Numerical Investigation of Ultrafiltration Profiles in Peritoneal Dialysis with Residual Icodextrin in Blood

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Abstract

Icodextrin (ICO) has better biocompatibility and an improved ultrafiltration profile in long-dwell peritoneal dialysis compared to those of glucose. However, the long-term repeated use of a single ICO osmotic agent may cause a change in the peritoneal transport characteristics, leading to a reduction in the ultrafiltration profile. Many studies have shown that such a reduction can be quite significant in some patients. In this study, the factors responsible for this decline are investigated via a series of numerical simulations. The peritoneal transport characteristics and ultrafiltration profile are predicted using a three-pore model. To account for the continuous absorption of ICO from the abdominal cavity during peritoneal dialysis, the three-pore model is modified to accommodate a non-constant concentration of ICO in blood. The simulation results show that the presence of residual ICO in blood results in poorer ultrafiltration behavior. Long-duration and repeated use and exposure to ICO result in a residual concentration of ICO in blood, which changes the mesothelial tissue around the blood capillaries in the peritoneal membrane and causes a reduction in ultrafiltration performance.

Keywords: Three-pore model, Peritoneal dialysis, Icodextrin, Ultrafiltration

1. Introduction

Peritoneal dialysis, in which the peritoneum in the patient’s abdomen is used as a membrane across which fluids and dissolved substances from the blood are exchanged, is an effective treatment for patients with end-stage renal disease or other chronic kidney diseases. Traditionally, peritoneal dialysis is performed using glucose as the osmotic agent. However, glucose has a number of practical disadvantages. For example, glucose has a small molecular size, and therefore diffuses rapidly into human blood. As a result, the osmotic gradient quickly dissipates, resulting in poor (or even negative) ultrafiltration during long dwells. In practice, this is a serious problem since many dialysis patients have high or higher-than-average peritoneal membrane transport characteristics, and thus the osmotic gradient dissipates rapidly irrespective of the dialysate solution used [1]. This therapeutic failure can be overcome to a certain extent by reducing the dwell time or increasing the glucose concentration. However, in both cases, the exposure of the patient to glucose is increased and thus the risk of peritoneal damage or systemic metabolic disturbance is also increased [2-4]. Consequently, various alternative osmotic agents for peritoneal dialysis have been proposed, including icodextrin (ICO), amino acid, and taurine [5]. ICO comprises a polydisperse mixture of high- molecular-weight, water-soluble glucose polymers. Most ICO polymers (> 85%) have a molecular weight of between 1638 and 45000 daltons, with only 6% having a molecular weight of less than 1638 daltons. ICO achieves a sustained ultrafiltration profile in long dwells as a result primarily of colloidal osmotic pressure [6]. Due to its colloidal properties, the osmotic pressure of ICO is lower than that of glucose-based peritoneal dialysis solutions. However, the ultrafiltration profile of ICO is three to five times more efficacious than that of glucose over long dwells in clinical experiments [7].

In the present study, the peritoneal transport characteristics and ultrafiltration profiles of ICO are simulated using a modified version of the three-pore model established by Rippe et al. in 1991 [8]. The three-pore model is computationally straightforward. However, its simplicity comes at the high cost of computation [9]. The three-pore model is based on the membrane model [10], with the transport restricted factor calculated in accordance with basic pore theory [11,12]. In general, the transport phenomena in peritoneal dialysis are governed by the principles of thermodynamics. The basic concepts and mathematical theory of peritoneal dialysis were reviewed by Wanieowski in 2006 [10].

Rippe and Levin [13] used the three-pore model to investigate the ultrafiltration profiles of ICO-based and glucose-based peritoneal dialysis solutions. In the three-pore model, the ICO concentration in the blood is assumed to be

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constant. However, in practice, ICO is absorbed continuously from the abdomen cavity during peritoneal dialysis, resulting in an increase in the ICO concentration in the blood. Furthermore, ICO may remain in the blood for as much as 3 to 7 days following treatment. Therefore, to simulate the peritoneal transport characteristics and ultrafiltration profile of ICO, the present study modifies the three-pore model to take into account a non-constant ICO concentration in blood and considers three dialysis scenarios, namely (1) patients with no previous exposure to ICO, (2) patients with a low ICO concentration in blood, and (3) patients with a high ICO concentration in blood. The simulation model used in this study only addresses the fluid dynamics after one acute use of one bag of ICO, not long-term repeated use.

2. Methods

In modeling the heteroporous structure of the peritoneal membrane, it was assumed that the membrane contains pores of three different types, namely large pores with a radius of around 250 ~ 300 Å, small pores with a radius of approximately 40 ~ 50 Å, and ultra-small pores with a radius of approximately 2 ~ 4 Å. The large pores permit the transport (exchange) of macromolecules (of the size of albumin and larger) via convective flow, while the small pores provide the main route for the exchange of small and medium-sized molecules via diffusion and convection. Finally, the ultra-small pores are permeable only to water. In the simulations, it was assumed that the water content of the ICO agent flows through the small and ultra-small pores osmotically. Furthermore, due to the relatively small number of ultra-small pores compared to that of small and large pores, the hydraulic conductivity of the ultra-small pores was ignored. The number of equivalent pores can be obtained by analyzing the fluid and solute transport in peritoneal dialysis. The peritoneal dialysis capacity of the patient was evaluated using a mathematical model based on the three-pore model and data selected due to their clinical availability [8,10,13,14]. Finally, the differential equations of the three-pore model were integrated using the fourth-order Runge-Kutta algorithm.

2.1 Parameter selection

The simulations performed in this study were based on modifying a few parameters given by Rippe and Levin [13] for the three-pore model. In implementing the three-pore model, the PS (permeability-surface area coefficient or mass transfer area coefficient) value for glucose was increased from 9.0 ml/min to 15.4 ml/min [8], whereas that for sodium was decreased from 16.8 ml/min to 6.0 ml/min [13]. Furthermore, the dextrin clearance via the peritoneal cavity was set to (PS+0.8) ml/min to account for the transcapillary clearance and the clearance to the peritoneal tissues (~0.8 ml/min).

ICO is a polydisperse preparation, with 5 to 6% of the mass spectrum in the 0.18 to 1.6 kD molecular weight (MW) range, around 80% of the mass spectrum in the 10 to 30 kD MW range, and approximately 8 to 9% of the mass spectrum in the 45 kD MW or more range [13]. To mimic this spectrum, the present simulations considered eight different mass fractions of ICO, as shown in Table 1. The molecular radii of the dextrin polymers (\(a_i\)) were computed as [13]:

\[
a_i = 0.486 (MW)^{0.385}
\]  

Table 1. Concentration percentages and transport parameters of 7.5 % icodextrin in 2050 ml of dialysate solution (note that the molecular weight (MW) and percentage data are chosen specifically to mimic the icodextrin mass spectrum reported in [13].)

<table>
<thead>
<tr>
<th>MW(kD)</th>
<th>50</th>
<th>30</th>
<th>20</th>
<th>10</th>
<th>3</th>
<th>1</th>
<th>0.53</th>
<th>0.19</th>
</tr>
</thead>
<tbody>
<tr>
<td>%</td>
<td>9</td>
<td>30</td>
<td>34</td>
<td>15</td>
<td>6</td>
<td>3</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>(C_D) (mmol/l)</td>
<td>0.14</td>
<td>0.75</td>
<td>1.275</td>
<td>1.125</td>
<td>1.5</td>
<td>2.25</td>
<td>2.83</td>
<td>3.95</td>
</tr>
<tr>
<td>(\sigma) (small pore)</td>
<td>0.903</td>
<td>0.771</td>
<td>0.653</td>
<td>0.463</td>
<td>0.221</td>
<td>0.103</td>
<td>0.657</td>
<td>0.032</td>
</tr>
<tr>
<td>(\sigma) (large pore)</td>
<td>0.065</td>
<td>0.045</td>
<td>0.034</td>
<td>0.020</td>
<td>0.008</td>
<td>0.004</td>
<td>0.002</td>
<td>0.001</td>
</tr>
<tr>
<td>(A_i/A_o)</td>
<td>0.002</td>
<td>0.015</td>
<td>0.037</td>
<td>0.105</td>
<td>0.289</td>
<td>0.472</td>
<td>0.565</td>
<td>0.685</td>
</tr>
<tr>
<td>(PS) (ml/min)</td>
<td>0.004</td>
<td>0.03</td>
<td>0.08</td>
<td>0.3</td>
<td>1.3</td>
<td>0.0</td>
<td>5.1</td>
<td>9.0</td>
</tr>
</tbody>
</table>

The dextrin PS coefficient was evaluated in accordance with the theory of restricted diffusion (and convection) across membranes with cylindrical pores. Table 1 shows the calculated values of the concentration and transport parameters for each of the considered mass fractions given 7.5% ICO in 2050 ml of dialysate solution.

2.2 Non-constant icodextrin concentration in blood

In the original three-pore model, the solute concentrations in the blood are assumed to be constant. However, in practice for conservation of mass, the concentration of ICO in the blood changes over time during peritoneal dialysis as a result of the continuous absorption of ICO from the abdominal cavity. The simulations performed in this study were based on a modified version of the three-pore model. From a previous study [6], Fig. 1 presents the typical plasma ICO profile over a period of 0 ~ 168 hours. The increase (decrease) rate of ICO concentration in blood can therefore be calculated. The rate is used to calculate the ICO concentration in blood. The ICO composition shown in Table 1 was used. The peak ICO...
concentration occurs after 12.7 hours. Furthermore, the ICO concentration remains above the baseline value for approximately 7 days. The magnitude of the plasma volume is assumed to be 4 L when calculating the ICO concentration in blood. The impact of amylase activity in plasma on the ICO profile is difficult to determine. Based on the absorption curve in Fig. 1, the absorption rates of the eight molecular-weight ICO polymers considered in the present study are shown in Table 2. Figure 2 presents the simulated ultrafiltration profiles obtained under the assumptions of a constant ICO concentration and various non-constant ICO concentrations, respectively. For the constant plasma level case (i.e., zero ICO concentration), the simulation results agree well with those of Rippe and Levin [13]. For the non-constant plasma level cases, the values shown in Fig. 1 were used as the inputs in the three-pore model. It should be noted that in the simulations done by Rippe and Levin [13], dextrin clearance was set as the PS calculated directly from the three-pore model plus 1.2 ml/min to account for absorption of ICO to the tissue. The ultrafiltration profiles for non-constant ICO concentrations are lower than that for a constant ICO concentration. Furthermore, the agreement between the simulation results and the calculated data presented in [13] improves as the value of PS decreases. The PS value was decreased from (PS+0.8) to (PS+0.6) to make the simulation data match the calculated data.

Table 2. Absorption rates of icodextrin polymers with various molecular weights.

<table>
<thead>
<tr>
<th>MW (kD)</th>
<th>Absorption rate (mmol/l/min)</th>
</tr>
</thead>
<tbody>
<tr>
<td>50</td>
<td>$5 \times 10^4$</td>
</tr>
<tr>
<td>30</td>
<td>$2.84 \times 10^4$</td>
</tr>
<tr>
<td>20</td>
<td>$4.83 \times 10^4$</td>
</tr>
<tr>
<td>10</td>
<td>$4.26 \times 10^4$</td>
</tr>
<tr>
<td>3</td>
<td>$5.68 \times 10^4$</td>
</tr>
<tr>
<td>1</td>
<td>$8.52 \times 10^4$</td>
</tr>
<tr>
<td>0.53</td>
<td>$1.07 \times 10^4$</td>
</tr>
<tr>
<td>0.19</td>
<td>$1.49 \times 10^4$</td>
</tr>
</tbody>
</table>

Figure 2. Simulated ultrafiltration profiles for constant and non-constant icodextrin concentrations. The constant plasma level contains no icodextrin. Cases with non-constant plasma level use values shown in Figure 1 as the inputs in the three-pore model.

2.3 Residual icodextrin concentration in blood

ICO-based dialysate solution has a higher molecular weight than that of glucose-based dialysate solution and therefore leads to improved ultrafiltration performance in both short- and long-dwell peritoneal dialysis treatments. Rippe and Levin [13] used the three-pore model to simulate the ultrafiltration profiles of both ICO-based and glucose-based peritoneal dialysis solutions assuming no ICO concentration in blood. In other words, the effects of ICO in blood on the ultrafiltration performance were not considered. The simulations performed in the present study consider both patients with no previous exposure to ICO and patients with previous exposure to 7.5% ICO in 2050 ml of dialysate solution, with the effects of ICO concentration in blood taken into account. The concentrations of 7.5% ICO solution corresponding to each considered mass fraction are shown in Table 1. The blood of patients with previous exposure to 7.5% ICO in 2050 ml of dialysate solution, contains certain ICO residues. The simulations consider two ICO concentration residues in blood, namely low concentration and significant concentration. In the simulations, the low and significant concentrations were set as 5 and 20% of the 7.5% ICO dialysate solution concentration, respectively. As shown in Fig. 3, for ICO concentrations in blood greater than 20%, the simulated ultrafiltration profile deviates significantly from the clinical profile in the first two hours of the dialysis treatment since the calculated drained dialysate volume for the case of a 30% residual concentration was obtained under the initial dialysate volume of 2050 ml. However, in practice, peritoneal dialysis removes excess water and waste from the body, and thus the curve of the drained volume is higher than that of the initial dialysate volume with normal ultrafiltration profiles. Thus, the upper bound on the ICO concentration in blood was deliberately set as 20% of the 7.5% ICO dialysate solution concentration. The simulations considered the following three dialysis scenarios:

Case 1: Patients with no previous exposure to dextrins (these results can be compared with those presented by Rippe and Levin [13]).

Case 2: Patients with a low concentration of ICO in their blood plasma.

Case 3: Patients with a significant concentration of ICO in their blood plasma.

Figure 3. Simulated ultrafiltration profiles for various concentrations of residual icodextrin concentration in blood.
3. Results

3.1 Effect of combined glucose and icodextrin dialysis on ultrafiltration profile

Figure 4 presents the simulated ultrafiltration profiles for cases 1 to 3 given a mixed dialysate solution comprising 1.36% glucose-based solution and 7.5% ICO-based solution. The simulation results for case 1 agree well with those in [13]. The values of the drained volume for cases 2 and 3 are lower than those for case 1, for which no residual ICO concentration in blood was assumed. A series of simulations were performed using mixed dialysate solutions comprising various concentrations of glucose and ICO, respectively. It was found that the ultrafiltration behavior was highly sensitive to the composition of the mixed solution. In general, a mixed solution comprising 1.36% glucose and 7.5% ICO was found to yield a good ultrafiltration effect over both short and long dwell times. As a result, the remaining simulations were performed with the dialysate agent comprising 1.36% glucose and 7.5% ICO.

![Figure 4](image)

Figure 4. Simulated ultrafiltration profiles for combined dialysate solution of 1.36% glucose and 7.5% icodextrin given various residual icodextrin concentrations in blood.

3.2 Effect of direct lymphatic absorption on ultrafiltration profile

During peritoneal dialysis, the dialysate solute is absorbed from the abdominal cavity via direct lymphatic absorption ($L_D$), tissue absorption, and varying degrees of capillary absorption. The parameter $L_D$ refers to the peritoneal lymph flow, which is fixed to 0.3 mL/min in Ripple’s model [13]. This value may change due to variation in intra-peritoneal pressure or other factors. Note that in the present study, the effect of the tissue absorption of the solutes is reflected within the values calculated for the PS parameter. Figures 5(a)-5(c) show the effect of direct lymphatic absorption on the ultrafiltration profiles for cases 1, 2, and 3, respectively. For case 1 and $L_D = 1.0$ mL/min, the ultrafiltration is insignificant, a result similar to that in [13]. Compared to case 1, cases 2 and 3 show more reduction in drained volume under a given $L_D$. Overall, the results in Fig. 5 show that for short-dwell dialysis treatment (about 4-6 hours), the residual ICO concentration in blood has no significant effect on the ultrafiltration behavior. However, for longer-dwell dialysis treatment (over 12 hours), even minor changes in the lymphatic adsorption rate have a significant effect on the ultrafiltration behavior for all three cases considered.

![Figure 5](image)

Figure 5. Simulated ultrafiltration profiles given various direct lymphatic absorption coefficients: (a) Case 1: Patients with no previous exposure to dextrins; (b) Case 2: Patients with a low concentration of icodextrin in their blood plasma; and (c) Case 3: Patients with a significant concentration of icodextrin in their blood plasma.

3.3 Effect of vascular surface area on ultrafiltration profile

In the three-pore model, the blood capillary walls are assumed to be the only barrier because the blood capillaries constitute a major barrier in the exchange of solutes and fluids through the peritoneum membrane. In clinical cases of peritonitis, an increase in the vascular surface area occurs. The increased vascular surface area can cause abnormal variations
in the drained volume during dialysis. In both clinical experiments and simulations, the blood capillary walls have a significant effect on the dialysis process because the blood capillaries are the major barrier in the peritoneal dialysis. In the present study, the effect of the capillary walls is modeled by relating the area parameter \( (a_0/\Delta x) \) with the vascular surface area, where \( a_0 \) is the nominal surface area of pores and \( \Delta x \) is the length of the diffusion path of the capillary walls. In the pore model, the value of \( a_0/\Delta x \) affects both the membrane ultrafiltration coefficient \( (LpS) \) and the permeability surface area \( (PS) \). Both parameters have a significant effect on the peritoneal dialysis transport process. In simulating the effects of an increased vascular surface area on the ultrafiltration behavior, the vascular surface area is defined as \( (a_0/\Delta x)^n \), where \( n \) is a scaling factor with values in the range of 0.5 to 2.0.

Figures 6(a)-6(c) present the simulated ultrafiltration profiles for cases 1, 2, and 3, respectively, for various vascular surface areas. In general, the results show that for short-dwell dialysis treatment (i.e., less than 720 minutes), the ultrafiltration performance improves with increasing vascular surface area, with the increases for cases 2 and 3 lower than that for case 1. However, for dwell times beyond 720 minutes, a fall in drain volume was found for cases 2 and 3 with a high vascular surface area. Figures 7(a) and 7(b) present the simulated ultrafiltration profiles for cases 1-3 for scaling factors of \( n = 1.5 \) and \( n = 2.0 \), respectively. The results confirm that for patients with residual ICO in the blood, an increase in the vascular surface area leads to a poor ultrafiltration profile. This effect is similar to that seen at high plasma colloid osmotic pressure reported by Venturoli et al [14].

4. Discussion

In the present simulations, the effect of a non-constant concentration of ICO is reproduced by adjusting the value of PS. Similarly, in previous studies [8,15,16], the PS values of various solutes were modified as required to improve the agreement between the simulated ultrafiltration profiles and the clinical data. In practice, extra absorptions or eliminations by the abdomen tissues cause a natural variation in the PS values during peritoneal dialysis [17-19]. However, due to the complex structure of the peritoneum, it is difficult to estimate the PS values exactly using the pore model [10]. Therefore, case should be taken in interpreting the present simulation results. Ideally, the simulation results should be compared with the equivalent clinical data in order to confirm the numerical findings.

It was shown in [6] that ICO may remain in the bloodstream for up to 3 to 7 days following administration. In [20], it was shown that the metabolism of ICO in nonuremic rats is much higher than that in peritoneal dialysis patients. Thus, in patients with end-stage renal disease or other forms of chronic kidney disease, there is a strong probability that ICO will remain in the blood following dialysis treatment. The simulation results presented in this study suggest that this residual ICO causes a decline in the ultrafiltration profile.

It is well known that the direct lymphatic absorption rate varies between individuals. In the present study, the direct lymphatic absorption rate in the three-pore model was assigned a default value of 0.3 ml/min in order to be consistent with clinical data. The simulation results showed that an increasing direct lymphatic absorption rate reduces the ultrafiltration profile. Even minor changes in the direct lymphatic absorption rate can hinder the efficiency of the peritoneal dialysis treatment. Note that an increased residual ICO concentration will cause increased re-absorption of fluid via the Starling...
forces (an increased plasma colloid osmotic pressure; Venturoli et al. [14] showed the importance of the plasma colloid osmotic pressure for the ultrafiltration behavior of ICO), not an increased rate of lymphatic absorption rate.

The present results show that an increased vascular surface area has no adverse effect on the ultrafiltration profile in short-dwell dialysis treatment using ICO dialysate solution. As a result, ICO is a suitable choice for short-dwell peritoneal dialysis (for example, continuous ambulatory peritoneal dialysis for less than 6 hours). However, for long-dwell dialysis treatment using ICO, the ultrafiltration performance declines with increasing vascular surface area. In other words, residual ICO in the blood stream results in a significant reduction in the ultrafiltration profile. The failure of ICO may be due to changes in the interstitium for the case of long-term repeated use of ICO, which may cause reductions in the osmotic conductance to ICO. Patients with a high vascular surface area have theoretical advantage when using ICO as an agent.

In previous studies of long-term repeated use of peritoneal dialysis [21,22], a significant reduction in the ultrafiltration profile was observed after several months. Moreover, in a study of automatic peritoneal dialysis (APD) patients [22], it was shown that the daytime ultrafiltration volume after 12 months of dialysis treatment using 7.5% ICO was only 204 ± 95 ml. This value is much lower than the simulated value reported by Rippe and Levin [13] and is also much lower than the value measured in the long-term dwell study of Ho-dac-Pannekeet et al. [19]. The discrepancy between the two sets of results can be attributed to two main factors. (1) ICO has high molecular weight; as a result, the presence of residual ICO in the bloodstream leads to a reduction in the ultrafiltration volume. (2) The peritoneal transport parameters ($L_pS$ and PS) are affected by structural changes of the peritoneum. In practice, the long-term success of peritoneal dialysis depends on the ability of the peritoneum to maintain its function as a dialyzing membrane despite changes in the mesothelial tissue surrounding the blood capillaries [19]. In animal studies [23,24], the mesothelial cell populations of mice exposed to 7.5% ICO showed a significant loss in density and an increased size. Such changes in the mesothelial structure around the human peritoneum prompt a reduction in the values of $L_pS$ and PS. Thus, a reduction in the ultrafiltration profile occurs (see Fig. 6(c)) for example, with $n = 0.5$.

ICO has better biocompatibility than that of glucose and results in an improved ultrafiltration profile in long-dwell dialysis treatment. However, long-duration and repeated use and exposure to ICO results in a residual concentration of ICO in the blood, which changes the mesothelial tissue around the blood capillaries in the peritoneum membrane and causes a reduction in the ultrafiltration performance. Accordingly, various peritoneal dialysis solutions and or procedures have been proposed. For example, Finkelstein et al. [25] and Dousdampanis et al. [26] showed that the adverse effects of residual ICO in the bloodstream can be reduced by performing dialysis twice-daily using standard peritoneal dialysis solutions containing 2.5% glucose and 7.5% ICO solution alternatively.

5. Conclusion

This study used a modified three-port model to investigate ultrafiltration profiles in peritoneal dialysis with residual ICO in blood. In contrast to the constant concentration of the ICO commonly used in the literature, the present model accounts for a non-constant concentration of ICO. The simulation results show that the presence of residual ICO in blood results in poorer ultrafiltration behavior. In addition, it is shown that variations in the mesothelial structure around the peritoneum blood capillaries prompt a reduction in the membrane ultrafiltration coefficient ($L_pS$) and permeability surface area (PS), and therefore cause a reduction in the ultrafiltration profile. In the short-dwell use of ICO for dialysis treatment, an increased vascular surface area improves the ultrafiltration profile. However, in long-dwell dialysis treatment using ICO, the ultrafiltration performance decreases with increasing vascular surface area. Long-duration and repeated use and exposure to ICO results in a residual concentration of ICO in blood, which changes the mesothelial tissue around the blood capillaries in the peritoneal membrane and causes a reduction in the ultrafiltration performance. Further modifications of the three-pore model to match clinical data will be considered in future studies.
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