

Impact of icodextrin on clinical outcomes in peritoneal dialysis: a systematic review of randomized controlled trials

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ABSTRACT

Background. Although icodextrin has been shown to augment peritoneal ultrafiltration in peritoneal dialysis (PD) patients, its impact upon other clinical end points, such as technique survival, remains uncertain. This systematic review evaluated the effect of icodextrin use on patient level clinical outcomes.

Methods. The Cochrane CENTRAL Registry, MEDLINE, Embase and reference lists were searched (last search 13 September 2012) for randomized controlled trials of icodextrin versus glucose in the long dwell exchange. Summary estimates of effect were obtained using a random effects model.

Results. Eleven eligible trials (1222 patients) were identified. There was a significant reduction in episodes of uncontrolled fluid overload [two trials; 100 patients; relative risk (RR) 0.30, 95% confidence interval (CI) 0.15–0.59] and improvement in peritoneal ultrafiltration [four trials; 102 patients; mean difference (MD) 448.54 mL/day, 95% CI 289.28–607.80] without compromising residual renal function [four trials; 114 patients; standardized MD (SMD) 0.12, 95% CI –0.26 to 0.49] or urine output (three trials; 69 patients; MD –88.88, 95% CI –356.88 to 179.12) with icodextrin use for up to 2 years. There was no significant effect on peritonitis incidence (five trials; 607 patients; RR 0.97, 95% CI 0.76–1.23), peritoneal creatinine

clearance (three trials; 237 patients; SMD 0.36, 95% CI –0.24 to 0.96), technique failure (three trials; 290 patients; RR 0.58, 95% CI 0.28–1.20), patient survival (six trials; 816 patients; RR 0.82, 95% CI 0.32–2.13) or adverse events.

Conclusions. Icodextrin prescription improved peritoneal ultrafiltration, mitigated uncontrolled fluid overload and was not associated with increased risk of adverse events. No effects of icodextrin on technique or patient survival were observed, although trial sample sizes and follow-up durations were limited.

INTRODUCTION

Icodextrin is a starch-derived iso-osmolar, high-molecular weight (16 200 Da) glucose polymer, which promotes sustained peritoneal ultrafiltration equivalent to that achieved with hypertonic (3.86/4.25%) glucose exchanges during prolonged (10–16 h) intraperitoneal dwells [1]. Peritoneal dialysis (PD) patients with impaired ultrafiltration, particularly high transporters, appear to derive the greatest benefit with respect to the enhancement of dialytic fluid removal [1–3]. As a result, the International Society of Peritoneal Dialysis *Ad Hoc* Committee on Ultrafiltration Management in Peritoneal Dialysis and the European Renal Best Practice working group recommend that icodextrin be used for the long dwell in high

transporter patients with a net peritoneal ultrafiltration of <400 mL during a peritoneal equilibration test (PET), lasting 4 h, with a 3.86% glucose solution [4, 5]. Uncontrolled studies have further suggested that the use of icodextrin as salvage therapy in PD patients with refractory fluid overload may prolong technique survival [6].

However, in spite of these attractive characteristics and its widespread clinical use, the effect of icodextrin on patient-level clinical outcomes, such as technique and patient survival, remains unclear. Moreover, it is also uncertain whether augmentation of peritoneal fluid removal by icodextrin might have unintended adverse consequences, such as accelerated decline of residual renal function (RRF). A systematic review of randomized controlled trials (RCTs) was undertaken to evaluate the clinical benefits and harms of icodextrin compared with conventional PD solutions in PD patients.

MATERIALS AND METHODS

The protocol of this systematic review has been published in the Cochrane Database of Systematic Reviews. Briefly, the review included all available RCTs (parallel and crossover trials), and quasi-RCTs comparing the effects of icodextrin on PD patient outcomes.

Search strategy

Electronic searches were performed in MEDLINE (1966 to September 2012), Embase (1988 to September 2012) and the Cochrane Renal Group Specialist Register by using optimally sensitive strategies for the identification of RCTs developed by the Cochrane Collaboration [7]. The following medical subject terms and text words were used: PD, biocompatible, icodextrin, continuous ambulatory PD (CAPD), continuous cycling PD (CCPD) and automated PD (APD). Results of searches were analysed in title and abstract form by two authors according to the inclusion criteria (Y.C., K.J.W.). Reference lists from identified articles, reviews and guidelines were then searched. Any differences and problems in data extraction were resolved by discussion among authors. When data were missing or incomplete, the investigators of the trial were contacted for clarification.

The risk of bias of included trials was assessed by using standard criteria (random sequence generation, allocation concealment; blinding of participants, investigators and outcome assessors; assessment of attrition, reporting and other biases, analysis by intention to treat; and completeness of follow-up) according to the Cochrane Handbook [8].

Study characteristics

The pre-specified clinical outcomes included peritoneal ultrafiltration, episodes of fluid overload, RRF (renal clearance and urine volume), peritoneal small solute clearance, peritoneal solute transport rate, peritonitis, adverse events (including skin rash), hospitalization, technique survival and patient survival.

Quantitative data synthesis

Results of individual trials are expressed as relative risks (RRs) with 95% confidence intervals (CIs) for categorical outcomes. Data were summarized using the random effects model. The fixed effect model was also analysed to ensure robustness of the model chosen and susceptibility to outliers. Where continuous scales of measurement were used to assess the effects of treatment, the mean difference (MD) was used, or the standardized MD (SMD) if different scales were used. To aid clinical understanding, an estimate of MD using the most commonly used metric in the analysed trials was provided when SMD was reported. When it was not possible to establish which data from crossover studies were from the first arm of the trial, studies were excluded from meta-analyses. Heterogeneity was analysed using a χ^2 test on $N-1$ degrees of freedom, with an α of 0.05 used for statistical significance and with the I^2 test [9]. I^2 values of 25, 50 and 75% corresponded to low, medium and high levels of heterogeneity. Subgroup analysis was used to explore possible sources of heterogeneity [patient population (incident versus prevalent), duration of treatment, PD modality (CAPD versus APD), membrane transport characteristics]. The data were analysed using Review Manager (RevMan Version 5.1. Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2011). P-values of <0.05 were considered statistically significant.

RESULTS

Trial flow

Electronic search identified 88 reports, of which two were excluded at title and abstract assessment stage. Analysis of the remaining 37 studies (85 articles) by full text identified 11 studies (1222 patients) published in 38 articles that were eligible and were included in this review. Search results are shown in Figure 1.

Description of studies

Eleven trials (1222 patients) assessed clinical outcomes of using icodextrin in one PD exchange daily [3, 10–20]. Of these, three trials assessed the effect of icodextrin in patients with high (H) or high average (HA) membrane transport properties [11, 12, 15]. A large variation in the concentration of glucose PD solution used in the control groups was observed across the trials. The characteristics of populations, interventions and analysed outcomes of included studies are provided in Table 1 (Supplementary data, Table S1).

Risk of bias in included studies

Trial allocation methods and concealment were incompletely reported in some studies. Allocation concealment was adequate in six trials (54.5%). Only four trials (36.4%) blinded participants and investigators. Intention-to-treat analysis was performed in seven trials (63.6%). Patients lost to follow-up ranged from 5 to 43.9%. Risks of bias domains of the included studies are shown in Figure 2 (Supplementary data, Table S2 and Figure S1).

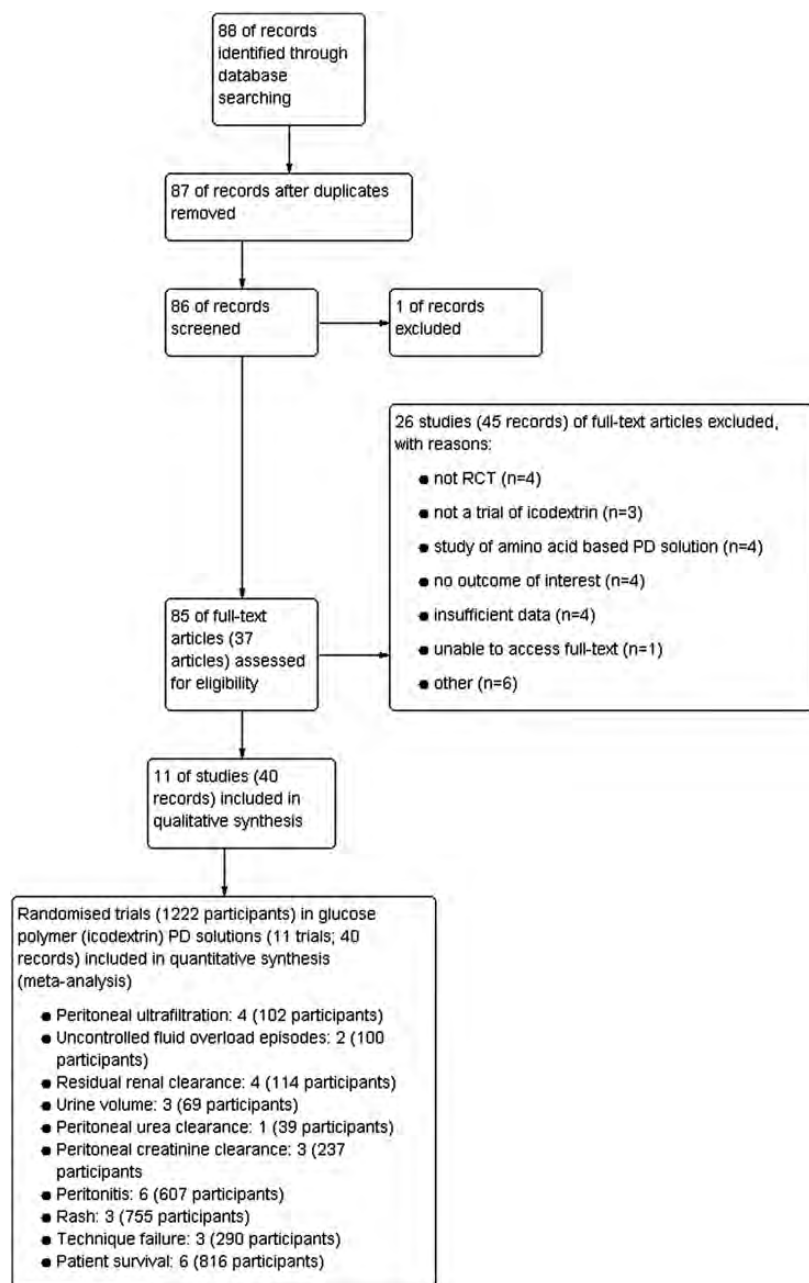


FIGURE 1: Flow chart with the number of retrieved citations by individual searches, reasons for exclusion and the final number of included trials.

Effects of interventions

The results presented below refer to those obtained using a random effects model.

Peritoneal ultrafiltration. The use of icodextrin uniformly resulted in improved peritoneal ultrafiltration compared with glucose exchanges (four trials; 102 patients; MD 448.54 mL/day, 95% CI 289.28–607.80, $P < 0.01$, $I^2 = 0\%$, Figure 3) for up to 24 months of treatment. However, this outcome may have been biased in favour of icodextrin as only one of these four trials allowed the use of hypertonic glucose PD solution (3.86%) in the control group.

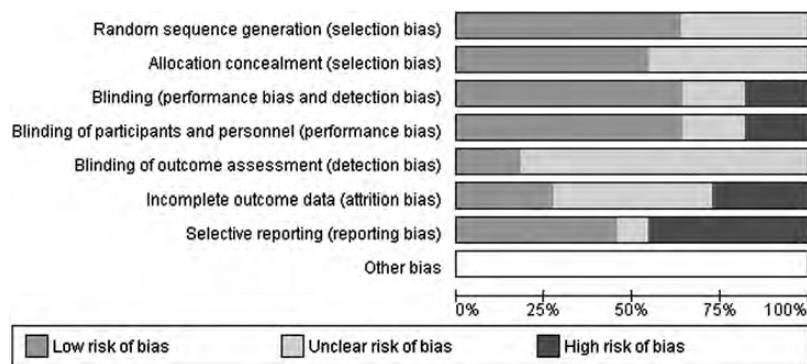
Episodes of uncontrolled fluid overload. The use of icodextrin led to a significant reduction in reported episodes of uncontrolled fluid overload (two trials; 100 patients; RR 0.30, 95% CI 0.15–0.59, $P < 0.01$, $I^2 = 0\%$, Figure 4).

Residual renal clearance. Icodextrin had no appreciable impact on residual renal clearance (four trials; 114 patients; SMD 0.12, 95% CI -0.26 to 0.49 , $P = 0.5$, $I^2 = 0\%$; Figure 5) up to 24 months of continuous therapy using icodextrin. This approximated to MD in renal creatinine clearance of 0.50 mL/min (95% CI -0.71 to 1.71).

Table 1: Studies of icodextrin versus standard glucose PD solutions

Reference	Year	Patient population (I/P)	Patient no.	Modality	Centres (n)	Study design	Control group intervention	Duration (months)
Bredie <i>et al.</i> [10]	2001	P	21	CAPD	1	Cross-over	1.36, 2.27 or 3.86% glucose	3
Davies <i>et al.</i> [11]	2003	P	50	CAPD/APD	10	Parallel	2.27% glucose	6
Finkelstein <i>et al.</i> [12]	2005	P	92	APD	6	Parallel	4.25% glucose	0.5
Konings <i>et al.</i> [3]	2003	P	40	CAPD/APD	7	Parallel	1.36% glucose	4
Lin <i>et al.</i> [13]	2009	P	201	CAPD	7	Parallel	2.5% glucose	1
Mistry <i>et al.</i> [14]	1994	P	209	CAPD	2	Parallel	1.36 or 3.86% glucose	6
Paniagua <i>et al.</i> [15]	2009	P	59	CAPD	4	Parallel	2.5 or 4.25% glucose	12
Plum <i>et al.</i> [16]	2002	P	39	APD	8	Parallel	2.27% glucose	3
Posthuma <i>et al.</i> [17, 18]	2000	I+P	38	CCPD	1	Parallel	1.36, 2.27 or 3.86% glucose	24
Takatori <i>et al.</i> [19]	2011	I	41	CAPD/APD	23	Parallel	1.5 or 2.5% glucose	24
Wolfson <i>et al.</i> [20]	2002	P	175 (efficacy) 287 (safety)	CAPD (efficacy) CAPD/APD (safety)	32 (efficacy) 42 (safety)	Parallel	2.5% glucose	1 (efficacy) 12 (safety)

I, incident; P, prevalent; CAPD, continuous ambulatory peritoneal dialysis; APD, automated peritoneal dialysis; CCPD, continuous cycling peritoneal dialysis.

**FIGURE 2:** Risk of bias graph of included trials.

Urine volume. Similar to residual renal clearance, icodextrin-induced increases in peritoneal ultrafiltration volumes did not significantly affect daily urine volumes (three trials; 69

patients; MD -88.88 mL/day, 95% CI -356.68 to 179.12 , $P = 0.5$, $I^2 = 0\%$). In fact, Davies *et al.* [11] reported better maintenance of urine volume with the use of icodextrin

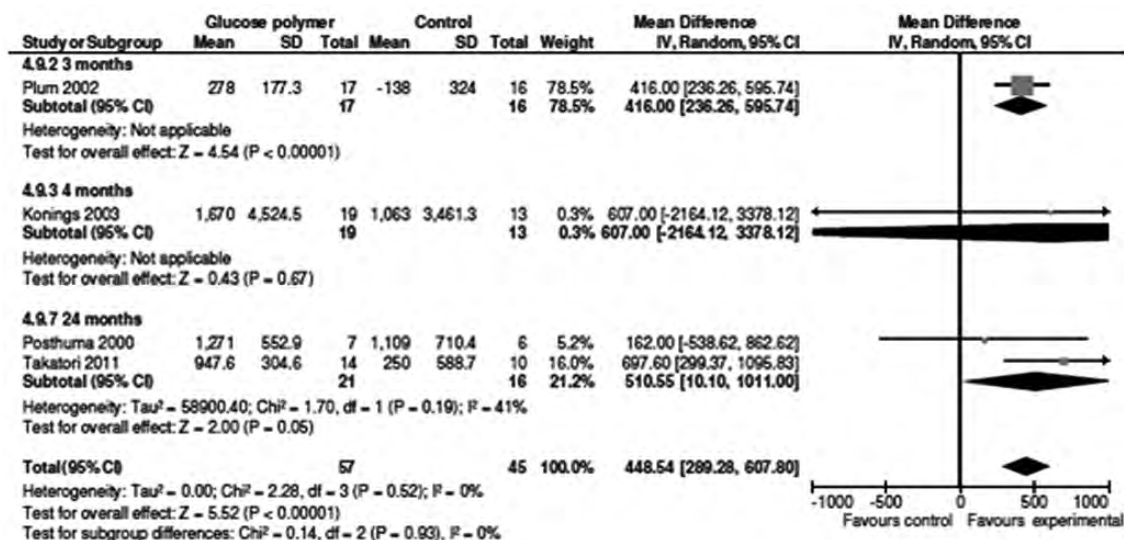


FIGURE 3: Effect of glucose polymer PD solution (icodextrin) use on daily peritoneal ultrafiltration (mL/day).

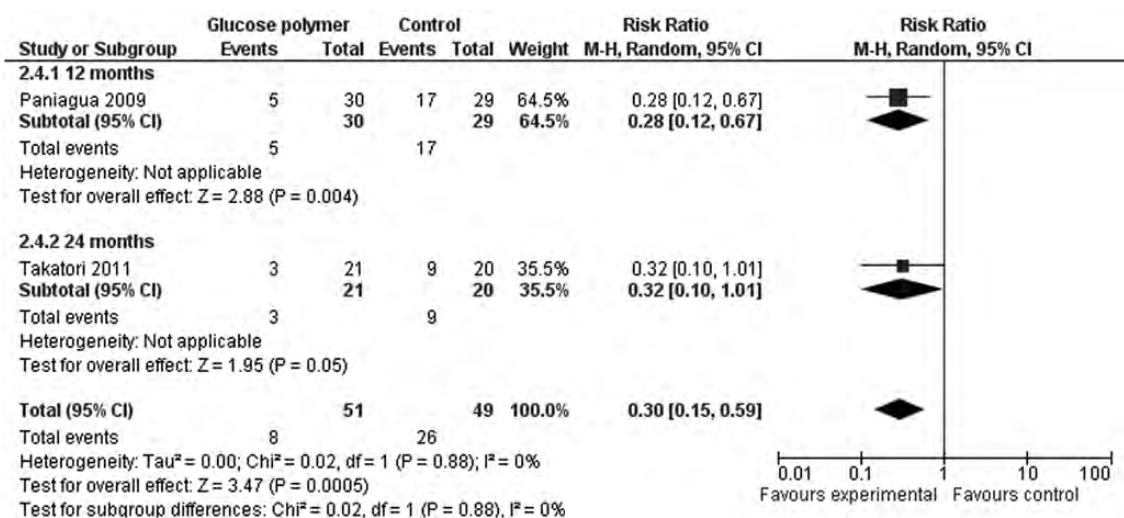


FIGURE 4: Effect of glucose polymer PD solution (icodextrin) use on uncontrolled fluid overload episodes.

at 6 months when compared with 2.27% dextrose PD solution use.

Peritoneal small solute clearance. Peritoneal urea clearance was significantly enhanced with the use of icodextrin (one trial; 39 patients; MD 0.39 mL/min, 95% CI 0.10–0.68) [16]. In contrast, the overall effect of icodextrin on peritoneal creatinine clearance was not significant [three trials; 237 patients; SMD 0.36, 95% CI –0.24 to 0.96, $P = 0.2$, $I^2 = 66\%$; estimated MD 0.38 mL/min (95% CI 0.13–0.64); Figure 6]. Moderate-to-severe heterogeneity was observed and appeared to be related to study design variability. Two studies were open label in design with unclear description of the number of patients in each PET category [16, 17]. Subgroup analysis according to PET category was performed by Lin *et al.* [13] who identified significantly higher peritoneal creatinine clearance measurements among patients with greater than low membrane transport characteristics. For instance, in those with H membrane

transport characteristics, change in peritoneal creatinine clearance from baseline at 4 weeks was 0.75 ± 0.23 mL/min in the icodextrin group compared with -0.17 ± 0.18 mL/min in the control group.

Peritonitis. There was no effect on peritonitis risk with icodextrin use (five trials; 607 patients; RR 0.97, 95% CI 0.76–1.23, $P = 0.8$, $I^2 = 15\%$).

Adverse events. The risks of rash (three trials; 755 patients; RR 2.51, 95% CI 0.59–10.72, $P = 0.2$, $I^2 = 38\%$) were not increased with icodextrin use compared with glucose exchanges. Four trials reported comparable incidence of adverse events with the use of icodextrin [13–15, 20].

Hospitalization. Based on two trials, the risk of hospitalization from all causes was comparable between the icodextrin and standard glucose solution group (45 versus 47%,

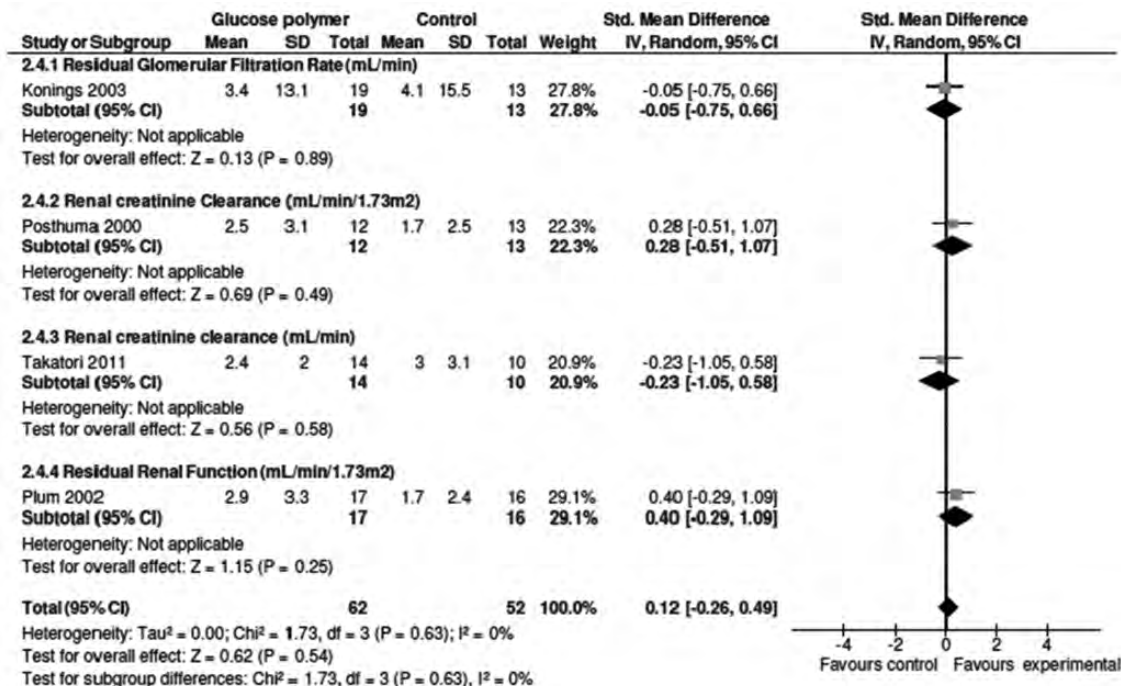


FIGURE 5: Effect of glucose polymer PD solution (icodextrin) on RRF.

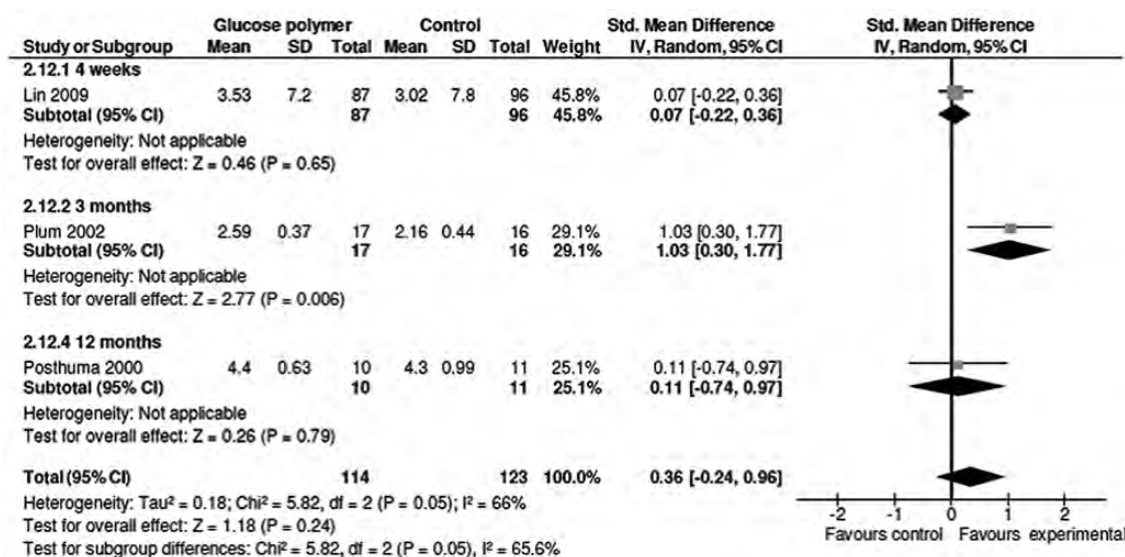


FIGURE 6: Effect of glucose polymer PD solution (icodextrin) on peritoneal creatinine clearance.

respectively) [20]. Paniagua *et al.* [15] reported shorter length of hospital stay in the icodextrin group at 7.66 days per patient-year compared with 10.68 days per patient-year in the standard glucose solution group; however, this was not statistically significant.

Technique survival. None of the trials was adequately powered with the majority having follow-up durations of <6 months (Table 1). Within these constraints, the use of icodextrin did not significantly influence technique failure (three

trials; 290 patients; RR 0.58, 95% CI 0.28–1.20, P = 0.1, I² = 0%).

Patient survival. In the context of low event numbers and short follow-up durations, all-cause mortality was not significantly different between individuals receiving icodextrin and those receiving standard glucose solution (six trials; 816 patients; RR 0.82, 95% CI 0.32–2.13, P = 0.7, I² = 0%).

Results using fixed effects models were not reported as there were no significant differences in results of analyses performed using random effects models.

DISCUSSION

This review demonstrated that the use of icodextrin in one PD exchange daily led to significantly increased peritoneal ultrafiltration volumes, peritoneal urea clearance and a lower risk of uncontrolled fluid overload compared with glucose PD exchanges alone. The augmentation of peritoneal ultrafiltration was not associated with any significant changes in residual renal clearance, urine volume, or peritoneal creatinine clearance and did not translate into improved hospitalization, technique survival or patient survival.

These results differ somewhat from an earlier meta-analysis of icodextrin [21]. Specifically, although both studies observed that icodextrin use was associated with a significant augmentation of peritoneal ultrafiltration, only the current systematic review examined the outcome of uncontrolled fluid overload and found a significant benefit of icodextrin. Technique survival and hospitalization were also only examined in the present study and found to be comparable between the icodextrin and glucose groups. The absence of benefit may have resulted from insufficient power; however, examining these outcomes from the present review highlights the need for a well-designed, large trial of sufficient follow-up duration to evaluate the impact of icodextrin on these clinically important outcomes. While icodextrin was observed to be associated with increased peritoneal creatinine clearance in the older review, the present systematic review found no significant difference between the intervention and control groups. These differences stemmed from a number of contributing factors, which included a different number of analysed studies (the present review was unable to obtain additional data from authors of two studies to perform quantitative analysis [12, 20]), and the use of SMD in the present review to account for differences in units of measurement of peritoneal creatinine clearance (mL/min [13, 16] compared with mL/min/1.73 m² [22]). Moreover, whereas the previous study identified that icodextrin use was accompanied by an increased frequency of skin rashes, no such association was seen in our study. Some of the apparent disparity in results may be related to differential recording of events (prior review has variably included exfoliative dermatitis as rash, for example, included in Konings *et al.* [3], but excluded in Wolfson *et al.* [20], in contrast, the present review has not included exfoliative dermatitis due to inconsistent reporting across trials), as well as the fact that the rash event number recorded in the earlier systematic review against the trial by Finkelstein *et al.* [12] was incorrect (recorded number five compared with actual number eight), thereby leading to an erroneous pooled estimate of effect. Other limitations of the review by Qi *et al.* [21], which did not apply to the current study, included restrictive selection criteria (exclusion of first phase of crossover studies, incident patients, paediatric patients, trials with <10 patients, trials not published in English) and exclusive reporting of outcomes using a fixed effects model. In contrast, the present review adopted a random effects model to account for the presence of clinical heterogeneity and included two additional studies including the first phase of a randomized crossover trial [10] and data

from a recently published RCT, which had the longest follow-up duration (24 months) of all icodextrin trials [19]. The current review is strengthened by well-defined adoption of sound methodology, which is critically important as these evidence-based summaries aim to inform guidelines and clinical practice.

The demonstrated benefit of icodextrin with respect to augmented peritoneal ultrafiltration in the present review was seen in both short- and long-term studies (up to 24 months) and when compared with various concentrations of glucose PD solutions, including hypertonic exchanges. For instance, Finkelstein *et al.* [12] observed a net change in ultrafiltration volume of 401.6 ± 79 mL/day in the icodextrin group compared with -6.98 ± 57.2 mL/day in the 4.25% glucose group at 2 weeks in 92 APD patients with higher peritoneal solute transport rate (defined as a dialysate:plasma creatinine ration at 4 h > 0.7). Importantly, the ultrafiltration benefit of icodextrin extended to patients with ultrafiltration failure (defined as 4-h net ultrafiltration <100 mL using 2.5% dextrose) and was superior to 4.25% glucose PD solution use (+373.8 ± 58.9 versus -239.7 ± 151.0 mL/day, respectively) [12]. Similarly, the subgroup analysis of the two trials with the longest follow-up (24 months; Figure 3) showed an MD of 510.55 mL/day (95% CI 10.10–1011), in favour of icodextrin [17–19]. Furthermore, when the use of icodextrin was compared with 2.5% glucose PD solution according to the PET category, Lin *et al.* [13] identified significant increases in ultrafiltration capacities in all patients except low transporters. Patients with higher peritoneal transport characteristics derived greater ultrafiltration benefit. The findings of this systematic review therefore support the recommendations of the European Renal Best Practice working group and the International Society of Peritoneal Dialysis *Ad Hoc* Committee on Ultrafiltration Management in Peritoneal Dialysis that icodextrin should be used in the long dwell of patients who are identified to have high peritoneal solute transport rates or ultrafiltration failure [4, 5].

Given that manipulation of peritoneal ultrafiltration via various interventions has not infrequently been reported to induce reciprocal changes in urine volume and residual renal clearance measurements [23, 24], these outcomes were specifically examined in the present review and found not to be compromised by icodextrin-enhanced peritoneal ultrafiltration.

Similarly, the additional fluid volume removed via the peritoneal cavity with icodextrin was not associated with increased peritoneal creatinine clearance measurements. It should be noted, however, that moderate-to-severe trial heterogeneity was detected, primarily related to variability in the peritoneal membrane transport characteristics of patients included in each trial. Indeed, significant enhancement of creatinine clearance with icodextrin use was reported by two trials, with benefit seen only in those individuals with higher peritoneal solute transport rates [12, 13]. In contrast, uniformly augmented peritoneal urea clearance with icodextrin use was reported by four trials. Only one of these studies was included in the meta-analysis due to insufficient level of available data from the remaining trials [12, 15, 20]. Two studies were conducted in patients with HA or high membrane

transporter characteristics [12, 15]. Further studies are therefore warranted to examine the effect of icodextrin on peritoneal small solute clearance according to peritoneal transport status.

Despite finding significant and clinically important improvements in both peritoneal ultrafiltration volumes and clinically observed refractory fluid overload in PD patients, including those with ultrafiltration failure, the present review was unable to discern a significant benefit of icodextrin on the patient-level outcomes of technique and patient survival rates. However, overall patient numbers were too small, trial durations too short and event rates too low to confidently exclude a type 2 statistical error due to inadequate statistical power. A large, well-designed, adequately powered RCT examining this issue in a broad cross-section of PD patients would be important to address these issues.

Reassuringly, icodextrin was not found to be associated with significantly increased harm compared with glucose exchanges alone. Skin rash was the most commonly reported adverse event, which led to the cessation of icodextrin in 0–4.3% of patients [12, 16, 20] across the identified trials. However, no trial reported the occurrence of rash severe enough to warrant hospitalization or additional therapeutic intervention other than cessation of icodextrin. It is unknown whether any of these patients were subsequently re-challenged using icodextrin. The use of icodextrin was also not associated with an increase in peritonitis rates. Although increased incidence of culture-negative peritonitis has been a problem in the past, this has been attributed to contamination of products during the manufacturing process by peptidoglycans released from *Alicyclobacillus acidocaldarius*, thermophilic acidophilic bacteria [25]. Since addressing this issue, further occurrence of sterile peritonitis has not been problematic and findings from this review support this.

The strength of this review is that it represents a comprehensive systematic review based on a previous publication of a detailed protocol [26], a thorough MEDLINE, Embase and Cochrane Controlled Trial Registry search, risk of bias assessment and inclusion of only RCTs or quasi-RCTs as pre-specified. Only the data from the first phase of the crossover RCTs were included for quantitative analyses in order to minimize the risk of the carry-over effect and potential introduction of bias related to time-dependent variables. Data extraction, data analysis and method quality assessment were performed by two independent investigators, and any differences in consensus were checked with an additional two reviewers.

Nevertheless, this review suffers from several limitations that relate largely to potential risk of bias in the included trials. Many trials failed to specify the method of randomization, allocation concealment and blinding of outcome assessors. Often, it was difficult to determine whether data were truly analysed on an intention-to-treat analysis and how the trial dealt with dropouts. Substantial variation in the glucose concentrations of PD solutions employed in the control group added clinical heterogeneity. Adverse events were not uniformly reported by trials making it difficult to comprehensively evaluate this outcome. In general, RCT sample sizes were small (raising the possibility of type 2 statistical error),

dropout rates were high (raising the possibility of attrition bias) and study designs were typically open-label (raising the possibilities of co-intervention and observer biases). Furthermore, the lack of standardized approach in reporting outcomes, such as residual renal clearance, created challenges for performing more inclusive, quantitative analyses. These limitations collectively limited the strength of conclusions that could be drawn.

In conclusion, this systematic review shows that the use of icodextrin improved peritoneal ultrafiltration (based on four trials), which translated into a decrease in episodes of uncontrolled fluid overload (based on two trials) and greater peritoneal urea clearance (based on one trial). The benefit extended to patients with high peritoneal solute transport rates and ultrafiltration failure. Icodextrin use was not associated with any significant changes in residual renal clearance, urine volume, peritoneal solute transport rate or peritoneal creatinine clearance and did not translate into improved technique survival or patient survival. However, the meta-analysis lacked statistical power to adequately evaluate these patient-level outcomes. This review also did not find any significant harm resulting from the use of icodextrin. Therefore, based on the best available evidence involving trials with generally suboptimal quality, icodextrin provides clinically important fluid management benefits in PD patients, especially those with impaired ultrafiltration, without added risks of harm. Larger studies are needed to adequately evaluate the impact of icodextrin on hard clinical end points, such as peritonitis, technique survival and patient survival.

SUPPLEMENTARY DATA

Supplementary data are available online at <http://ndt.oxfordjournals.org>.

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CONFLICT OF INTEREST STATEMENT

D.W.J. is a consultant for Baxter Healthcare Pty Ltd and has previously received research funds from this company. He has also received speakers' honoraria and research grants from Fresenius Medical Care. He has previously been a consultant to Gambro Pty Ltd. He is an International Society of Peritoneal Dialysis Councillor and is a current recipient of a Queensland Government Health Research Fellowship.

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