

Peritoneal Dialysis Is an Option for Acute Kidney Injury Management in Patients with COVID-19

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Keywords

COVID-19 disease · Peritoneal dialysis · Acute kidney injury

Abstract

In December 2019, cases of acute respiratory illness of unknown origin were reported in Wuhan, China. The disease is caused by “severe acute respiratory syndrome coronavirus 2”. After identifying severe lung damage, injury to other organs, such as the kidney, has been identified. Peritoneal dialysis is a renal replacement therapy (RRT) and is at least as effective as other extracorporeal therapy options, with significant cost-effective advantages. However, this strategy is rarely used for the management of acute kidney injury in severe lung disease. In this review, we explore PD as an RRT strategy that may be a key instrument in countries and hospitals with limited access to all RRTs. © 2020 S. Karger AG, Basel

Introduction

In December 2019, cases of severe acute respiratory syndrome of unknown origin were reported in Wuhan, in the Hubei province of China [1, 2]. The disease was fi-

nally shown to be caused by “severe acute respiratory syndrome coronavirus 2” (SARS-CoV-2) [3]. The World Health Organization recognized this disease as a pandemic, and by April 2020, cases have been reported in 211 countries, with more than 1.9 million confirmed cases [4]. In Mexico, about 256,848 cases have been diagnosed in all of the states [5]. Since the beginning of the epidemic, kidney injury associated with COVID-19 disease has been documented, in percentages as high as 15% [6].

However, the available data suggest that the prevalence of acute kidney injury (AKI) in patients with COVID-19 is variable. In another cohort study ($n = 1,099$), 5.3% of patients required admission to the intensive care unit (ICU) and only 0.5% of patients had AKI [7].

There are 3 proposed mechanisms for kidney injury that result from direct damage by cytokines (cytokine release syndrome, increased cytokine production, and hemophagocytic syndrome), organ crosstalk (heart disease or viral myocarditis, alveolar damage, rhabdomyolysis, elevation of peak airway pressure, and intra-abdominal hypertension), and systemic complications (volume overload, endotoxins, endothelial damage, loss of fluid into the interstitial space, and hypotension) [8]. The hypothesis of damage induced by inflammatory cytokines points to the systemic inflammatory state that

originates from the infection itself and from acute tubular necrosis, as well as to direct injury associated with the presence of the virus in the kidney. This is because previously, the angiotensin-converting enzyme and dipeptidyl peptidase-4 were identified as areas of junction for SARS-CoV and MERS-CoV [9, 10]. Unpublished data suggest that SARS-CoV-2 can directly infect tubular epithelium and induce acute kidney damage due to the presence of direct cytotoxicity and may promote CD68 macrophage activity, in addition to C5bC9 complement deposits that act as mediators of tubular injury. Other studies found a direct parenchymal infection of tubular epithelial cells and podocytes with marked acute tubular injury and erythrocyte aggregation occurs in severe lethal COVID-19 [11]. On the other hand, COVID-19 RNA has been found in the plasma of 15% of patients through real-time PCR [12]. This test also demonstrated that COVID-19 RNA is found in up to 91.7% of AKI patients [13].

Access to Renal Replacement Therapies in AKI for COVID-19 Disease in Developing Countries

The presence of a greater number of AKI cases in patients with COVID-19 disease is a matter of debate. Some case series did not demonstrate an increased presence of AKI cases in patients with COVID-19 disease. They report that SARS-CoV-2 infection does not produce AKI and does not worsen the existing state of CKD in patients with COVID-19 disease [14]. However, these studies may not reflect possible scenarios in populations with a higher prevalence of obesity, diabetes, and CKD.

In the absence of established drugs or vaccines for severe COVID-19 disease, there is a pathophysiological justification for the implementation of therapies such as direct hemoperfusion, plasma adsorption on resin, continuous kidney replacement therapy (CKRT), and high doses of CKRT with MCO or HCO8 membranes. However, in developing countries, access to renal replacement therapies (RRTs) such as CKRT is limited and clinicians may find themselves in scenarios not necessarily similar to those described in developed countries.

Access to renal function replacement therapies in low- and lower middle-income countries (LLMICs, gross national income < USD 4035) is known to be often scarce, with variations observed in regions of the same country or different areas of the same city. In these countries, lack of resources is the main reason for not providing dialysis therapies. While CKRT is used in approximately 30% of

AKI patients in high-income and upper-middle-income countries, less efficient alternative therapies are used more frequently in LLMICs (22%). Paradoxically, and despite its value in low-resource settings, PD treatment is infrequent, both in LLMICs (7%) and in high-income and upper-middle-income countries (3%) [15]. Although PD was the first RRT strategy in the management of AKI [16], there is little evidence on its use in the current COVID-19 pandemic as an RRT strategy in the treatment of AKI.

Efficacy of Peritoneal Dialysis in the Management of AKI

The efficacy of PD in the management of AKI is at least as efficient as hemodialysis (HD) and possibly as efficient as hemodiafiltration [17, 18]. Currently, the best evidence is found in a meta-analysis from Liu et al. [19] (analysis of 6 studies with 484 patients), where PD therapy and extracorporeal RRT are compared for management of AKI. In this study, PD therapy has little or no difference with other extracorporeal therapies concerning all-cause mortality and recovery of kidney function (Moderate level of evidence). On the other hand, PD may be slightly less effective in the removal of ultrafiltration volume (low level of evidence) and has no difference for infectious complications (low level of evidence). The efficacy of the correction of acidosis or Kt/V dosage may be higher in extracorporeal therapies; however, the evidence for this argument is very low [19].

A randomized study of patients with AKI and multi-organ failure admitted to the ICU that required RRT evaluated the outcomes of 125 patients assigned to RRT modalities in the continuous veno-venous hemodiafiltration mode ($N = 62$) and tidal peritoneal dialysis (TPD) ($N = 63$). The primary outcome of the study was that survival in patients at 28 days treated with TPD, compared to continuous veno-venous hemodiafiltration (69.8 vs. 46.8%, $p < 0.01$), is superior. Infectious complications were significantly lower and other outcomes such as the recovery of kidney function (60.3 vs. 35.5%) were higher in the TPD group [20]. Other clinical trials that compare extracorporeal therapies versus PD for AKI management indicate that, in regards to the correction of uremia, acidosis, fluid overload, and hyperkalemia, results are not different between the groups. Nonetheless, the cost-benefit advantage is more favorable for the PD group [17].

Peritoneal Dialysis in Patients with Acute Lung Injury or Severe Pneumonia

It is believed that the elevation of intraperitoneal pressure (IPP) generated by PD may alter diaphragmatic movement, thereby decreasing pulmonary compliance, which could hinder the mechanical ventilation management and worsen respiratory failure [21–23]. This argument does not have solid scientific evidence; Vieira et al. [22] evaluated the effects of AKI while weaning from mechanical ventilation in a retrospective observational study. The RRT used in this study for all patients was HD, and the possible effects of PD on ventilator dynamics are not mentioned [22]. Almeida et al. [24] studied the effect of PD on mechanical ventilation in patients with AKI and evaluated 106 patients treated with RRT [24], in PD mode, and 80 with HD. The evaluation of respiratory mechanics showed improvement in lung compliance after 3 PD sessions and resistance of the respiratory system (R_{sr}) remained without significant changes. On the other hand, an increase in the IPP after the first dialysate infusion was observed, but this became normalized in subsequent draining. Oxygenation parameters, like FiO_2 , were the same during the first and second PD sessions and decreased after the second session. PaO_2/FiO_2 progressively increased after the first PD session, and the analysis adjusted for the presence or absence of chronic obstructive pulmonary disease, lung infection, and mechanical ventilation time showed no differences from those previously described [24]. A recent study compared the effect of PD versus HD on the respiratory mechanics of patients with AKI; the prospective cohort study evaluated 154 patients, 37 on PD and 94 on HD. Researchers analyzed pulmonary static compliance, R_{sr} , and the oxygenation index for 3 days and evaluated patients at 3 separate times, 1, 2, and 3 (pre and post dialysis). The results showed that pulmonary static compliance increased, with no differences between the groups, R_{sr} remained stable among the patients with continuous PD and decreased among the HD patients, and oxygenation index increased in both groups. The authors conclude there is improvement in ventilatory mechanics in both groups, without significant differences [25].

Clearance of Inflammatory Cytokines in Peritoneal Dialysis

The proposed pathophysiological mechanisms for kidney injury related to COVID-19 disease, based on direct cytokine damage [8], may make the usage of addi-

tional treatments, such as extracorporeal techniques or the so-called blood purification techniques, appealing. These techniques include (but are not limited to) hemofiltration, hemoperfusion, intermittent or continuous high volume hemofiltration, plasmapheresis, or adsorption [26].

The clearance of inflammatory cytokines in PD has been demonstrated in experimental models. Altmann et al. [27] proved that circulating interleukin 6 (IL-6) is eliminated through PD. Recombinant human IL-6 (RH IL-6) was administered intravenously to wild-type mice with AKI and then with PD was performed in high doses. RH IL-6 was determined in the liquid from PD, and high levels of RH IL-6 were found. Similarly, levels constantly decreased as the treatment progressed. Importantly, there is no crossed reaction between endogenous murine IL-6 and RH IL-6 by ELISA, which indicates that circulating IL-6 enters the peritoneal dialysis fluid and may be effectively removed [27].

The adequacy of PD in removing inflammatory substances has been scarcely studied in humans. Zhao et al. [28] evaluated the effectiveness of PD for the removal of inflammatory toxins. The results of the study showed that inflammatory factors, including TNF- α , IL-6, and PCT, decreased significantly after treatment compared to pre-treatment. They concluded that PD is effective for the removal of these substances [28]. Other authors have evaluated the efficacy of PD for cytokine clearance in pediatric populations, specifically in the cytokine-mediated capillary leak syndrome after cardiopulmonary bypass (CPB). Measurement of cytokine levels by ELISA in blood plasma, and peritoneal fluid (PF) from samples of 18 neonates, showed a significant increase of serum concentrations of IL-6, IL-8, and IL-10 after CPB. The study also found that concentrations of IL-6 and IL-8 in PF exceeded serum concentrations, while IL-10 concentrations were higher in serum. They concluded that PF may be a repository for harmful inflammatory cytokines after CPB, and removal of PF by PD could reduce serum cytokine concentrations [29].

Peritoneal Dialysis in Pronation Strategies

One of the strategies to improve oxygenation in patients with acute respiratory distress syndrome (ARDS) is to use the prone position, which favors the decrease of the pleural pressure gradient in the dependent regions and reduces arteriovenous shunts. It promotes an equitable distribution air and ventilation/perfusion ratio as well [30].

The utility of PD in the management of AKI in patients with ARDS in the pronation position has seldom been studied. This is in part because it is thought that increasing IPP may cause a decrease in lung capacity. When IPP is greater than 18 cm H₂O, vital lung capacity decreases by more than 20%. However, this IPP threshold can be achieved with multiple small volume cycles [31].

Klisnick et al. [32] reported a case of a 38-year-old patient with CKD and neurogenic pulmonary edema, treated with mechanical ventilation, in the prone position, and automated PD as RRT. This treatment achieved 1 L of ultrafiltration per day and 11.3 mL/min/1.73 m² of Cr clearance. The prescription consisted of 1.5 L cycles with glucose bags of 1.36–3.86%, an IPP < 18 cm H₂O was monitored, and 40 L of dialysate per day was achieved. Although they observed an increase in pulmonary capillary wedge pressure due to the prone position, the infusion of the dialysis liquid was not affected [32]. Experience by Maryanne Y. Sourial and cols, describes 16 patients with PD who required pronation, in whom PD cycles were suspended while the patients were in the prone position, and they received HD or CKRT as supplementary treatment (if possible and depending on the location of the patient). After returning to the supine position, the PD replacements were restarted [33].

Experience in PD in the Management of AKI Associated with COVID-19

Evidence of PD in the management of AKI during the COVID-19 pandemic is limited. However, Maryanne Y. Sourial's group at the medical center in the Bronx, NY, refer to the need to start an urgent peritoneal dialysis program, due to the high demand for dialysis and shortages of personnel and supplies. The experience of this group indicates that PD is a viable strategy for HD in conditions of critical resource scarcity. These authors describe the results obtained in 30 patients with RRT requirement, reporting a mortality of 47%. The success of PD treatment was achieved in 63% of patients. However, there were significant difficulties such as lack of training of nursing personnel and availability of supplies, as well as lack of adequate clearance and ultrafiltration for patients in UCI, in addition to half of the patients requiring pronation strategies, which limit PD therapy for long periods of time [33].

Preliminary data from other medical groups have been discussed in online forums, such as that presented on April 23, 2020, by the International Society for Peritoneal

Dialysis (ISPD)/International Society of Nephrology webinar “Use of PD for COVID-19-associated AKI: clinical experience and updated 2020 ISPD guidelines,” where PD was defined as a potentially effective and safe strategy in the management of AKI, with advantages over CKRT strategies as a reduction in workload for staff [34].

PD Catheter Insertion Techniques during the COVID-19 Pandemic

In an environment where optimizing resources is relevant, increasing availability of PD patients, percutaneous catheter insertion with and without image guidance can be performed at bedside by surgeons' interventional radiologists and nephrologists and may be considered for peritoneal access [35]. Medical groups have derived this practice during the COVID-19 crisis, which affects the installation of catheter placement at the bedside of patients by transplant surgeons in ICU patients and by interventional radiologists using fluoroscopic guidance in non-ICU and nonintubated patients. They report the use of the PD catheter immediately after insertion, with low volumes of 1–1.5 L the first 24 h, with subsequent increase to volumes greater than 2–2.5 L [33].

The other experiences on inserting a PD catheter into the patient's bedside come from data reported on April 23, 2020, by the ISPD/International Society of Nephrology webinar “Use of PD for COVID-19-associated AKI: clinical experience and updated 2020 ISPD guidelines,” where Hugh Cairns and Elaine Bowes at Kings College Hospital, London, UK, describe that insertion of the PD catheter is performed by a senior nurse or by the consulting nephrologist; 27 of 32 attempts were successful [34]. Mika Nagatomo's group described PD catheter insertion to the rectovesical pouch using a portable X-ray machine at the bedside and infused the peritoneal dialysate [36].

Data prior to the COVID-19 pandemic mention that the insertion of the PD catheter can be performed by percutaneous techniques guided or not guided by radiological techniques and procedures that can be performed by interventional radiologists, surgeons, and nephrologists. Other viable techniques are minilaparotomy in the patient's bed [35]. When compared to open procedures, percutaneous catheter placement with image guidance turns out as a cost-effective and safe procedure, including urgent-star PD [37]. Al Hwiesh described a percutaneous bedside placement of PD catheters without image guidance in 40 catheters in 38 patients. Exit-site infection occurred in 5% at month, and early exit-site leakage was

observed in only 1 catheter; bowel perforation or serious hemorrhage was not reported. Catheter survival was 95% at 6 months and 87.5% at 12 months [38]. Like any other procedure, prophylactic antibiotic should be used at the time of PD access insertion according to ISPD guidelines [39].

There are recommendations during the surgical procedure that could minimize the risk of leak, such as the use of a cord suture to secure the deep cuff, which should be placed in the rectus muscle, and a paramedic over a midline incision in the peritoneal cavity [35]. In patients who have anticoagulation, it is always preferable to avoid vascular access when possible, so PD may be a suitable alternative. Therefore, placement of a peritoneal access should be minimally invasive and preferably image guided. Even in some protocols, heparin is instilled in the bags to decrease the clot formation due to thrombotic risk [33]. The best practices consensus protocol by interventional radiologists recommends removing anticoagulants 5 days before the procedure [37].

Management of Peritoneal Fluid in Patients with COVID-19 Disease

The recommendations for the management of peritoneal effluent in patients with COVID-19 disease include doing nothing more than what is usual practice and adding chlorine solution in a ratio of 500 mg/L for 1 h into the toilet before discharging remains. It is recommended to avoid the splashing of drops that may result from pressing the toilet discharge button [40].

Insights of Peritoneal Dialysis in COVID-19 Pandemic

Continuous PD is a form of CKRT and may be used in critically ill patients. The efficacy of PD in the management of AKI is at least as efficient as HD and possibly as efficient as hemodiafiltration [17, 18]; however, in conditions of high morbidity as in current pandemic conditions, this strategy may not make a difference with other extracorporeal therapies concerning all-cause mortality and recovery of kidney function [19]. This includes patients with severe lung disease [25], such as that seen in COVID-19 disease. There is no evidence to support that pulmonary dynamics are severely altered by FP in the abdominal cavity [24]. Conversely, some studies support the fact that lung mechanics improve in a similar way to other RRT strategies [25].

The possibility of a prolonged pandemic poses the threat of equipment shortages and supply chain deficiencies [41]. In countries with scarce economic resources, access to extracorporeal RRT is limited and in many cases this alternative does not exist. In these vulnerable areas, PD may have clear advantages, over the need for minimally trained personnel, as well as the essential infrastructure required to offer treatment [17]. Another advantage is that in most of these countries, there is extensive experience for the employment of PD strategies [15]. Interestingly, the information available on the experience of this strategy in the management of AKI comes from high-resource countries, which means that in conditions of extreme morbidity, such as the COVID-19 pandemic, PD is useful and effective as a dialysis modality [33–35].

Strategies for prescribing PD in AKI are widely distributed (peritoneal dialysis for AKI, according to ISPD guidelines). The recommendation is to look for a weekly Kt/V urea of 3.5, which provides results comparable to those of daily HD, albeit this dose may not be necessary for all patients, and a lower goal of weekly Kt/V close to 2.1 may be acceptable [42]. Probably in the COVID-19 crisis, continuous APD would be the preferred modality because it minimize the number of connections and disconnections; also, fewer changes can be made to prescriptions, monitoring electrolyte disturbances. However, the available modality will always be the best. Unfortunately, APD machines are not available in some places in developing countries [35].

Recently, Ponce et al. [21] published PD prescription recommendations, which highlight the strategies with short cycles for patients with severe hyperkalemia, metabolic acidosis, fluid overload, or uremic symptoms, for which the modalities of HVPD or PD of tide would be the modalities of choice, in this case the total volume of dialysate must reach 30–36 L [43]. Strategies such as tidal PD may decrease patient monitoring time and therefore lessen exposure in medical personnel. Given the lack of evidence to predict the behavior of PD in patients with ARDS, the measurement of IPP may help to estimate the volume of PF, with a maximum permissible volume for an IPP of 18 cm H₂O [44].

Expert recommendations mention that PD can be started early, before patients develop ARDS. However, when ARDS occurs, PD should not be used as the first option for RRT [43]. Regarding patients requiring pronation, there are few reports of cases where PD was used successfully [31, 32]; however, there is insufficient information to recommend PD when the patient is in this po-

sition. Therefore, other RRT strategies should be considered [43], mainly due to the resulting technical problems and possible difficulties in handling the mechanical ventilator [35].

Conclusion

Peritoneal dialysis is a modality of RRT at least as efficient as other extracorporeal RRT options with important cost-effective advantages, making it a key instrument in countries without access to all RRTs. There is no theoretical justification for it to be not used in patients with severe acute respiratory syndrome as those observed in COVID-19 disease. The prescription of PD in severe lung disease must be adapted to each patient specifically, according to international guidelines. Complementary studies are required to establish clear management guidelines in this group of patients.

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Conflict of Interest Statement

The authors declare no conflicts of interests.

Funding Sources

This research was conducted without sponsorship.

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