Randomized controlled study of icodextrin on the treatment of peritoneal dialysis patients during acute peritonitis

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ABSTRACT

Background. The clinical benefits of using icodextrin during acute peritonitis in peritoneal dialysis are uncertain. On the premise that high glucose concentration might jeopardize the peritoneal defense during peritonitis, icodextrin administration during acute peritonitis could have the potential to improve the peritonitis outcome whilst improving ultrafiltration.

Methods. We conducted a single-center, open-label, randomized controlled trial in which 53 adult continuous ambulatory peritoneal dialysis patients underwent randomization to receive either icodextrin or original glucose-based dialysis solution. The primary outcome measure was the peritoneal dialyzate white cell count on Day 3. Secondary outcome measures comprised the need of additional hypertonic exchanges, fluid control as denoted by changes in body weight, and the clinical outcome of peritonitis including 30-day and 120-day all-cause mortality.

Results. Between icodextrin and control treatment groups, there were no statistically significant differences in the peritoneal dialyzate white cell count on day (1829 versus 987/mm³, P = 0.13). There was neither improvement in primary cure rate (31.8 versus 32.3%, P = 1.00), nor was there any change in 120-day mortality after icodextrin use (13.6 versus 12.9%, P = 1.00). However, requirement of hypertonic dialysis exchange was much more frequent in the control group than in those randomized to icodextrin (35.5 versus 0%, P = 0.001). Body weight did not change significantly in the icodextrin group, but body weight in the control group increased from 63.3 ± 14.5 kg at baseline to 64.2 ± 14.2 kg at Day 5 (P = 0.0002) and 65.2 ± 14.1 kg at Day 10 (P < 0.0001).

Conclusions. As compared with glucose-based peritoneal dialysis solution, use of icodextrin achieved better ultrafiltration and fluid control during acute peritonitis complicating continuous ambulatory peritoneal dialysis, although we found no evidence of a worthwhile clinical benefit on peritonitis resolution. (ClinicalTrial.gov number, NCT0104446 [ClinicalTrial.gov]).

Keywords: CAPD, icodextrin, peritoneal dialysis, peritonitis, ultrafiltration

INTRODUCTION

Antibiotics administration, either systemically or intraperitoneally, is considered the standard of care for peritonitis complicating peritoneal dialysis [1]. Despite the current standard treatment of peritonitis, peritonitis has remained an important cause of technique failure. Adjunctive treatment strategy should be explored to reduce the duration of peritoneal inflammation and complication of ultrafiltration.

Avoidance of glucose administration during acute peritonitis is posited to offer clinical benefits in terms of treatment outcome. This possibility is supported by a commonly observed phenomenon of falling ultrafiltration during acute peritonitis episodes. As such, peritoneal dialysis patients suffering from acute peritonitis are more likely to receive hypertonic glucose dialyzate in order to facilitate fluid removal. This raises the concern of absorbing glucose through the peritoneum to cause hyperglycemia [2] and increased glucose load within the peritoneal cavity, both of which might ultimately impair the peritoneal defense against bacterial infection.

Early clinical human data have also demonstrated a potential positive effect of icodextrin on certain aspects of the peritoneal defense system [3], although they were derived from maintenance peritoneal dialysis patients not with acute peritonitis. Interestingly, icodextrin solution has been shown in human trials to reduce intra-abdominal adhesion during surgery [4, 5]. Whether a similar benefit of preventing peritoneal adhesion formation during acute peritonitis can be observed in the peritoneal dialysis population remains unknown.

In terms of the ultrafiltration advantage of icodextrin as compared with glucose-based dialyzate, several randomized controlled trials have been performed. In the MIDAS Study, 9 patients in the glucose group and 14 patients in the icodextrin
group experienced acute peritonitis. During these infective episodes, the mean overnight ultrafiltration volumes decreased slightly from 218 ± 354 to 185 ± 218 mL in the glucose group, but significantly increased in the icodextrin from 570 ± 146 to 723 ± 218 mL [6]. Similar findings have also been reported in a randomized study involving patients on continuous cyclic peritoneal dialysis and with peritonitis [7]. Since most antibiotics used for peritonitis treatment (including vancomycin, cephalosporins and gentamicin) have been shown to be compatible and stable with icodextrin in numerous in vitro studies [8–11], safety issue of icodextrin can be justified as a treatment option in the presence of peritonitis.

The present study was designed to evaluate the a priori hypothesis that treatment with icodextrin during acute peritonitis would improve the treatment outcomes of peritonitis complicating peritoneal dialysis. The effectiveness of icodextrin for decreasing glucose exposure, extent and severity of peritonitis was evaluated in the setting of acute peritonitis complicating peritoneal dialysis among patients who are not receiving icodextrin.

MATERIALS AND METHODS

In this prospective open-label randomized controlled study, we enrolled 56 patients with peritoneal dialysis-related peritonitis within our center. All the participants provided written informed consent. The study was designed and conducted in compliance with the principles of Good Clinical Practice regulations. The institutional ethics committee board approved the study. No pharmaceutical company was involved in the design of the study, data collection or analysis, or the writing of the manuscript.

Study participants

Patients who met the following inclusion criteria were eligible: age of 18 years or older on peritoneal dialysis; diagnosis of peritonitis complicating peritoneal dialysis with Baxter connection system; and willingness to give written consent and comply with the study protocol. Peritonitis was defined according to the standard diagnostic criteria and based on at least two of the following criteria: abdominal pain or cloudy peritoneal dialysis effluent, leukocytosis in peritoneal fluid effluent (white blood cell count at least 100/mm³), or positive Gram stain or culture from effluent [1]. Patients were excluded if they had any of the following: pre-existing icodextrin use; known allergy or hypersensitivity to icodextrin, starch or have a glycojen storage disease; participation in another interventional study within the last 30 days of randomization; contraindication to icodextrin; history of a psychological illness or condition that would interfere with the patient’s ability to understand the requirement of the study and/or comply with the study procedures.

Methods

Patients meeting the enrollment criteria were randomized after informed consent to one of the two treatment groups: either icodextrin dialyze or control treatment (continuing with original glucose-based dialyze). All patients used Ultrabag (Baxter Healthcare Corporation) peritoneal dialysis fluids. Treatment assignment by sealed envelopes was used. We used the simple randomization method instead of blocked randomization. The treatment allocation was not blinded to patients and investigators. Patients randomized to the icodextrin treatment arm were advised to perform the night dwell with icodextrin, with a view to decrease the glucose concentration of the remaining dialysis solutions. Those subjects already receiving 2.5% glucose solution were allowed to switch to 1.5% glucose solution during the icodextrin treatment period, at the discretion of the physicians. Patients randomized to the control treatment group continued to receive original glucose-based dialysis solution. Changes in the glucose concentration of dialysis solutions were made as necessary during the treatment period. Additional hypertonic dialysis exchanges due to fluid excess were left to the physician’s discretion.

Bacterial culture of peritoneal dialysis effluent in our unit was performed using the BacTAlert bottles (Organon Teknika Corp, Durham, NC, USA) following the manufacturer’s instructions. Patients were instructed to bring the first cloudy fluid or come to the dialysis center immediately. For each episode of peritonitis, we recorded the initial peritoneal dialyze white blood cell count, and then the serial white blood cell counts on scheduled follow-up visits (Day 3 and Day 5). Peritoneal fluid was drained after standard dwell at night, which should last for at least 6 hours. Cell counts were obtained by placing an aliquot (3–5 mL) of drained fluid immediately into ethylenediaminetetraacetate (EDTA) tubes. For each episode of peritonitis, we also recorded the patient age at the time of peritonitis, gender, the presence of diabetes mellitus, duration of peritoneal dialysis prior to the onset of the peritonitis episode, and the causative microorganisms. We also recorded the patients’ body weight on Days 1, 5 and 10 of peritonitis course, and their requirement for extra hypertonic peritoneal dialysis exchange.

At the same time, peritonitis episodes were treated with standard antibiotic protocol of our center, in accordance with the latest International Society for Peritoneal Dialysis (ISPD) guidelines [1]. Initial antimicrobial therapy for peritonitis consisted of intraperitoneal administration of cefazolin and cefazidine. Intravenous antibiotics were used when the patient appeared septic clinically. Prophylactic oral nystatin 500 000 U t.i.d. was prescribed with concomitant antibiotics in all cases. The antibiotics regimen was modified once the culture results and sensitivities became available. In general, patients received antibiotics for 14 days. When Pseudomonas or Xanthomonas species was isolated, patients received two antibiotics, which were to be continued for at least 21 days. When Staphylococcus aureus was isolated, patients were treated for at least 21 days. Relapse of peritonitis is defined as another peritonitis episode with the same organism or one sterile episode within 4 weeks of completion of the antibiotic therapy. In general, Tenckhoff catheters were removed if the dialysis fluid did not clear by Day 10. Alternatively, if the peritonitis failed to respond to appropriate antibiotics within 5 days, catheter removal was removed as suggested by the ISPD guidelines [1]. Primary cure refers to complete resolution of signs and symptoms of peritonitis, with negative cultures and no further episodes of peritonitis within 28 days following the cessation of antibiotic
treatment, by the assigned antibiotic treatment. Secondary cure refers to cure after adjustment of antibiotics or changing to second line antibiotics.

**End points**

The primary outcome measure of this study was the peritoneal dialyzate white cell count. Among the markers of treatment outcome, the peritoneal dialyzate total white cell count on Day 3 was compared. This surrogate marker is chosen because it has been validated as a predictive factor of treatment outcomes [12].

The secondary end points include the need of additional hypertonic exchanges, fluid control as denoted by changes in body weight, and the clinical outcome of peritonitis including 30-day and 120-day all-cause mortality. Peritonitis has been shown to be associated with increased odds of mortality within 120 days [13].

**Statistical analysis**

Statistical analyses were performed by SPSS for Windows software version 16.0 (SPSS Inc., Chicago, IL, USA). Numerical data are expressed in mean ± SD. Treatment outcome and data between groups were compared using Student’s t-test or Wilcoxon’s matched-pairs signed-rank test as appropriate. Percentages were compared by means of Fisher exact test. A two-tailed P < 0.05 was regarded as statistically significant.

Based on our previous study, peritoneal dialysate fluid cell count is expected to be $1600 ± 3500/mm^3$ on Day 3, while a cell count of $1000/mm^3$ was associated with a less favorable response [12]. We define an improvement in cell count to $800 ± 100/mm^3$ on Day 3 to be clinically meaningful (i.e. over 95% cases would have cell count $<1000/mm^3$ on Day 3). A sample size of 48 would achieve 20% power to detect the difference between the groups with a significant level (alpha) of 0.05 using a two-sided two-sample $t$-test. This sample size is estimated by the Power Analysis and Sample Size for Windows software (PASS 2000, NCSS, Kaysville, Utah, USA).

**RESULTS**

The study randomized 56 patients with peritonitis to receive either icodextrin or control treatment (Figure 1). Of those recruited, one patient in the icodextrin group and two in the control arm were excluded. A total of 53 patients were analyzed; 22 received icodextrin and 31 received control treatment (original glucose-based dialysis solution).

The two groups were well matched for all baseline characteristics, and were comparable with respect to age, baseline albumin level, residual renal function, percentage of anuria, peritoneal solute transport characteristics, duration of peritoneal dialysis and the presence of diabetes mellitus (Table 1). All

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**FIGURE 1:** Consolidated Standards of Reporting Trials diagram showing the number of patients recruited, randomized, followed and analyzed.
received continuous ambulatory peritoneal dialysis. Most patients were men (73%); had diabetes mellitus (62%); and were receiving three peritoneal dialysis exchanges daily (62%). The median interval from the start of dialysis to peritonitis was 2.0 years. The profile of bacterial isolates from the patients with peritonitis is summarized in Table 2. There was a statistically nonsignificant trend of higher incidence of \textit{Pseudomonas aeruginosa} peritonitis in the icodextrin group; overall, the number of such cases was small.

The peritoneal dialyze white cell count on Day 3, the primary end point in our study, were 1829 ± 2454 and 987 ± 1471/mm$^3$ in the icodextrin and control treatment groups respectively ($P = 0.13$). We further analyzed the treatment outcomes between the two groups (Table 3). The primary cure rate of the original antibiotic regimens for the primary end point in our study, were 1829 ± 2454 and 987 ± 1471/mm$^3$ in the icodextrin and control treatment groups. The body weight in the control group increased from 63.3 ± 14.5 kg at baseline to 64.2 ± 14.2 kg at Day 5 ($P = 0.0001$). The body weight in the icodextrin group were similar to Day 5 (63.3 ± 10.5 kg versus 62.9 ± 10.3 kg at baseline, $P = 0.19$) and Day 10 (63.9 ± 11.3 kg versus 62.9 ± 10.3 kg at baseline, $P = 0.085$).

Three patients (14.3%) assigned to icodextrin treatment group required modification of dialysis fluid concentration because of increased ultrafiltration, all of them within the first 5 days of starting icodextrin. Modification included change from 2.5 to 1.5% glucose solution for a period of 7–17 days (in three patients) and temporary discontinuation of icodextrin (in one patient). None of these adverse events required in-hospital treatment.

**DISCUSSION**

In this randomized controlled trial of peritonitis complicating peritoneal dialysis, patients treated by icodextrin experienced a much lower rate of requiring additional hypertonic peritoneal dialysis exchange to mitigate the ultrafiltration problem. To our knowledge, this is the only published report on icodextrin acute treatment for peritonitis. The impact of icodextrin on ultrafiltration and reducing episodes of uncontrolled fluid overload has been previously demonstrated in general peritoneal dialysis patients, and recently confirmed in a meta-analysis [14].

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**Table 1. Baseline demographic characteristics**

<table>
<thead>
<tr>
<th>Age (years)</th>
<th>55 ± 14</th>
<th>61 ± 13</th>
<th>0.15</th>
</tr>
</thead>
<tbody>
<tr>
<td>Women</td>
<td>4 (18.2%)</td>
<td>10 (32.3%)</td>
<td>0.35</td>
</tr>
<tr>
<td>Body weight (kg)</td>
<td>62.9 ± 10.3</td>
<td>63.3 ± 14.5</td>
<td>0.89</td>
</tr>
<tr>
<td>Serum albumin (g/L)</td>
<td>34.0 ± 6.0</td>
<td>31.9 ± 5.3</td>
<td>0.19</td>
</tr>
<tr>
<td>Vintage of dialysis (years)$^b$</td>
<td>2.2 (0.9–3.3)</td>
<td>1.8 (1.1–3.3)</td>
<td>0.73</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>12 (54.5%)</td>
<td>21 (67.7%)</td>
<td>0.40</td>
</tr>
<tr>
<td>Primary glomerular disease</td>
<td>4 (18.2%)</td>
<td>7 (22.6%)</td>
<td>0.75</td>
</tr>
<tr>
<td>Number of exchanges daily</td>
<td>3.4 ± 0.5</td>
<td>3.4 ± 0.5</td>
<td>0.87</td>
</tr>
</tbody>
</table>

**Peritoneal transport status$^c$**

| High | 5 (22.7%) | 5 (16.1%) | 0.18 |
| High-average | 3 (13.6%) | 13 (41.9%) |
| Low-average | 11 (50%) | 10 (32.3%) |
| Low | 2 (9.1%) | 2 (6.5%) |
| Anuria | 13 (59.0%) | 18 (58.1%) | 1.00 |
| Residual renal function (mL/min/1.73 m$^2$)$^b$ | 0 (0–2.3) | 0 (0–3) | 0.55 |
| Original number of 1.5% glucose peritoneal dialysis exchange per day | 2.0 ± 1.0 | 1.7 ± 1.0 | 0.25 |
| Original number of 2.5% glucose peritoneal dialysis exchange per day | 1.3 ± 1.3 | 1.7 ± 1.1 | 0.30 |
| Initial peritoneal fluid white cell count/mm$^3$ | 5779 ± 4980 | 5534 ± 6348 | 0.88 |

$^a$Plus–minus values are mean ± SD unless otherwise indicated.

$^b$Median (interquartile range) values.

$^c$Missing data in one patient for each group.

**Table 2. Causative organisms of peritonitis**

| Gram-positive only | 10 (45.5%) | 16 (51.6%) |
| Gram-negative only | 8 (36.4%) | 10 (32.3%) |
| Streptococcus | 5 (22.7%) | 9 (29.0%) |
| Staphylococcus aureus | 4 (18.2%) | 2 (6.5%) |
| Coagulase negative staphylococci | 2 (9.1%) | 5 (16.1%) |
| \textit{Pseudomonas aeruginosa} | 4 (18.2%) | 3 (9.7%) |
| \textit{Escherichia coli} | 1 (4.5%) | 4 (12.9%) |
| \textit{Klebsiella pneumoniae} | 2 (9.1%) | 2 (6.5%) |
| Polymicrobial | 4 (18.2%) | 4 (12.9%) |
| Culture negative | 3 (13.6%) | 2 (6.5%) |
Given the frequent ultrafiltration problem during acute peritonitis, the benefit of icodextrin should be expected to be augmented in the setting of peritonitis. We observed such benefit of icodextrin in fluid control, but the use of icodextrin did not translate into better peritonitis resolution as reflected by the peritoneal dialysate white cell count. Primary cure rate, relapse rate and mortality of peritonitis were also not affected by icodextrin use.

Acute peritonitis in peritoneal dialysis patients can markedly jeopardize net ultrafiltration capacity when glucose solution is used. Transient increase in small solute clearance, similar to those of rapid transporters, is believed to cause enhanced rate of glucose absorption and thus decreased peritoneal transcapillary ultrafiltration rate. Furthermore, peritonitis tends to aggravate dialyze protein loss, and peritoneal fluid absorption rate is often increased during peritonitis. In clinical practice, therapeutic maneuvers for impaired peritoneal ultrafiltration during peritonitis include empiric use of diuretic, advice on oral fluid restriction and increased use of hypertonic exchanges. A better alternative of icodextrin treatment has been confirmed in our randomized controlled trial. Here we show that icodextrin led to significantly less requirement of hypertonic exchanges. These findings have clinical implications because patients in the control group, on the contrary, showed significant weight gain even with extra hypertonic exchanges. Over one-third of the patients assigned to control treatment (and none in the icodextrin group) required additional hypertonic exchanges, although our unblinded trial design could have influenced the clinicians’ decision in prescribing hypertonic exchanges. Despite the possibility of ascertainment bias, the significant net body weight gain in the control treatment group suggests a genuine beneficial effect of icodextrin. It is therefore plausible to postulate that icodextrin can abrogate the adverse ultrafiltration effect of acute peritonitis.

Drawbacks of the present study are the crude measurement of fluid and extracellular volume; we relied on body weight and the clinical need of hypertonic exchanges to reflect the fluid status. Ideally, dual-energy X-ray absorptiometry and body mass composition monitoring should be used. Caution should be heeded in drawing conclusion from our study with open-label design. One could argue that observer bias, as stated before, could have affected the use of hypertonic exchanges. However, the effect of open-label treatment on the...
peritoneal fluid white cell count on Day 3 should have been negligible. Another potential limitation of the study is that our study is not powered to address the hard clinical outcomes such as all-cause or peritonitis-related mortality. Long-term outcomes including residual renal function loss or peritoneal membrane preservation were also not monitored. Peritoneal dialyze white cell count, the primary outcome in this study, was measured from the first bag of effluent drained out in the morning. Although the drained volume differed between glucose-based dialyze and icodextrin, it should not affect the white cell count concentration after a standard dwell time that lasts for more than 6 hours. Finally, one may also question the external validity of our study because we only recruited patients on continuous ambulatory peritoneal dialysis and without pre-existing icodextrin use.

**CONCLUSION**

Icodextrin use has better efficacy than glucose-based dialysis solution in managing ultrafiltration problem during peritonitis complicating continuous ambulatory peritoneal dialysis. Besides improved fluid control, nonetheless, we could not demonstrate additional benefit of sparing glucose exposure. In particular, the primary outcome of peritoneal dialyze white cell count on Day 3 was not significantly different between icodextrin and conventional glucose-based dialysis solution treatment. In summary, our findings support the use of icodextrin during acute peritonitis mainly for the purpose of improved fluid control.

**ACKNOWLEDGEMENTS**

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**CONFLICT OF INTEREST STATEMENT**

None declared.

**REFERENCES**


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