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REVIEW ARTICLE

Prolonged intermittent kidney replacement therapy: overcoming challenges in the critically ill patient in low-resource settings

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ABSTRACT

Acute kidney injury is a frequent complication of critical illness in intensive care units and has a negative prognostic impact. Kidney replacement therapy (KRT) is frequently needed and the treatment modalities used in these settings include continuous kidney replacement therapy (CKRT), intermittent haemodialysis (IHD) and peritoneal dialysis (PD). Haemodynamic instability is common in critically ill patients and the different KRT modalities affect haemodynamics in different ways. CKRT is often considered the modality of choice due to its lower dialysate flow, extracorporeal blood flow and ultrafiltration rates, leading to better haemodynamic stability. In poor socio-economic settings, however, the high cost of CKRT is a major barrier limiting its widespread use.
This brief narrative review makes the case for increased use of prolonged intermittent kidney replacement therapy (PIKRT), frequently called sustained low-efficiency dialysis (SLED), a form of KRT that uses standard IHD machines to deliver prolonged dialysis sessions at reduced flow rates, with good haemodynamic stability, and at a lower cost. PIKRT is an effective alternative for treating acute kidney injury in critically ill patients in low-resource settings.

Keywords: acute kidney injury; kidney replacement therapy; prolonged intermittent kidney replacement therapy; PIKRT; sustained low-efficiency dialysis; SLED.

INTRODUCTION

Acute kidney injury (AKI) affects between one-third and two-thirds of all patients admitted to the intensive care unit (ICU), with approximately 20% of these patients requiring kidney replacement therapy (KRT) [1,2]. In the majority of critically ill patients, AKI is a complication of severe illness such as systemic sepsis that causes the condition by multiple mechanisms. In a smaller number of patients, it is caused by diseases such as vasculitis, glomerulonephritis or interstitial nephritis. In large multicentre studies [3,4], KRT was required in approximately 10–15% of critically-ill patients with AKI, and overall in-hospital mortality was around 40–45% in patients treated with KRT [5,6].

The available modalities for KRT in acute settings include continuous kidney replacement therapy (CKRT), intermittent haemodialysis (IHD), prolonged intermittent kidney replacement therapy (PIKRT), frequently called sustained low-efficiency dialysis (SLED), and peritoneal dialysis (PD). The different variations of CKRT include continuous veno-venous haemofiltration (CVVH), continuous veno-venous haemodialysis (CVVHD) and continuous veno-venous haemodiafiltration (CVVHDF).

In poor socio-economic settings, the availability and the cost of the modality are important factors in its choice, in addition to other circumstances such as the experience and availability of trained staff. There is a lack of evidence for judging the outcomes of one modality over the other [7]. The ideal modality should therefore be selected based on patient and centre-specific factors including haemodynamic and volume status, metabolic derangements, local expertise and available resources [8].

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The main advantage of CKRT is its superior haemodynamic stability, so that it is recommended in haemodynamically unstable patients, as is often the case in the ICU [9]. Continuous, gentle ultrafiltration allows for more fluid removal in haemodynamically unstable patients, who are often oliguric or anuric, and for continuous intravenous fluid administration and continuous correction of metabolic abnormalities over a 24-hour period. An important disadvantage of CKRT is the need for prolonged anti-coagulation. Variations in delivered dialysis dose and efficiency also arise frequently, as circuit disconnections occur due to clotting of the dialysis lines or because the patient has to be moved, during treatment, for therapeutic and diagnostic manipulations such as radiological or surgical procedures [8].

Haemodynamic instability is reported to complicate 10–70% of IHD treatments compared to 9–43% of CKRT sessions, though definitions vary in published studies [10]. IHD offers more rapid control of life-threatening emergencies such as hyperkalaemia, pulmonary oedema and severe metabolic acidosis [11].

In regions suffering from limited resources, CKRT is not always available, due to its relatively high cost and need for trained staff. Managing haemodynamically unstable patients then becomes more challenging, especially in life-threatening situations [12,13]. PIKRT makes use of existing IHD infrastructure and staff, with adjustments to the standard dialysis prescription to provide better haemodynamic stability. Raina et al. [14] have reported that PIKRT (in the form of SLED) was used in 25% of centres in developing countries and 20% in better-resources settings.

Below, we provide a brief overview of the principles of PIKRT, its advantages and disadvantages, and compare the outcomes of PIKRT and CKRT. We make the case that PIKRT is an easily accessible, effective and affordable treatment for treating AKI in critically ill patients, especially in resource-limited settings, and suggest that it be more widely used.

PRINCIPLES AND DELIVERY OF PIKRT

PIKRT was first described in the form of extended daily dialysis for the support of critically ill patients with AKI by Kumar et al. [15]. It is a hybrid form of KRT, combining the advantages of CKRT, with better haemodynamic tolerability, and IHD, with more rapid metabolic control and lesser need for anti-coagulation. PIKRT is provided using the same machines and infrastructure used for IHD, adjusting the flow rates to be slower and more suitable for haemodynamically unstable patients, and extending the treatment time (6–12 h, vs 3–4 h for IHD) to compensate for the lower efficiency. It is usually provided 4 to 7 times per week [15,16]. PIKRT can be also delivered using CKRT machines and supplies, albeit at higher cost.

Purified water for PIKRT can be prepared using a portable/built-in reverse osmosis machine or there may be a connection to a central water purification system. When using IHD infrastructure for PIKRT, the prescription is adjusted to lower the rates of dialysate flow (Qd), replacement fluid flow and the blood flow (Qb). These modifications result in reduction of the efficiency of solute clearance and, consequently, treatment is provided for a prolonged duration to compensate for the reduced efficiency. Compared to CKRT, clearance is increased, with a shorter duration of treatment. If reducing the efficiency is difficult, as in the case of limited lowering of Qd in some older haemodialysis machines, a dialyser with a small surface area (e.g. paediatric dialyser) can be used to reduce dialysis efficiency.

Many variations of PIKRT have been described, based on the method of solute clearance applied. PIKRT modalities based on diffusive clearance include sustained low-efficiency (daily) dialysis (SLED/SLEDD) and extended daily dialysis (EDD), whereas modalities using convective clearance include haemofiltration and accelerated veno-venous haemofiltration (AVVH). Modalities based on both diffusive and convective clearance include sustained low-efficiency (daily) diafiltration (SLED-f /SLEDD-f) [12,17]. Examples of prescriptions for SLED and SLED-f using standard IHD infrastructure are illustrated in Figures 1A and 1B, respectively.

ADVANTAGES OF PIKRT

In addition to better haemodynamic tolerability in critically ill patients compared to IHD, other advantages of PIKRT include the non-continuous method, allowing for machine-free time for the patient's daily care, investigations, and transport out of the ICU for procedures such as radiological investigations or surgical procedures. This approach may even lead to more ventilator-free days [12]. Significantly fewer days of mechanical ventilation (17.7 vs. 20.9, P = 0.047) were reported for SLED compared to CVVH in the study by Schwenger et al. [13]. Early mobilisation in the ICU is associated with greater muscle strength and improved mobility at hospital discharge [14]. Applying PIKRT at night (nocturnal PIKRT) enables patients to sleep while performing the procedure with minimal interruption. The entire daytime can be used for different procedures when most personnel are available [7]. When compared with CKRT, applying PIKRT is less expensive, which is an advantage in low socio-economic settings. Anti-coagulation use during KRT, with increased risk of bleeding, is a major concern. PIKRT, being of shorter duration than CKRT and

using greater Qb, permits less exposure to anti-coagulation, including the possibility of heparin-free dialysis with the use of frequent saline flushes (Figure 1) [15,16]. It should be noted that employing frequent saline flushes carries the risk of volume overload, so that the infused amount needs to be included in the ultrafiltration goal.

DISADVANTAGES OF PIKRT

One of the most important disadvantages of PIKRT is hypophosphataemia, which can lead to tissue hypoxia [18,19] and ventilator dependence [20]. Early detection and management are important because the effects of phosphate depletion can occur without overt hypophosphataemia. A suggested regimen is starting oral supplementation when serum phosphate is less than 1.1 mmol/L. Intravenous phosphate supplementation should be considered at serum phosphate levels less than 0.6 mmol/L [20].

Adapting drug dosing is another important consideration while implementing PIKRT. Higher drug clearance is expected for PIKRT than for CKRT. Post-session dosing should be considered for drugs such as antimicrobials and anti-seizure medications to ensure proper therapeutic levels [12,18].

Exposure to endotoxins with subsequent activation of inflammation and oxidative stresses [18] is of concern while prescribing PIKRT due to greater blood-dialysate contact time. Using water for dialysis which is not ultrapure can theoretically result in activation of these processes. However, limited data are available on this effect and also on the value of the prophylactic use of endotoxin filters [12,21].

PIKRT AND HAEMODYNAMIC STABILITY

Haemodynamic instability is an important complication of extracorporeal treatment that affects dialysis efficiency and consequently patient outcomes. It can result in early discontinuation of dialysis, organ injury from hypoperfusion, and may adversely affect mortality and kidney recovery in critically ill patients [22]. Better haemodynamic stability was proposed for PIKRT than IHD due to extending the treatment time and lowering the ultrafiltration rate. Reducing osmotic shifts through reducing the efficiency of solute clearance (mainly due to Qd reduction) is another factor accounting for better haemodynamic tolerability in critically ill patients [12]. In a study by Ratanarat et al. [23], mean arterial pressure increased after completion of the first session of PIKRT and for the first three consecutive days of daily PIKRT, together with gradual improvement of

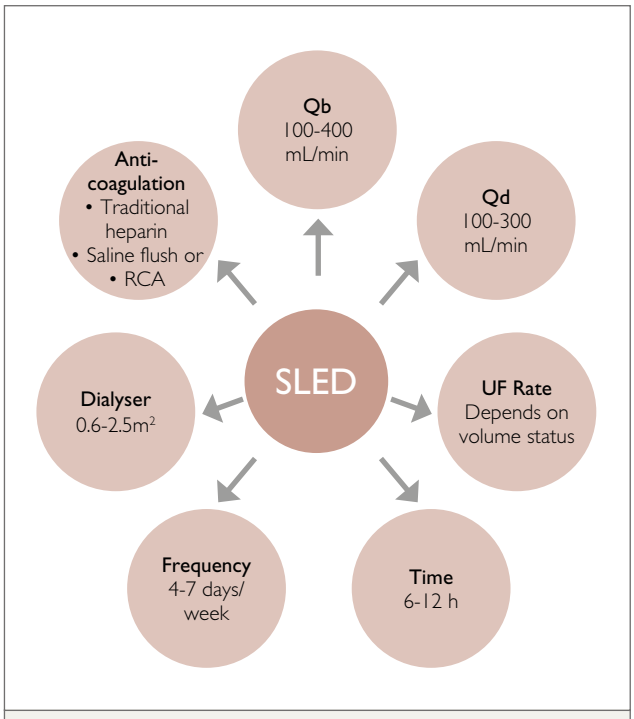

Figure 1A. Suggested technique for PIKRT using SLED (employing diffusion) with a conventional dialysis machine [18].
Abbreviations: PIKRT, Prolonged intermittent kidney replacement therapy; SLED, sustained low-efficiency dialysis; Qb, extracorporeal blood flow rate; Qd, dialysate flow rate; RCA, regional citrate anti-coagulation; UF, ultrafiltration.

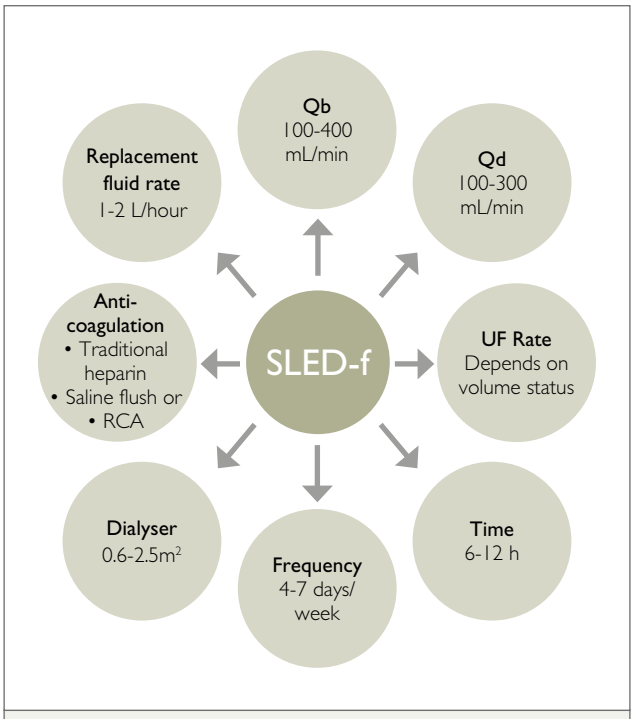

Figure 1B. Suggested technique for PIKRT using SLED-f (employing diffusion and convection) with a conventional dialysis machine [18].
Abbreviations: PIKRT, Prolonged intermittent kidney replacement therapy; SLED-f, sustained low-efficiency diafiltration; Qb, extracorporeal blood flow rate; Qd, dialysate flow rate; RCA, regional citrate anti-coagulation; UF, ultrafiltration.

vasopressor scores. Significant improvement in haemodynamic parameters in patients receiving CKRT compared to IHD was found in a meta-analysis by Rabindranath et al. [24]. Haemodynamic stability was similar for CKRT and SLED. In another meta-analysis by Zhang et al. [25], CKRT and SLED were found to be preferable to IHD in haemodynamically unstable patients with AKI. When comparing modalities of PIKRT, no significant haemodynamic differences were observed between SLEDD-f and SLED despite the patients treated with SLED-f being more critically ill [26]. Although PIKRT is known to offer better haemodynamic stability than IHD, hypotension is still one of its complications. Higher rates of haemodynamic instability were observed during SLED as a modality of PIKRT. Session termination due to haemodynamic instability was observed in 13% of cases, with an incidence of intradialytic hypotension of 36% in our centre's experience [27]. In a systematic review, the risk ratio of hypotension during SLED was 2.0 (95% CI: 0.18–20) [28]. Hypotension occurred more frequently with SLED than with CKRT [29]. Some of the variation in the reported incidence of haemodynamic instability during KRT can be attributed to differences in the definitions used [12]. A proposed contributor to this haemodynamic instability is the small quantities of acetate present in standard bicarbonate dialysate. This can cause a pronounced increase in blood acetate levels, exacerbating cardiovascular instability. In the study by Unakorov et al. [30], patients with post-cardiac surgery AKI were treated with SLED, with either acetate-containing bicarbonate dialysate or acetate-free dialysate, in which acetate was replaced by hydrochloric acid. The use of dialysate containing acetate resulted in blood acetate levels up to 12 times the normal level. Vasodilatation due to increased nitric oxide, hypoxia and increased tumour necrosis factor have all been proposed mechanisms for acetate-induced cardiac depression and hypotension [31].

OUTCOME COMPARISONS

There are fewer outcome studies that compare PIKRT and CKRT than differentiate CKRT and IHD [7,32,33]. This may be because PIKRT is a somewhat modified form of IHD that uses the same technique but with a modified prescription. However, the available data indicate that patient and kidney outcomes across KRT modalities in critical care settings are comparable [34], allowing modality selection to be guided by clinician preference, local resources and practicality. No difference was found between ICU mortality, in-hospital mortality or 90-day mortality in the study by Schwenger et al. [13]. However, they reported reduced nursing time and lower cost for SLED compared to CKRT. Similarly, no difference was observed between SLED and CVVHDF in 30-day mortality in our centre in Cairo, Egypt [29]. A systematic review of 50 trials showed a possible reduced risk of mortality for SLED compared to CKRT, possible higher risk of mortality compared with PD, and no difference in comparison with IHD. When SLED was combined with haemofiltration (SLED-f), it was found to be the most effective intervention at reducing mortality, although the level of certainty was low [32]. Better kidney function recovery has been reported with the use of CKRT than with other modalities, including PIKRT [28]. In a study by Aydin et al. which included 120 patients [32], there was no difference in mortality among the three cohorts who were treated with CKRT, SLED or IHD, respectively; however, CKRT was associated with better kidney recovery than IHD or SLED [32].

CONCLUSIONS

PIKRT, using standard IHD machines and supporting infrastructure, can be used safely and effectively as a method of KRT for critically ill patients with AKI in low-resource settings. In the absence of clear superiority of one dialysis modality over another, the choice of modality should be guided by the local centre's facilities and available expertise. PIKRT may also be viewed as complementary to CKRT and used during weaning from it [9].

Conflict of interest

The author has no conflicts of interest to declare.

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