Role of Albumin Peritoneal Dialysis for Bilirubin Removal after Complicated Liver Transplant

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ABSTRACT
Background: Hyperbilirubinemia has been implicated to have nephrotoxic and hepatotoxic effects. Thus, removal of excessive bilirubin in patients with severe jaundice and renal failure could potentially benefit the recovery of hepatic and renal function. In experimental animal and anecdotal reports in humans, albumin containing peritoneal dialysis (PD) may be successful in removing bilirubin.

Methods: We used albumin-enriched (4 g/L to 8.4 g/L) PD in a patient with primary hepatic allograft dysfunction with severe jaundice and renal failure.

Results: Plasma and peritoneal concentrations of bilirubin (total/direct) before initiation of PD were 23.9/14.8 mg/dL and 4.1/2.5 mg/dL, respectively. After the addition of 8.4 g of albumin per liter of PD fluid, the concentrations were 32.4/21.3 mg/dL and 0.1/0.1 mg/dL, respectively.

Conclusions: There was no significant benefit of this therapy in improving hyperbilirubinemia. However, a higher concentration of albumin in PD fluid might have been more effective.

INTRODUCTION
Mild to moderate hyperbilirubinemia frequently occurs within the first postoperative week of liver transplantation. This is due to functional cholestasis, a temporary and reversible state that usually requires no specific therapy. However, severe jaundice with serum bilirubin levels >30 mg/dL usually indicates severe allograft dysfunction and is frequently associated with hemodynamic instability, encephalopathy, and pulmonary and renal failure. Uncomplicated jaundice per se does not cause multiple organ failure, however it may be an important contributing factor in the presence of other factors such as infections, transplant rejection, and surgical complications. In vitro studies have...
demonstrated multiple toxic effects of bilirubin on cell respiration, membrane integrity, and transport functions. Although the primary cause of renal failure in hepatorenal syndrome is intense renal vasospasm leading to renal hypoperfusion, it is thought that toxic tubular damage as a result of the accumulation of bilirubin and bile salts within the tubules may also play a role. Moreover, hyperbilirubinemia also has been implicated to impair immune response and have neurotoxic and hepatotoxic effects. In view of these toxic effects, it would seem prudent to remove the excessive bilirubin and bile salts. For this, various therapies have been used, including phototherapy, plasmapheresis, and plasma separation with bilirubin adsorption, which, in selected cases, have led to successful removal of bilirubin and clinical improvement. A few animal studies and anecdotal reports in humans suggest that peritoneal dialysis may be an attractive route for the removal of bilirubin.

This article reports a case of hepatic allograft dysfunction with severe jaundice and an attempt to remove bilirubin via albumin-enriched peritoneal dialysis.

**CASE HISTORY**

A 64-year-old white man with end-stage liver disease secondary to nonalcoholic steatohepatitis received an orthotopic liver transplant. He had significant blood loss intraoperatively, requiring multiple transfusions. His postoperative course was complicated by hepatic artery thrombosis for which re-exploration was performed, which led to bile duct injury that necessitated biliary drain placement. Because of hemodynamic instability and respiratory failure, the patient had a prolonged stay in the intensive care unit. His hospital course was further complicated with multiorganism sepsis including multidrug-resistant pseudomonas, hepatic dysfunction, and renal failure caused by hemodynamically mediated acute tubular necrosis that required renal replacement. Although the patient was in a positive fluid balance with a significant generalized edema and ascites, fluid removal was challenging because of his hemodynamic instability even with continuous venovenous hemofiltration. As a result, the patient was initiated on peritoneal dialysis (PD), which provided continuous dialysis and fluid removal, as well as the possibility of removal of some of the excessive bilirubin that had accumulated because of his hepatic allograft failure.

The patient’s PD prescription constituted a total of 12 liters of 1.5% Dianeal solution over 24 hours, with 1-liter exchange every 2 hours. Bilirubin removal was studied on 2 different concentrations of albumin in the PD fluid.

<table>
<thead>
<tr>
<th>Serum bilirubin (mg/dL) (total/conjugated)</th>
<th>Peritoneal fluid bilirubin (mg/dL) (total/conjugated)</th>
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<tbody>
<tr>
<td>Day 0: Pre PD initiation 23.9/14.8</td>
<td>4.1/2.5</td>
</tr>
<tr>
<td>Day 1: PD fluid with 4.2 g albumin/L 29/19.1</td>
<td>1.6/0.9</td>
</tr>
<tr>
<td>Day 2: PD fluid with 8.4 g albumin/L 32.4/21.3</td>
<td>0.1/0.1</td>
</tr>
<tr>
<td>Day 3: No albumin in PD 30.4/19.3</td>
<td>Not available</td>
</tr>
<tr>
<td>Day 4: No albumin in PD 29.9/19.2</td>
<td>2.6/1.4</td>
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Albumin was added (4.2 g/L of PD fluid on day 1, and 8.4 g/L of PD fluid on day 2) to 1.5% Dianeal during the first 2 days, whereas albumin-free Dianeal was used for the subsequent 2 days to determine if the addition of albumin in the first 2 days had increased bilirubin removal. Plasma and peritoneal bilirubin concentrations are shown in Table 1. The authors did not find any significant bilirubin removal with PD with or without the addition of albumin.

The patient was diagnosed with primary allograft nonfunction and a liver biopsy showed mild cholestasis. His hospital course was further complicated by an acute myocardial infarction, acute pancreatitis, ventilator-associated pneumonia, and multiorganism sepsis, which eventually led to his death.

DISCUSSION

Hyperbilirubinemia is an independent risk factor for increased mortality. In the 1940s, it was shown that bilirubin formed complexes with albumin, each molecule of albumin binding 2 molecules of bilirubin at pH 7.4, and that 1 gram of albumin binds 15 mg of bilirubin in vitro.5 These observations were followed by experimental evidence suggesting that protein enriched peritoneal dialysis increases the clearance of bilirubin in rats suffering from obstructive jaundice.6 This was further supported by case reports from Grollman and Odell7 and Hobolth and Devantier,8 demonstrating that measurable amounts of indirect as well as direct bilirubin could be extracted by PD when the dialyzing fluid contained albumin (4 g/dL to 5 g/dL). These preliminary reports prompted us to use albumin-enriched PD, with the goal to provide the patient with renal replacement therapy and the additional benefit of improving hyperbilirubinemia. Contrary to the earlier observations and consistent with the reports of Shoshkes et al9 and Krebs and Flynn,10 we did not find PD an effective therapy for the removal of bilirubin. The discrepancy may be the result of the lower concentration of albumin we used in our PD solution.

Our results suggest that PD with the addition of albumin at the concentration used in our patient (4.2 g/L to 8.4 g/L) does not result in any significant bilirubin removal. Further studies with higher albumin concentration (up to 50 g/L) are needed to resolve this important clinical question. Moreover, several non-cell-based liver support systems are currently undergoing clinical trials. The Liver Dialysis Unit, (HemoTherapies, San Diego, CA) a charcoal-based, blood detoxification system has been approved by FDA for the treatment of drug toxicity and liver failure.11 However, in small controlled trials it has not demonstrated a survival benefit in either acute or chronic liver disease.12 The Molecular Adsorbent Recycling System (MARS, Teraklin Corporation; Rostock, Germany), also referred to as Extra-corporeal Albumin Dialysis (ECAD) exposes patients’ ultrafiltrate to an albumin-rich solution across a highly permeable membrane. The ultrafiltrate then courses through another cartridge to undergo conventional hemodialysis, thus providing both hepatic and renal support. In 13 patients with chronic liver disease and encephalopathy, applying MARS System improved serum bilirubin, bile acids, and creatinine, but not serum ammonia levels. Moreover, 9 out of 13 (69%) patients demonstrated improvement in both liver and renal function indices.13 In another study of 13 patients with hepatorenal syndrome, treatment with MARS system improved serum bilirubin and creatinine levels in the treated patients (n=8) vs. controls (n=5), with a reduction in mortality from 100% to 75%. However, because of the small number of the patients it did not reach statistical significance.14
REFERENCES


