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PERITONEAL DIALYSIS IN ACUTE KIDNEY INJURY: BRAZILIAN EXPERIENCE

Peritoneal dialysis (PD) was the first modality of renal replacement therapy (RRT) successfully used for patients with acute kidney injury (AKI) (1). In 1970, acute PD was widely accepted for AKI treatment, but its practice progressively declined in favor of hemodialysis techniques until, currently, PD is underutilized for AKI around the world (2–4). Recently, Brazilian experiences with PD in AKI have been published, and interest in using PD to manage selected AKI patients has been increasing.

Here, we review recent literature and studies of PD for the treatment of AKI patients performed at the Botucatu School of Medicine, Sao Paulo State University, Brazil.

PD PRESCRIPTION FOR AKI PATIENTS

To overcome some of the classical limitations of PD for AKI, such as a high chance of infection and lack of metabolic control, we proposed the prescription of high-volume PD (HVPD). The continuous HVPD modality is designed to achieve higher small-solute clearances. It is performed using automated cyclers, a flexible catheter, and a high volume of dialysis fluid. Each session lasts 24 hours, and sessions are repeated daily. The total dialysate volume per session ranges from 36 L to 44 L.

In a prospective study of 30 consecutive AKI patients (mean age: 59 ± 8 years), we assessed the efficacy of HVPD (5). Of the 30 patients, 66% were in the intensive care unit on the day of their first PD session (mean Acute Physiology and Chronic Health Evaluation II score: 32.2 ± 8.6). The cause of AKI was ischemia in 67% of the patients, and the most usual cause of ischemia was sepsis.

Peritoneal dialysis was performed using a Tenckhoff catheter, 2-L exchanges, and 35- to 50-minute dwell times. The prescribed Kt/*V* was 0.65 per session, with the duration of a session being 24 hours. Total daily exchanges ranged from 18 to 22. This HVPD was effective in the correction of blood urea nitrogen (BUN), creatinine, bicarbonate, and pH. Daily ultrafiltration (UF) rates were 2.1 ± 0.62 L; urea clearances, 17.3 ± 5.01 mL/min; and weekly delivered Kt/*V*, 3.8 ± 0.6. Serum albumin remained stable after PD treatment, and the mortality rate was 57%. This important study showed that HVPD is able to adequately treat critically ill AKI patients without significant complications. The main limitations of the study were its single-center nature, its small number of patients, and its lack of a control group.

PD COMPARED WITH HEMODIALYSIS FOR AKI PATIENTS

Our group also performed a randomized trial in 120 AKI patients comparing HVPD (60 patients) with daily intermittent hemodialysis [dHD (60 patients)] for efficacy and security (6). The HVPD technique was performed as previously described (5), and the dHD technique was performed using a double-lumen central venous catheter and polysulfone filters. The prescribed Kt/*V* for each dHD session was 1.2.

In that study, baseline characteristics were similar in both patient groups, which included older adults (mean age: >60 years) with high scores on the Acute Physiology and Chronic Health Evaluation II and the Acute Tubular Necrosis–Injury Severity Score. Most patients were on vasoactive drugs (>60%). Ischemic AKI caused by sepsis was the predominant condition.

The RRT modalities being studied both achieved metabolic and acid–base control. Delivered dose was significantly lower for HVPD than for dHD (Kt/V: 3.59 ± 0.61 vs 4.76 ± 0.65), but daily UF volume was more than 2 L and similar for both modalities. No significant difference in the rate of infectious complications was observed between the two groups. High-volume PD did not cause uncontrolled hyperglycemia. Serum albumin was low and similar for both groups, and it declined equally in HVPD and dHD even though significant protein loss in the PD effluent was observed. Mortality did not differ significantly between the groups (58% for HVPD vs 53% for dHD). The rate of renal recovery was similar for both modalities, but HVPD was associated with a significantly shorter time to recovery (7.2 ± 2.6 vs 10.6 ± 4.7 days).

Some important points can be drawn from this well-planned and well-executed randomized controlled trial. In critically ill AKI patients, HVPD can provide an adequate weekly RRT dose and efficiency and safety similar to those achieved with dHD. Mortality rates with HVPD and dHD were similar, but HVPD was associated with faster recovery of renal function. The limitations of

the foregoing study were its single-center nature and its exclusion of hypercatabolic patients.

In another prospective study (nearing conclusion), we compared HVPD with extended HD (eHD) on outcome in AKI patients (Ponce D, Berbel MN, Abrão JMG, Goes CR, Balbi AL. High volume peritoneal dialysis versus extended daily hemodialysis in acute kidney injury patients. Presented at the 13th Congress of the International Society for Peritoneal Dialysis; Mexico City, Mexico; 23–26 July 2010). The eHD (n = 143) and HVPD (n = 89) groups were similar in sex, severity of AKI according to the Acute Tubular Necrosis–Injury Severity Score, and AKI causes. The presence of sepsis in the eHD group trended toward statistical difference (62.3% vs 44.9%, p = 0.054). The groups were different in age (HVPD: 64.6 ± 21.2 years; eHD: 68.6 ± 24.2 years; p = 0.01), pre-dialysis BUN and creatinine (eHD: 88 ± 38.6 mg/dL and 3.8 ± 1.2 mg/dL respectively; HVPD: 101.5 ± 28.9 mg/dL and 5.4 ± 1.9 mg/dL), fluid overload (eHD: 56.1%; HVPD: 23.6%; p = 0.0006), need for mechanical ventilation (eHD: 96.7; HVPD: 73%; p < 0.0001), and dose of vasoactive drugs (noradrenalin: 0.68 ± 0.22 μg/kg/min in eHD vs 0.26 ± 0.12 μg/kg/min in HVPD; p = 0.004).

The groups were different in metabolic and fluid control. Levels of BUN and creatinine stabilized faster in the eHD group than in the HVPD group. Delivered Kt/V and UF were higher in the eHD group. The mortality in the eHD group was higher than that in the HVPD group (71.8% vs 56.2%, p = 0.023). The groups showed no differences in recovery of kidney function or in need for chronic dialysis. The higher mortality in the eHD group was probably a result of the worse clinical condition of those patients.

Although the foregoing study was not a randomized trial, the results obtained so far suggest that HVPD can be an alternative even for hemodynamically unstable AKI patients, in the absence of contraindications to PD use. Further analysis of the results of the study will be undertaken shortly—for example, evaluating the catabolic state of the patients in each group and the improvement in nutrition status after each dialysis session, plotting the patient and kidney survival curves, and evaluating the patients by prognostic score level to identify whether, in the same severity range, patients in both groups show similar changes.

PD DOSE FOR AKI PATIENTS

The optimal dialysis dose for the treatment of AKI is controversial, and data on the effect of PD dose on AKI are very limited.

From January 2005 to January 2007, we randomly assigned critically ill patients with AKI to receive higher- or lower-intensity PD therapy (7). The main outcome measure was death within 30 days. The patients in both groups were treated with continuous HVPD as described earlier.

Peritoneal access was established by percutaneous placement of a flexible (Tenckhoff) catheter by nephrologists using a trocar-introduced paramedian approach on either the left or right periumbilical abdominal wall. The prescribed HVPD dose was determined using the Kt/V urea formula (8,9), with K being the volume of dialysis solution prescribed in 24 hours (in milliliters) multiplied by 0.6 (considering that the dialysate-to-plasma relationship for urea is 0.6/1 h), t is the treatment duration (1 day), and V is the urea distribution volume in liters by the Watson formula. The prescribed Kt/V value was 0.8 per session for the high-intensity group and 0.5 per session for the low-intensity group. The exchanges used dwell times of 30 – 60 minutes, for a total of 36 – 48 L solution and 18 – 22 exchanges daily. In patients with fluid overload, PD solution containing 2.5% or 4.25% glucose was used.

The delivered HVPD dose was determined using the Kt/V urea formula, with K being the mean dialysate-to-plasma BUN (in milligrams per 100 mL) before and after dialysis, multiplied by the drained volume in milliliters over 24 hours, divided by the distribution volume of urea in milliliters. Blood samples were collected at the beginning and end of each HVPD dialysis session and analyzed for levels of creatinine, potassium, bicarbonate, glucose, and sodium. To measure BUN, 3 aliquots of spent dialysate (3 mL each) were collected at 8-hour intervals during every session (8,9).

Of the 61 enrolled patients, 30 were randomly assigned to higher-intensity therapy, and 31, to a lower-intensity PD dose. The two study groups had similar baseline characteristics. Sepsis was the main cause of AKI; heart failure was the second most frequent cause. Uremic symptoms or azotemia were the main indications for dialysis.

The two groups received treatment for 6.1 days and 5.7 days respectively (p = 0.42). At 30 days after randomization, 17 deaths had occurred in the higher-intensity group (55%), and 16 deaths in the lower-intensity group (53%, p = 0.83).

The groups showed significant differences in the PD dose prescribed compared with the dose delivered (higher-intensity group: 0.8 vs 0.59, p = 0.04; lower-intensity group: 0.5 vs 0.43, p = 0.89). The groups had similar metabolic control after four PD sessions (BUN: 69.3 ± 14.4 mg/dL and 60.3 ± 11.1 mg/dL respectively; p = 0.71).

We concluded that increasing the intensity of continuous HVPD therapy does not reduce mortality and does not improve metabolic control or recovery of kidney function among critically ill patients. A delivered Kt/V of 0.5 per session seems to be enough to provide metabolic control. A delivered Kt/V higher than 0.6 per session by this technique is probably not practicable, because PD dose is limited by dialysate flow and membrane permeability, and clearance per exchange can decline if a shorter dwell time is applied.

There is concern that the prescribed volumes of PD fluid to treat AKI may be too expensive for some developing countries. However, Brazilian data (currently unpublished) show that the cost of one HVPD session is more expensive than one conventional or extended HD session, but cheaper than one continuous RRT session. Data from India, where dialysate is locally manufactured, showed that the cost of HD equipment per session is much more expensive than the cost of PD equipment (US$120 vs US$6); however, manual exchanges and rigid catheters were used, and the prescribed total volume of dialysate was 20 L per session (10).

THE REAL ROLE OF PD FOR AKI PATIENTS

We recently performed a prospective study in 204 AKI patients assigned to HVPD (prescribed Kt/V: 0.60 per session) to explore the real role of HVPD in metabolic and fluid control and to identify risk factors associated with death (11).

Mean age of the patients was 63.8 ± 15.8 years, 70% were in the intensive care unit, and sepsis was the main cause of AKI (54.7%). Encouraging results were observed for metabolic control. After four sessions, BUN and creatinine levels stabilized at around 50 mg/dL and 4 mg/dL respectively. The acid–base balance normalized after two sessions.

Work by Phu *et al.* (12) and Bazari (13) reported that intermittent PD failed to control acidemia because PD impairs diaphragm mobilization, with a resulting increase in intra-abdominal pressure and a reduction in pulmonary compliance and ventilation. Lack of mobilization was also reported to cause tissue and organ hypoperfusion and to maintain acidosis (14).

Results of other of our prospective descriptive studies have suggested that AKI patients on invasive mechanical ventilation treated with PD show improvement in mechanical ventilation and oxygenation without changes in intra-abdominal pressure. We evaluated static compliance, respiratory system resistance, and the partial pressure O_2/FiO_2 ratio in patients undergoing PD. Static compliance increased progressively after exchanges of dialysate, respiratory system resistance and intra-abdominal pressure were stable during HVPD sessions, and partial pressure O_2/FiO_2 progressively increased (Almeida Puatto C, Ponce D, Balbi AL. Evaluation of mechanical ventilation in patients with acute kidney injury undergoing continuous peritoneal dialysis or daily hemodialysis [Portuguese]. Presented at the Anais do XVI Congresso Paulista de Nefrologia; Atibaia, Sao Paulo, Brazil; 16–19 September 2011).

Fluid removal and nitrogen balance progressively increased and stabilized at about 1200 mL and 21 g/d respectively after four sessions. Similar results were obtained by Chitalia *et al.* (10) and Ponce–Gabriel *et al.* (5,7,11), whose studies showed UF values around 2 L per session. However, a UF between 1 L and 2 L is not enough for most AKI patients, who are mainly septic and have fluid overload. Weekly delivered Kt/V was 3.5 ± 0.68, similar to that seen in previous studies, which showed that PD clearance is limited by dialysate flow, membrane permeability, and area (5–8,11).

Concerning infectious complications, the rate of peritonitis was similar to rates reported in the literature (12% – 15%). In most patients with infection, the catheter was removed and the dialysis method changed because no success was obtained with antibiotic treatment. The main mechanical complication was early leakage (10%), which accords with findings in other studies (5–7,11).

With respect to AKI outcome, 23% of patients recovered renal function, 6.6% remained on dialysis after 30 days, and 57.3% died. In relation to metabolic control and delivered dialysis dose, we observed no significant difference between HVPD-treated patients who survived (S) and who did not survive (NS), a result that is consistent with work published by the US VA/NIH Acute Renal Failure Trial Network (15) and by Bellomo *et al.* (16) in the ATN and RENAL trials respectively.

Clinical parameters and prognostic scores in the NS patients were more severe than those in the S patients. Old age and sepsis were identified as risk factors for death. The two groups presented statistically significant differences in UF and nitrogen balance. After three HVPD sessions, UF and nitrogen balance were statistically higher and less negative in S than in NS patients. Persistence of urine output, an increase of 1 g in nitrogen balance, and achievement of 500 mL in UF after three sessions were identified as favorable prognostic factors. Those results agree with findings in previous studies that low urine output, fluid overload, and sepsis are associated with worse prognosis in AKI patients (17).

Unfortunately, with respect to nitrogen balance, critically ill patients are rarely capable of maintaining

positivity, especially when the situation of stress is unresolved. In a departure from previous studies, our research showed that nitrogen balance in patients treated with PD becomes less negative with treatment (5,6; Goes CR, Berbel MN, Pinto MPR, Balbi AL, Ponce D. Evaluation of the metabolic effects of high-volume peritoneal dialysis in the treatment of patients with acute kidney injury [Portuguese]. Presented at the Anais do XVI Congresso Paulista de Nefrologia; Atibaia, Sao Paulo, Brazil; 16–19 September 2011). In the literature, the association of nitrogen balance with clinical prognosis in AKI patients with dialysis has been reported. Our findings are similar to those reported in the work of Scheinkestel *et al.* (18), who observed that nitrogen balance was inversely associated with hospital and intensive care unit outcomes.

We concluded that HVPD is effective in selected patients, providing adequate metabolic and fluid control. However, after three sessions, if UF is low or nitrogen balance is negative, substitution or addition of other RRT techniques should be considered.

The main limitations of our study are that the results are not presented by intention to treat and that patients whose the dialysis method was changed (from HVPD to HD) were excluded from the survival analysis.

BRAZILIAN STUDIES: CONCLUSIONS AND THE FUTURE OF PD IN AKI

This review of Brazilian studies shows that PD can be successfully used as a modality of RRT to treat a selected group of AKI patients. Recently, PD has shown efficacy similar to that achieved with dHD and eHD in critically ill AKI patients.

Age and sepsis were risk factors associated with death in AKI patients treated by PD; higher urine output and UF, and positive nitrogen balance were factors protective against mortality.

Peritoneal dialysis is a simple, safe, gentle, and proven way to correct metabolic, electrolytic, acid–base, and volume disturbances generated by AKI. Careful prescription—using a high volume of dialysate, frequent cycles, and flexible catheters, with accurate measurement of efficiency—may help to overcome some of the classical limitations such as the risk of peritoneal infection, protein loss, and limited capacity to modulate fluid and solute removal. Such an approach may help to maintain PD as a suitable alternative for the treatment of AKI patients who have no contraindications to PD use, especially in countries in which more sophisticated technologies are not available. However, after three sessions, if UF is low or nitrogen balance is negative, substitution or addition of other RRT techniques should be considered.

Nevertheless, given the paucity of good-quality evidence in this important area, further studies on the use and limitations of PD for AKI and the effect of PD on clinical outcomes in AKI patients are necessary.

DISCLOSURES

The authors have no financial conflicts of interest to declare.

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