Prolonged Intermittent Renal Replacement Therapy

Fahad Edrees, Tingting Li, and Anitha Vijayan

Prolonged intermittent renal replacement therapy (PIRRT) is becoming an increasingly popular alternative to continuous renal replacement therapy in critically ill patients with acute kidney injury. There are significant practice variations in the provision of PIRRT across institutions, with respect to prescription, technology, and delivery of therapy. Clinical trials have generally demonstrated that PIRRT is non-inferior to continuous renal replacement therapy regarding patient outcomes. PIRRT offers cost-effective renal replacement therapy along with other advantages such as early patient mobilization and decreased nursing time. However, due to lack of standardization of the procedure, PIRRT still poses significant challenges, especially pertaining to appropriate drug dosing. Future guidelines and clinical trials should work toward developing consensus definitions for PIRRT and ensure optimal delivery of therapy.

Key Words: Prolonged intermittent renal replacement therapy, Sustained low-efficiency dialysis, Extended daily dialysis, Intensive care unit, Acute kidney injury

INTRODUCTION

Acute kidney injury (AKI) is extremely common in the hospitalized patient and is associated with high morbidity and mortality. Intermittent hemodialysis (IHD) and continuous renal replacement therapy (CRRT) have been the mainstay of renal support for the critically ill patients with AKI. Hybrid therapies, which provide renal replacement therapy (RRT) for an extended period but on an intermittent basis, are becoming more popular as nephrologists seek to provide safe and cost-effective RRT to the critically ill patient with kidney failure. The goal of the hybrid therapy, now commonly referred to as prolonged intermittent renal replacement therapy (PIRRT), should be to provide RRT that is dose equivalent to the current recommendations for IHD and CRRT without compromising efficacy or patient safety.

In the original description of hemodialysis by W.J. Kolff, the duration of the treatment was 690 minutes, with a blood flow of 116 mL/min.[1,2] At the present time, this type of treatment would be considered a form of PIRRT because duration of the treatment is significantly longer, and the blood flow is markedly lower than that of an average IHD session. The concept of having a hybrid therapy combining the efficiency of IHD and the hemodynamic stability of continuous venovenous hemodialysis was further explored by Kudoh in 1988.[3,4] He developed a dialysis system in which solute removal and ultrafiltration were controlled separately. This new technique, which was called "slow continuous hemodialysis", maintained the efficacy of hemodialysis and the hemodynamic stability of CRRT in acutely ill patients with AKI.[5] Over the years, various hybrid techniques have been adopted at centers worldwide using different machines and protocols.

PIRRT has been primarily used as a substitute for CRRT in hemodynamically unstable critically ill patients with AKI. The choice of performing PIRRT over CRRT has been influenced by various factors such as: drive to reduce costs by avoiding expensive CRRT solutions, unavailability of CRRT machines, and ability to provide adequate RRT in hemodynamically unstable patients while allowing downtime for procedures and physical therapy. In some institutions, including ours, PIRRT is used as a transition therapy from CRRT to IHD as the patient's hemodynamic status slowly improves during the hospitalization. If patient's hemodynamic status has improved to warrant discontinuation of CRRT, but yet not stable for IHD, PIRRT is a reasonable option to prevent additional hypotensive episodes which can impair renal recovery.[6,7] In the setting of dialysis nursing shortage, PIRRT can be used as a substitute for one-on-one IHD as well. Recent surveys have demonstrated that the choice of PIRRT in the treatment of critically ill patients with AKI is becoming popular worldwide.[8-10]

TERMINOLOGY

Various terminologies have been used in the literature to describe and define the hybrid modality that cannot be classified as either IHD or CRRT (Table 1). These have included go-slow dialysis, slow hemodialysis, extended daily venovenous high-flux hemodialysis, sustained low-efficiency dialysis (SLED), sustained low-efficiency daily dialysis, extended daily dialysis (EDD), and daily shift continuous venovenous hemodialysis.[18-20,24-26] In the setting of convective clearance, the term accelerated venovenous hemofiltration has also been used.[16] When

From the Department of Medicine, Division of Nephrology, Washington University in St. Louis, St. Louis, MO.

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Address correspondence to Anitha Vijayan, MD, Department of Medicine, Division of Nephrology, Washington University in St. Louis, 660 S Euclid Ave, Campus Box 8129, St. Louis, MO 63110. E-mail: avijayan@dom.wustl.edu

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both convective and diffusive clearances are simultaneously used, additional terminologies such as sustained low-efficiency daily diafiltration and sustained hemodiafiltration (S-HDF) have also been coined in the literature.[11,21] The term PIRRT, which was originally used in 2002, encompasses both convective and diffusive methods and is becoming the accepted term to describe the hybrid form of RRT.[22,27]

TECHNOLOGY

PIRRT has traditionally been performed by adapting an IHD machine to allow for lower dialysate and blood flow rates. In the various descriptions of PIRRT in the literature, the therapy has been achieved with Fresenius (2008 H/K, 4008S ArRT Plus; Fresenius Medical Care AG & Co. KGaA, Germany) and Gambro (Baxter International, USA) (AK200S Ultra, Integra) IHD machines with minor software modifications that allowed for lower blood and dialysate flow rates.[18,21] Other dialysis machines include Nikkiso DBB-02 (Nikkiso Co. Ltd., Japan) used in Japan to provide S-HDF. More recently, the Fresenius Genius system, which contains a dialysate tank with up to 75 L of ultrapure germ and endotoxin-free bicarbonate dialysate solution, has also been used for PIRRT.[17,19] In this device, the spent dialysate is returned to the bottom of the same tank and remains demarcated from the ultrapure dialysate because of differences in density and temperature.[17,28] This system offers the convenience of a single machine without the need for external water supply during therapy. The NxStage System One (NxStage Medical Inc, USA), which is popular for home hemodialysis and CRRT, has also been used in the United States for PIRRT using either the convective or diffusive mode.[16,24] This machine requires prebagged 5-L bicarbonate solutions, and up to 9 bags (45 L) can be hung simultaneously. There are no data to recommend one specific machine over another for PIRRT, and Table 1 summarizes an overview of the terminology and technology used for the various hybrid modalities.

CLINICAL SUMMARY

- Prolonged intermittent renal replacement therapy (PIRRT) provides safe and cost-effective renal support to critically ill patients with acute kidney injury.
- There is significant heterogeneity among institutions in the delivery of PIRRT, with regard to technology, prescription, and anticoagulation.
- Appropriate dosing of medications, especially antibiotics, remains challenging as the pharmacokinetics depends not only on the type of filter, frequency, and duration of PIRRT but also on the timing of drug administration in relation to the prolonged therapy.
- Standardization of terminology and establishment of prescription guidelines may lead to increased utilization of this modality of renal replacement therapy.

CLINICAL APPLICATION AND PRESCRIPTION

PIRRT is usually reserved for patients in the intensive care unit (ICU) although some institutions, including ours, have provided it in step-down units with highly specialized nursing for a particularly vulnerable patient population. One example is the cardiac step-down unit with patients with severe heart failure, with or without left ventricular assist device. Vascular access for PIRRT is usually a temporary or tunneled dialysis catheter. If PIRRT is being prescribed for an ESRD patient with an arteriovenous graft or fistula, placement of a dialysis catheter similar to that required for CRRT should be strongly considered. Alternatively, patients require very close monitoring to ensure that accidental needle dislodgement does not occur during the prolonged course of therapy. The prescription for PIRRT is based on the principle that increasing duration of treatment compared to a standard IHD session will still provide adequate clearance despite lower dialysate flow (Qd) and blood flow (Qb) rates. The typical duration of PIRRT is between 6 and 12 hours with Qd of 100 to 200 mL/min and Qb of 150 to 400 mL/min. PIRRT can be performed daily or 3 to 6 days per week (Table 2).

Urea Kinetics and Dosing of Therapy

Urea kinetic modeling in the setting of critical illness and AKI is known to have significant flaws due to frequent fluctuations in fluid balance, hypercatabolic state, and alterations in regional blood flow, all of which can affect the volume of distribution of urea. Urea kinetics does not account for the clearance of higher weight molecules, which can also have significant impact on patient outcome. Despite these drawbacks and due to the lack of a more superior marker, the current guidelines regarding the dose of CRRT and IHD in AKI are based on fractional urea clearance (Kt/Vurea).[29-31] For patients with AKI, the Kidney Disease Outcomes Quality Initiative expert panel recommended that IHD should be prescribed to achieve a single pool (sp) Kt/Vurea of 1.3, 3 times per week.[31] The recommendation for CRRT was an effluent flow rate of 20 to 25 mL/kg/h, which is approximately equivalent to Kt/Vurea of 0.8 per day.[32] It should be noted that urea clearance is proportional to the blood concentration, and therefore, the clearance is greatest at the beginning of therapy. Thus, the weekly urea clearance cannot simply be a sum of the Kt/Vurea of individual treatments. The weekly standard (Std) Kt/Vurea has been derived to compare different modalities of treatment in AKI.[33] A spKt/Vurea of 1.3 at 3 times per week is equal to StdKt/Vurea of 2 (not 3.9).[33] CRRT at 20 mL/kg/h of effluent flow rate is equivalent to a weekly StdKt/Vurea of approximately 6.[33,34]

The Hannover Dialysis Outcome study compared 14-day mortality and renal recovery at 28 days in patients randomized to intensified extended dialysis (IED) and standard extended dialysis (SED) in 156 patients with AKI.[35] The goal of the randomization was to maintain blood urea nitrogen level at 56 to 70 mg/dL in the SED group and <42 mg/dL in the IED group, with no calculation of Kt/Vurea. There was no significant difference in either the primary outcome (survival was 70.4% in IED group vs 70.7% in SED group, $P = .97$) or the secondary