 = 0\%$; moderate certainty evidence; Fig. 5).

Peritoneal ultrafiltration

Icodextrin solution did not lead to a significant increase in peritoneal ultrafiltration compared with glucose solutions in six RCTs of 252 patients (MD, 186.76 mL/day; 95% CI, -47.08 to 420.59; $P = 0.12$, $I^2 = 64\%$; low certainty evidence; Fig. 6). Moderate to severe heterogeneity might have been derived from the study design. The design of five studies was open-label and dropout rates were high in all of them. These results might also be biased and attenuated in relation to icodextrin because hypertonic 3.86% and 4.25% glucose PD solutions served as controls without restrictions in two trials [15, 19].

Urine volume

Icodextrin was not associated with urine volume in four RCTs of 136 patients (MD, 106.08 mL/day; 95% CI, -173.29 to 385.45; $P = 0.13$, $I^2 = 39\%$; low certainty evidence; Additional file 2: Figure S1). However, one RCT demonstrated that icodextrin was associated with significantly higher daily urine volumes than glucose dialysate at 12 months [19].

Residual renal function

Residual renal function determined from glomerular filtration rates or renal creatinine clearance was similar between icodextrin and glucose PD solution in five RCTs of 181 patients (MD, 0.56 mL/min; 95% CI -0.37 to 1.49; $P = 0.24$, $I^2 = 0\%$; moderate certainty evidence; Additional file 2: Figure S2). Among the included studies, one study used the averages of creatinine and urea clearance to indicate residual renal function [14], and this was adopted and evaluated in the preceding SR [8].

Peritoneal function

We adopted dialysate-to-plasma creatinine ratio (D/P Cr) as a marker of peritoneal function. However, the amount of clinical research was insufficient to evaluate outcomes, and icodextrin did not affect the D/P Cr with a moderate level of heterogeneity in two RCTs that included 105 patients (MD, 0.001; 95% CI, -0.07 to 0.07; $P = 0.97$, $I^2 = 65\%$; very low certainty evidence; Additional file 2: Figure S3).

Peritonitis

Overall peritonitis rates did not significantly differ between icodextrin and glucose PD solutions in eight RCTs of 1034 patients (RR, 0.95; 95% CI, 0.79 to 1.15; $P = 0.62$, $I^2 = 0\%$; low certainty evidence; Additional file 2: Figure S4).

Rash

The occurrence of rash elicited by icodextrin and glucose PD solutions did not significantly differ in four RCTs of 855 patients (RR, 1.84; 95% CI, 0.48 to 7.09; $P = 0.35$, $I^2 = 46\%$; low certainty evidence; Additional file 2: Figure S5). Most reports are based on comparative trials that processed at the time when icodextrin entered the market.

Discussion

The present review found that the quality of evidence supporting icodextrin was moderate and significantly associated with a decreased frequency of uncontrolled fluid overload compared with glucose solutions. However, icodextrin did not contribute to improved all-cause mortality and technical survival. In addition, icodextrin was not associated with increased urine volumes, or the D/P creatinine ratio as an indicator of peritoneal creatinine clearance. Recent results have been consistent with those of an earlier systematic review, which concluded that icodextrin alleviated uncontrolled fluid overload better than glucose solutions [5]. Uncontrolled fluid overload was not strictly

defined in the studies included herein, and only one study found excessive volumes lead to technical failure [16]. On the other hand, icodextrin was not associated with a significant increase in peritoneal filtration compared to glucose solutions in the present SR. The lack of significance might be derived, at least in part, from the following. The present SR included prospective RCTs that allowed the choice of dialysates with glucose concentrations up to 4.25% [15, 19]. These studies had considerable weight in the overall evaluation of peritoneal ultrafiltration outcomes. Additionally, the present SR defined peritoneal ultrafiltration as overall daily output, and not as a longer dwell period. Therefore, some studies did not meet our inclusion criteria. The volume of peritoneal ultrafiltration was significantly greater in the control than the icodextrin group in one study, which could be explained by the dialysate comprising > 2.5% glucose [19]. The study protocol required that the control group underwent four exchanges of dialysate with glucose, whereas icodextrin was applied once for the long dwell and the glucose dialysate was exchanged twice in the experimental group. Another explanation might be associated with a need to convert the standard error or 95%CI into standard

deviation, which contributed heterogeneity [18, 21]. These factors might have diminished the advantage of icodextrin in terms of peritoneal ultrafiltration compared with glucose solutions.

One study recommended that APD and icodextrin should be considered for patients with high or high-average solute transport and that issues related to high transport could be avoided by using icodextrin for the long exchange to prevent fluid reabsorption [22]. Patients with fluid reabsorption in the long dwell should be identified to maximize the benefits of icodextrin and consider its appropriate indication in clinical practice.

The occurrence of rash in icodextrin was marginally significant compared with glucose solution. Previous studies have concluded that the incidence of rash is not significantly higher for icodextrin than glucose solutions, and notable, rash was most frequently reported when icodextrin first entered the market [13, 23]. However, the prevalence of rash has remarkably decreased since then [10, 11]. The present SR included maculopapular reactions as rash, unlike previous studies. Consequently, the incidence of rash did not significantly differ between icodextrin and glucose solutions.

Here, we determined which outcomes were important to clinical practice after discussion at two consecutive panel meetings. Differences in their opinions were addressed by voting among committees and the process

of creating an SR was developed. Four independent investigators collected the studies for review and analyzed the data. A standardized method of peritoneal function assessment has not been established and the numbers of RCT were insufficient to evaluate the reliability of this parameter as an indicator. Therefore, the importance of peritoneal function, determined as D/P creatinine, was not as critical as all-cause mortality and technical survival. Finally, the last panel meeting concluded that peritoneal function as an outcome should be modified and downgraded.

The present review had some limitations. Firstly, the degree of heterogeneity was high in eligible studies with respect to the glucose concentrations of control PD dialysates. Secondly, some outcomes had no definite criteria or indicators, which might have resulted in selection bias derived from the extracted studies. As to technical survival, we defined it as the number of patients who were forced to discontinue PD and transitioned to HD treatment, while death, transplantation, recovery of renal function, and loss to follow-up were not counted. Consequently, the difference in the definition of technical survival resulted in a discrepancy of the number of events reported in each study. Thirdly, we use icodextrin for patients with excessive fluid tendencies in clinical practice. However, the patients in the reviewed studies did not necessarily have issues with fluid management. This discrepancy might lead to a

concern regarding routine icodextrin treatment for more efficient water removal among patients on PD without a fluid excess. Finally, subgroups were not analyzed when analytical findings found no overall effect. Therefore, patients that might benefit from icodextrin could not be confirmed for each outcome.

Conclusions

The present SR suggests that icodextrin could reduce the frequency of uncontrolled fluid overload and ameliorate impaired peritoneal ultrafiltration among patients with PD. However, all-cause mortality, technical survival and peritoneal ultrafiltration did not significantly differ between icodextrin and PD solutions. The present SR reflects an important relationship between icodextrin dialysate and patient-centered outcomes among PD patients.

Supplementary information

The online version of this article (<https://doi.org/10.1186/s41100-019-0253-4>) contains supplementary material, which is available to authorized users.

Additional file 1: The PRISMA checklist of items to include when reporting a systematic review.

Additional file 2: Figure S1. Effects of icodextrin on urine volume. **Figure S2.** Effects of icodextrin on residual renal function. **Figure S3.** Effects of icodextrin on peritoneal function. **Figure S4.** Effects of icodextrin on peritonitis. **Figure S5.** Effects of icodextrin on rash.

Abbreviations

APD: Automated peritoneal dialysis; CAPD: Continuous ambulatory peritoneal dialysis; CCPD: Continuous cycling peritoneal dialysis; CI: Confidence interval; CPG: Clinical practice guideline; D/P Cr: Dialysate-to-plasma creatinine ratio; GRADE: Grading of Recommendations Assessment, Development and Evaluation; JSDT: Japan Society for Dialysis Therapy; MD: Mean difference; PD: Peritoneal dialysis; PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA); RCTs: Randomized controlled trials; RR: Relative risk; SR: Systematic review

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YT, HY, and YI contributed to the research concept and study design. AK, YT, TF, EF, and KW contributed to the data acquisition and AK, YT, TF, EF, KW, and HY contributed to the data analysis/interpretation. AK, YT, TF, and HY contributed to the quality assessment of risk of bias. YT, HY, YI, and HN contributed to the supervision or mentorship. All authors contributed important intellectual content during manuscript drafting or revision and approved the final version of the submitted manuscript.

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Competing interests

The authors declare that they have no competing interests.

Author details

¹Division of Community Medicine, Tohoku Medical and Pharmaceutical University, 1-15-1 Fukumuro, Miyagino, Sendai, Miyagi 983-8536, Japan. ²Department of Healthcare Epidemiology, School of Public Health, Graduate School of Medicine, Kyoto University, Yoshida-honmachi, Sankyo-ku, Kyoto 606-8501, Japan. ³Department of Nephrology, Seirei Sakura Citizen Hospital, 2-36-2 Eharadai, Sakura, Chiba 285-8765, Japan. ⁴Division of Blood Purification, Tohoku University Hospital, 1-1 Seiryomachi, Aoba-ku, Sendai, Miyagi 980-8574, Japan. ⁵Department of nephrology, St. Luke's International Hospital, 9-1 Akashicho, Chuo, Tokyo 104-8560, Japan. ⁶Department of Oral and Maxillofacial Surgery, National Hospital Organization Toyohashi Medical Center, Hamamichigami-50 Imurecho, Toyohashi, Aichi 440-8510, Japan. ⁷Division of Nephrology, Department of Internal Medicine, Tokyo Saiseikai Central Hospital, Tokyo, Japan. ⁸Division of Nephrology and Rheumatology, Department of Internal Medicine, Aichi Medical University School of Medicine, 1-1 Yazakokarimata, Nagakute, Aichi 480-1195, Japan. ⁹Department of General Internal Medicine, Saitama Medical University, 38 Morohongo, Moroyama-machi, Iruma-gun, Saitama 350-0495, Japan.

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