

Peritoneal Dialysis Clearance of Unconjugated Bilirubin in Children and Neonates

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ABSTRACT

Background: Neonates with unconjugated hyperbilirubinemia are vulnerable to a neurological disorder with devastating permanent sequelae (kernicterus). The two traditional methods to manage these patients are phototherapy and exchange blood transfusion. Peritoneal dialysis is a widely applied therapeutic measure to clear the plasma from its uremic toxins as well some of these exogenous toxins.

Objectives: This study was conducted to measure the peritoneal clearance of unconjugated bilirubin (uB) and thus give a provisional idea of the applicability of peritoneal dialysis in management of neonates with unconjugated hyperbilirubinemia.

Methods: The study included 7 patients (3 children & 4 neonates) who had unconjugated hyperbilirubinemia and were treated with acute peritoneal dialysis for a concomitant renal impairment. Patients were divided into 3 groups according to the underlying pathology. Group I consisted of 2 patients with hepatorenal failure, Group II included 3 neonates with neonatal sepsis and multiorgan failure and Group III was one child and one neonate with unconjugated hyperbilirubinemia due to hemolysis and renal failure from hypotension and shock. Patients were subjected to history taking, complete physical examination and initial investigations to verify the underlying etiology. For all patients the level of uB and urea were measured in the serum at the beginning (P1), end (P2) and mid-dialysis (P), the ascitic fluid (A) at the beginning of dialysis and in the peritoneal fluid at the mid-dialysis (D). The percentile of P2/P1, the ratio of, D/P and A/P and the peritoneal clearance were calculated for both uB and urea.

Results: For urea, the mean percentile ratio of P2/P1 was 55% for D/P was 0.45 and A/P was 0.62. Peritoneal clearance of urea was 26.64 l./hour/1.73 m². For uB P2 increased than P1 in group I, decreased in group III and was variable in group II. The mean ratio of P2/P1 was 135% in group I, 22% in group II and 97% in group III. Ascitic fluid was present only in the 2 cases of group I, the A/P was 0.35. The peritoneal fluid uB (P) was detected in 4 cases (2 in group I & 2 in group II). In these 4 cases the mean D/P ratio of uB was 0.03 and the peritoneal clearance of uB was 1.7 Uhour/1.73 m².

Conclusion: Unconjugated bilirubin can be dialyzed by peritoneal dialysis. Its clearance is about 1/15 that of urea. The high protein content of the peritoneal fluid (ascitic fluid) may improve clearance of unconjugated bilirubin. Further studies are needed to prove efficiency of peritoneal dialysis in the management of neonates with unconjugated hyperbilirubinemia.

INTRODUCTION

Peritoneal dialysis is the method of renal replacement therapy used by approximately 100,000 patients worldwide. Peritoneal dialysis involves the transport of solutes and water across a membrane that separates the blood in the peritoneal capillaries and the

dialysis solution in the peritoneal cavity. The peritoneal membrane that acts as a dialyzer is actually a heteroporous, heterogeneous, semi permeable membrane with a relatively complex anatomy and physiology. During the course of a peritoneal dialysis dwell, three transport processes occur simultaneously.

Solutes *diffuse* down the concentration gradient, the relative hyperosmolarity of the peritoneal dialysis solution leads to *ultrafiltration* of water and associated solutes across the membrane. Water and solutes are constantly *absorbed* from the peritoneal cavity both directly and indirectly into the lymphatic system.

Factors affecting *diffusion* include the concentration gradient, the effective peritoneal surface area, the intrinsic membrane resistance and the molecular weight of the solute concerned. Diffusion in the peritoneal dialysis depends on the peritoneal rather than the blood flow. *Ultrafiltration* depends on the concentration gradient for the osmotic agent, the effective peritoneal surface area, the reflection coefficient for the osmotic agent (i.e. glucose), the hydrostatic pressure gradient and the oncotic pressure gradient. Due to "sieving" of the solute at the peritoneal membrane, it does not move across the membrane in direct proportion to its concentration in blood. The sieving effect is accounted for by the ultrapores. Fluid absorption occurs via the lymphatics at a relatively constant rate of about 1.0-2.0 mL/minute with little or no sieving.

The increasing use of peritoneal dialysis in renal insufficiency calls for a better understanding of its advantages. Hypothermic peritoneal dialysis was studied in the treatment of acute experimental hemorrhagic pancreatitis⁽²⁾. Peritoneal dialysis can efficiently clear uremic toxins as urea (molecular weight = 60) and creatinine (molecular weight = 113). Large molecules as

albumin (molecular weight = 35000) can also pass the peritoneal membrane. Little is known about the efficiency of peritoneal dialysis in the clearance of other endogenous toxins as unconjugated bilirubin (molecular weight = 584.655).

Patients with liver diseases develop ARF secondary to hepatorenal syndrome, various liver diseases like cirrhosis, grade III/IV encephalopathy, fulminant hepatic failure, and obstructive jaundice. In these three groups the factors leading to ARF are volume depletion, gastrointestinal bleed, sepsis, drugs [aminoglycosides and NSAID] along with hyperbilirubinemia. Various types of ARF with contemporaneous liver injury are malaria, sepsis, hypovolemia with ischemic hepatic injury, acute pancreatitis, rifampicin toxicity, paroxysmal nocturnal hemoglobinuria, CuSO₄ poisoning, post abortal, ARF following delivery including HELLP syndrome and of uncertain etiology. ARF associated with liver disease has a high mortality (42.5%)⁽³⁾. Hepatic dysfunction has been associated with renal transplantation⁽⁴⁾. Parasitic infestations known to cause hepatic as well as renal dysfunction includes malaria especially falciparum malaria^(5,6,7) and severe leptospirosis⁽⁸⁾.

AIM OF THE WORK

The aim of this study is to measure the peritoneal clearance of unconjugated bilirubin and thus give a provisional idea of the applicability of peritoneal dialysis in management of neonates with unconjugated hyperbilirubinemia.

PATIENTS AND METHODS

Patients

The invasive nature of peritoneal dialysis did not allow its approval in the study in patients with unconjugated hyperbilirubinemia and normal renal function. This study included 7 patients (3 children & 4 neonates) who had unconjugated hyperbilirubinemia and were treated with acute peritoneal dialysis for a concomitant renal impairment. Due to the limited number of patients who satisfied these criteria in the 3.5 years of the study, statistical data could not be obtained.

Patients were treated in the New Children Hospital, Al-Haram Insurance Hospital, the New Cairo University Hospital and King Khaled General Hospital, Hafr el-Batin K.S. A. from January 1997 to July 2001. All patients (3 children & 4 neonates) received supportive therapy, antibiotics for sepsis as well as acute peritoneal dialysis. All patients died from sepsis or the original hepatic or cardiac disease at different intervals after the study.

Patients were divided into 3 groups according to the underlying etiology of hyperbilirubinemia.

Group I included 2 children; *Case 1*, a female child 4 years old with fulminant hepatitis. *Case 2*, a male child 5 years old with chronic viral hepatitis. Both cases had both liver cell as well as hepatorenal failure.

Group II included 3 neonates (*case 3*, a full term male; *case 4*, a full term female; *case 5*, a preterm female with a gestational age of 29 weeks and a postnatal age of 2

weeks and a uody weight of 1.05 kg). All cases had neonatal sepsis and renal failure as a part of multiorgan failure.

Group III included 2 cases (*case 6*, a child 3.5 years old who received multiple blood transfusions during an open heart surgery for a complex congenital heart disease and *case 7*, a neonate with severe cephalohematoma). Both cases had unconjugated hyperbilirubinemia due to excessive hemolysis and acute renal failure from hypotension and shock.

Methods

Patients were subjected to:

1. Initial assessment

History taking, complete physical examination and initial investigations to verify the underlying etiology. The body surface area (BSA) in meter² was calculated from the body weight (W) in kg and the length (H) in cm using the de-Bois formula.

$$BSA = 0.007184 \times W^{0.425} \times H^{0.325}$$

2. Peritoneal dialysis sessions

Acute peritoneal dialysis was done for all patients. Thirty runs were done with the standard protein free dialysate. Dwell time was 20-40 minutes. Dwell volume was (30-40) mL/kg/run.

3. Initial dialysis parameters

- The level of uB and urea were measured for all patients in the serum at the beginning (P1), end (P2) and the 15th mid-dialysis run (P) and were expressed in mg/dL. The level of unconjugated bilirubin was calculated by the subtraction of the level of direct bilirubin from the level of the total bilirubin.

- The level of uB and urea were measured in the ascitic fluid (A) at the beginning of dialysis in cases with ascites (case 1 & 2) and were expressed in mg/dL.
- The level of uB and urea were measured for all patients in the peritoneal fluid at the mid dialysis (D) and were expressed in mg/dL.
- The total time of dialysis sessions (T) was measured from the beginning of the first run to the end of the 30th run and was expressed in hours.
- The total volume of the drain (V) was measured for all the sessions and was expressed in liters.

4. Calculation of ratios, percentiles and clearance for urea & uB

- The percentile of P2/P1 for both uB and urea was measured in all cases.
- II The ratio DIP for urea was measured in all cases.
 - a The ratio DIP for uB was measured in cases (1-4) with detectable P uB.
 - The ratio Ai? for both uB and urea was measured in cases 1 & 2.
 - The peritoneal clearance for uB was calculated in cases (1-4) with detectable (P) using the equation;

Clearance of a solute = Volume of the dialysis drain x (Dialysate/Plasma level of the solute). As the plasma level is expected to change steadily during the dialysis session the dialysate level of the solute was measured at the mid dialysis and the plasma level was measured simultaneously.

The corrected clearance was calculated using the surface area of the patient and was

expressed as (liter/hour/1.73 m²).

- The corrected peritoneal clearance for urea was calculated in all cases using the same equations.

RESULTS.'

The studied patients had an age range of (31 weeks postconceptional age — 5 years) with plasma urea (95 - 220) mg/dL, plasma unconjugated bilirubin (2.1 - 9.1) mg/dL before dialysis.

For urea, the level of P2 was less than P1 in all cases. P2/P1 urea was (44-78)%, mean 55%. A/P urea was 0.62 in cases 1 & 2. DIP urea was (0.34-0.61) with a mean of 0.45. The peritoneal clearance of urea was (20.22-32.17) mean 26.64 L/hour/1.73 m².

For unconjugated bilirubin, the P2/P1 uB was different in the three studied groups. In the 2 cases of group I, P2 uB increased more than P1 uB, P2/P1 uB was (120-150)%, mean 135%. In the 3 cases of group II, P2 uB was variable compared to P1 uB, P2 uB increased in cases 3 & 4 and decreased in case 5 the P2/P1 uB was (17-136)%, mean 97%. In the 2 cases of group III, the level of P2 uB was less than P1 uB, the P2/P1 uB was (21-23)%, mean 22%.

Ascitic fluid was present only in the 2 cases of group I (case 1 & 2). In these 4 cases the ascitic fluid was dark yellow, A was (0.1-4.1) mg/dL mean (0.25) mg/dL, A/P uB (0.24 & 0.45), mean 0.35. The mid-dialysis peritoneal fluid uB (P) was detected in 4/7 cases (cases 1-4). In these 4 cases D was (0.1-0.5) mg/dL mean (0.25) mg/dL, the D/P uB was (0.025-0.053), mean 0.03. The peritoneal

clearance of uB was calculated in these 4 cases only, with a range of (1.1-2.4) and a mean of 1.7 L/hour/1.73 m².

DISCUSSION

Post-dialysis urea was decreased to about half its predialysis level. In cases 1 & 2 of the group with hepatorenal failure the serum level of unconjugated bilirubin increased in spite of the continuous clearance of uB indicating a continuous rate of uB production exceeding the summation of peritoneal clearance and the natural excretion. The uB does not contribute in the pathogenesis of liver cell failure. During liver failure there is an accumulation of toxic substances secondary to the loss of liver function. In order to eliminate these substances various extracorporeal depuration therapies have been employed. Peritoneal dialysis has a non-significant role in the management of patients with hepatic coma⁽⁹⁾. Recently, Aviles J et al., 2001⁽¹⁰⁾ studied the efficiency of dialysis with albumin in the treatment of patients with advanced hepatic insufficiency. They used a new treatment, MARS (Molecular Adsorbent Recirculating System), in 3 patients diagnosed with severe liver failure. This system consists of an albumin rich (20%) dialysate circuit, with two areas of depuration. In one area, the albumin dialysate is in contact with blood through a high-flux albumin coated membrane, where albumin bound substances are eliminated. In the other area, the albumin dialysate is in contact with a standard bicarbonate dialysate through a low-flux membrane, which permits the elimination of water soluble substances.

The albumin of the circuit is continuously regenerated through charcoal and ion exchanger filters. All patients underwent a complete clinical and biochemical evaluation before and after each treatment. All of them showed an improvement of their clinical (attenuation of pruritus and encephalopathy) and biochemical (decrease of bilirubin levels) parameters. During the period of treatment 2 patients developed an increase in plasma creatinine levels together with a decrease of urinary volume. There were no hemodynamic or technical complications during the treatment⁹⁾. In our study, cases of liver cell failure were included to help in the calculation of the peritoneal clearance of uB. No clinically significant contribution of the traditional peritoneal dialysis in the management of the patients of liver cell failure is expected.

In cases of group III with unconjugated hyperbilirubinemia due to excessive hemolysis P2 was normalized by the end of the dialysis sessions. In these cases, the cause of unconjugated hyperbilirubinemia was self limited. It is not clear whether peritoneal dialysis enhanced the normalization of P2. Neonates with unconjugated hyperbilirubinemia are the most likely group to benefit from the peritoneal dialysis. Peritoneal dialysis is superior to exchange blood transfusion in many aspects; the peritoneal dialysate is a long standing, sterile, pyrogen free, universal crystalloid that is suitable to all patients compared to the blood used for the exchange transfusion that should be fresh, compatible and serologically screened before utilization. In expert hands the introduction of

the acute peritoneal dialysis catheter is as easy as the introduction of the umbilical vein catheter. Complications of the peritoneal dialysis catheter introduction (hemorrhage or perforation) are acute and easily detected compared to the late thrombotic complications of the umbilical venous catheters. Peritoneal dialysis is a smooth procedure associated with less cardiovascular complications than the exchange blood transfusion. Still exchange blood transfusion is more efficient and is more suitable for the cases of severe hyperbilirubinemia.

In group II, with neonatal sepsis P2 increased in 2 cases and decreased in one case. The heterogeneous pathogenesis of hyperbilirubinemia in patients with neonatal sepsis (liver cell failure & cholestasis) may contribute in these variable results.

Urea and uB were detected in the ascitic fluid (A) of cases 1 & 2. Urea was detected in the mid-dialysis peritoneal fluid samples (D) in all patients while uB was detected in 4/7 patients only. The A/P ratio for uB was almost equal to the A/P and the D/P ratios for urea and was about 15 fold the D/P ratio for uB.

Gutierrez et al., 1981⁽¹¹⁾ compared the biochemical level of different solutes in serum with the residual peritoneal fluid in peritoneal maintenance dialysis. The study showed linear correlation coefficient to be higher than 0.64 in BUN, phosphorus, creatinine, uric acid, calcium and potassium, which allows a statistically certain conclusion to be drawn to the serum levels of residual peritoneal fluid. The results of glucose, chloride, bilirubin, osmolality, LDH, bicarbonate, albumin,

cholesterol, sodium, globulines and alkaline phosphatase studies, gave an insufficient linear correlation coefficient, which makes it impossible to offer the necessary guarantees for the use of residual fluid". The long standing presence of the ascitic fluid in the peritoneal cavity may contribute to the higher (A) uB compared to the (D) uB. The proteins of the ascetic fluid may bind the dialysed uB and prevent its absorption.

The mean peritoneal clearance of urea was 15 fold the peritoneal clearance of uB in the 4 cases with detectable (P) uB. The higher molecular weight of uB compared to that of urea can contribute to its lower peritoneal clearance. The addition of albumin to the dialysate improved the peritoneal clearance of uB in experimental animals. Extraction of non-conjugated bilirubin by peritoneal dialysis with a human serum albumin solution was studied in an experimental study in Gunn rats⁽¹²⁾. Intermittent peritoneal dialysis with a buffered solution containing rat plasma proteins was carried out for rats subjected to common bile duct ligation in an attempt to reduce plasma bilirubin levels. Dialysis was performed during the second postoperative week. Provided that rat plasma protein was present in the dialysing fluid, dialysis significantly reduced ($p < 0.01$) the levels of total plasma bilirubin, conjugated bilirubin and serum GPT in the experimental animals⁽¹³⁾. The addition of human serum albumin (HSA) to peritoneal dialysate increases the clearance of bilirubin in rats suffering from obstructive jaundice. The acceptor properties of the fluid can be enhanced by using HSA that does not

contain standard stabilizing additives and has been purified by further adsorption on activated carbon. Bilirubin-containing dialysate fluid, as well as the ascitic fluid of cirrhotic patients, can be regenerated by a combination of membrane ultrafiltration and carbon adsorption. These observations suggest a potentially useful scheme for continuous, regenerative peritoneal dialysis in the treatment of hepatic insufficiency⁽¹⁴⁾.

To conclude, unconjugated bilirubin can be cleared by peritoneal dialysis. Its clearance is 1/15 that of urea with a promising evidence of better clearance on addition of protein to the dialysate. These results deserve further controlled studies large enough to permit confirmation and to prove practical applicability of peritoneal dialysis in the treatment of neonates with unconjugated hyperbilirubinemia of different etiologies.

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