Review

The role of continuous renal replacement therapy (Crrt) in Coronavirus disease 2019 (Covid-19) patients

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ABSTRACT

Even without the presence of the novel Coronavirus disease 2019 (COVID-19), acute kidney injury has been a serious problem in medicine for decades, with mortality rate up to 70% among those who eventually required renal replacement therapy, and the number has not changed significantly for the last 30 years despite major advances in technology and experience. On the other hand, even without acute kidney injury, COVID-19 was a major cause of death globally in the year 2020, but the occurrence of acute kidney injury among COVID-19 patients is an independent risk factor of increased mortality. Continuous renal replacement therapy has been recommended to treat acute kidney injury in COVID-19 patients instead of conventional intermittent hemodialysis. Moreover, its use might have another beneficial role in stopping the progression of severe COVID-19 by removing pro-inflammatory cytokines during cytokine storm syndrome, which is postulated as the pathophysiology behind severe and critically severe cases of COVID-19. This review will cover a brief history of continuous renal replacement therapy and its modalities, before digging up more into its use in COVID-19 patients, including the optimum filtration dose and timing, membrane filtration used, vascular access, anticoagulation therapy, and drug dosing adjustment during continuous renal replacement therapy.

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Contents

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1. Continuous renal replacement therapy history

Continuous renal replacement therapy (CRRT) was invented to overcome limitations of intermittent hemodialysis in critically ill patients with acute renal failure who are not stable enough to handle the hemodynamic stresses. Therefore, in 1977, continuous arteriovenous hemofiltration was first used to treat 12 patients suffering from renal failure and severe fluid overload. Continuous arteriovenous hemofiltration, however, requires both arterial and venous catheters, while its driving pressure relies on the patient's mean arterial pressure. In the early 1990s, venovenous therapy was introduced as a more superior technique compared to arteriovenous therapy, with more reliable flow rate via circuit rather than patient's own blood pressure and avoidance of complications associated with arterial catheterization [1].

2. Continuous renal replacement therapy modalities and functions

Continuous renal replacement therapy is a type of renal replacement therapy modality that is frequently used in the critical care setting due to its capability in maintaining stable hemodynamic [2]. In order to prevent hemodynamic fluctuation during renal replacement therapy, CRRT provides slower solute and volume clearance per unit time, which usually takes 24 h a day. In CRRT, solute and volume clearance are gained by convection (hemofiltration), diffusion (hemodialysis), or a combination of both of these methods [3,4].

There are several types of CRRT techniques that has been developed and frequently used nowadays including continuous venovenous hemofiltration, continuous venovenous hemodialysis, or continuous venovenous hemodiafiltration. The differences between these types are based on the mechanism of fluid and solute clearance [2].

Continuous venovenous hemofiltration produces high-rate ultrafiltration across semipermeable hemofilter membrane that is made by hydrostatic gradient pressure whereas solute clearance in continuous venovenous hemofiltration happens through convection. In continuous venovenous hemodialysis modes, solute clearance happens through diffusion from blood to dialysate which is perfused across the external surface of the membrane. Continuous venovenous hemodiafiltration is a hybrid mode which combines the dialysate flow of continuous venovenous hemodialysis and high ultrafiltration rate of continuous venovenous hemofiltration and the use of fluid replacement. The hybrid combination of these two modes provide clearance of low molecular weight solute (<500—1.500 Da) and higher molecular weight solute (1.000—20.000 Da) which happened through convection. In addition to diffusion and convection, solute absorption through the membrane binding site contribute to the overall solute clearance in CRRT [3].

3. Continuous renal replacement therapy indications

Generally, indication for CRRT is the same with renal replacement therapy which include volume overload, severe metabolic acidosis, electrolyte disturbances, and uremic symptoms. Other than these absolute indications for CRRT, acute progressive declining in renal function could also be one of the considerations. More detailed explanation about CRRT indications are described in other review articles elsewhere [2—5].

3.1. Volume overload

In patients with acute renal injury, volume overload occurs due to the diminished ability of the kidneys to maintain fluid and electrolyte balances under resuscitation condition (IV crystalloid, blood products, medication) which result in fluid accumulation in both interstitial and intravascular compartments. This condition may happen in patients with or without previous oliguric or anuric condition. In patient with volume overload, renal replacement therapy is usually started when there is a sign of organ dysfunction and is refractory to loop diuretic agents [6].

3.2. Acid-base abnormalities

Impaired renal function results in the increase of anion which causes metabolic acidosis. Severe metabolic acidosis condition that does not respond towards alkali administration or is refractory to any treatments would benefit from the usage CRRT. CRRT is usually suggested when the arterial blood pH is less than 7.1 and bicarbonate level is lower than 12 mmol/L [7].

3.3. Electrolyte abnormality

Hyperkalemia is the most frequently observed electrolyte abnormality in acute kidney injury patients that can result in malignant arrythmias and cardiotoxicity. Refractory hyperkalemia (>6,5 mmol/L despite medical treatment) is one of the absolute indications of renal replacement therapy. CRRT provides effective slower correction of potassium plasma. Other electrolyte abnormality that should be a factor of consideration in initiating CRRT are hyper- or hyponatremia and hyperphosphatemia [8].

3.4. Progressive azotemia and uremia

Severe and late uremic symptoms such as uremic encephalopathy and uremic pericarditis is an indication for immediate renal replacement therapy. Other manifestations of uremia in acute kidney injury patients which should be put in consideration are platelet dysfunction, impaired nutrition, increased susceptibility to infection and sepsis, heart failure, and pulmonary edema. For these reasons, there has been a rising debate whether prophylactic renal

replacement therapy should be done prior to the development of severe uremic manifestation.

3.5. Drug and toxin removal

Renal replacement therapy can be used to clear up drug and toxins from circulation although intermittent hemodialysis is more preferable than CRRT in this setting due to its rapid clearance, which can prevent the emergence of serious complication. Renal replacement therapy is effective to remove smaller molecules (non-protein bound) such as toxic alcohols, lithium, salicylate, valproic acid, and metformin.

3.6. Epidemiology of acute kidney injury in COVID-19

Although majority of COVID-19 cases are considerably mild, around 13.8—25.5% of cases are considered as severe cases [9,10], while 5—6% of the patients require mechanical ventilation or intensive care unit treatment and are considered as critically severe cases [11,12]. Severe cases are described as having either: (1) respiratory rate >30x/minute, (2) SaO 2 ≤93%, or (3) PaO2/FiO2 ratio ≤300 mmHg [13]. Whereas critically severe cases are described as having either: (1) shock, (2) respiratory failure which require the use of mechanical ventilation, or (3) other organ failure and requirement of intensive care unit treatment [13].

Acute kidney injury, a form of organ failure, is found in 3—15% of COVID-19 patients [14,15], and even higher in COVID-19 patients who were admitted to the intensive care unit (14.5—50%) [14,16], and therefore is highly implicated in critically severe cases of COVID-19. Acute kidney injury is also an independent risk factor of increased mortality in COVID-19 patients [15]. Among COVID-19 patients who developed acute kidney injury, about 1.5—9% [17,18] of them required CRRT, and the requirement was found even higher (5.6—23%) [19,20] among severe cases. Despite the efforts, mortality rate of COVID-19 patients receiving renal replacement therapy is unfortunately also high, varying from 51.6 to 100% [11,21—24].

3.7. Etiology and pathophysiology of AKI in COVID-19

Although the exact mechanism of acute kidney injury in COVID-19 is still unclear, COVID-19 acute kidney injury is mostly believed to be a part of collateral damage from the body's excessive inflammatory reaction against COVID-19, which leads to multi-organ failure, rather than its specific clinical feature. Patients from other types of viral infection, such as H1N1 influenza, had also been reported to develop acute kidney injury in a similar number of incidence (18% of H1N1 patients develop acute kidney injury, similar to 3—15% of COVID-19 patients) [25].

The mechanism of injury seems to be due to acute tubular necrosis incurred by sepsis and shock. COVID-19 is also known to activate pro-thrombotic state which may affect the kidneys, causing damages to the renal microcirculation. Histopathological findings post-mortem of COVID-19 patients showed erythrocyte aggregates and microthrombi in peritubular capillaries of the kidneys [26].

Another possible mechanism is the relationship between SARS-CoV-2 and angiotensin-converting-enzyme-2 (ACE2) receptors. ACE-2 receptors are found plentiful in the kidneys and SARS-CoV-2 are known to bind to them, this relationship might have a role in acute kidney injury pathophysiology via direct cytopathic effects [27]. A post-mortem study reported the findings of SARS-CoV-2 particles within the kidneys of non-survivors, this suggests that direct invasion of the kidneys do happen [28]. In contrast, a case report described that in a COVID-19 positive patient who developed acute kidney injury, they did not find viral genetic materials in his

genito-urinary system [29]. These conflicting reports indicate that much is still unknown about the prevalence and the clinical significance of direct viral invasion in COVID-19 acute kidney injury.

3.8. Management of acute kidney injury in COVID-19

In any case, prevention of acute kidney injury development should be the top priority, but when acute kidney injury has already developed, efforts should be made to prevent progression to more severe stages of acute kidney injury. Up to date, there is no specific management of acute kidney injury in COVID-19 patients, management is still based on general guidelines of acute kidney injury by Kidney Disease: Improving Global Outcomes (KDIGO) [30,31]. Indeed, very few studies already published described the use of CRRT in COVID-19 acute kidney injury and its efficacy, and most literature relating to COVID-19 acute kidney injury used Kidney Disease: Improving Global Outcomes guideline as the basic recommendation. Because there is yet evidence to state that COVID-19 acute kidney injury is significantly different to acute kidney injury caused by other disease, several aspects described in this section are based on acute kidney injury in critically ill patients/septic conditions from etiologies other than COVID.

Several conditions that are associated with acute kidney injury and COVID-19 are: hemodynamic disturbance, hypovolemia, inflammation process and cytokine release, fluid overload, hypercoagulable process, and cardiogenic shock. Both hemodynamic disturbance and hypovolemia result in poor circulation and thus renal perfusion, therefore fluid resuscitation and restoration of hemodynamic are vital to prevent further acute kidney injury progression. Viral infection, inflammatory reaction, and cytokine release may cause direct insult to kidney cells, interstitial inflammation, and even contribute to hemodynamic instability. Unfortunately, standardized and effective management for these conditions have not been found. The role of antivirals, ACE2 receptor blockers, anti-inflammatory drugs, and extracorporeal cytokine removal is still under investigations. When there is fluid overload, diuretics and renal replacement therapy may be useful to alleviate renal congestion. COVID-19 is strongly associated with hypercoagulable state, where obstruction of renal microcirculation has been shown in post-mortem study, however the role of anti-coagulant in specifically prevent acute kidney injury due to microthrombi has not been studied. Lastly, cardiogenic shock may also be associated with acute kidney injury due to cardiorenal syndrome and potential strategies to prevent worsening is by optimization of cardiac output [32].

3.9. Indications of renal replacement therapy in COVID-19 patients

Due to still lack of evidence, indications for renal replacement therapy in COVID-19 patients are the same with patients without COVID-19, which include severe electrolyte imbalance and metabolic acidosis, uremia and uremic pericarditis, or hypervolemia [25]. However, hypervolemic COVID-19 patients with severe ventilator dependent respiratory failure (VDRF) may benefit from early initiation of renal replacement therapy because volume overload in this case reduces the efficacy of ventilator support [25].

Cytokine storm syndrome, which involve the uncontrolled and extravagant release of cytokines and may result in disseminated intravascular coagulation, endothelial dysfunction, and finally multiple organ dysfunction syndromes, has been proposed as one mechanism to explain the pathogenesis of severe COVID-19 [33,34]. It was reported that severely ill COVID-19 patients in Wuhan had significantly higher levels of pro-inflammatory cytokines (IP10, MCP1, MIP1a and TNF α) compared to patients with mild symptoms [35]. CRRT may also offer a potential role in blood purification to

remove inflammatory factors in severe COVID-19 patients with high inflammatory response [13].

3.10. Continuous renal replacement therapy use in COVID-19 patients

Similar to acute kidney injury without COVID-19, management mostly include general and supportive management, with renal replacement therapy initiated when necessary [25]. National Institutes of Health (NIH) COVID-19 Treatment Guidelines Panel recommends the use of CRRT in COVID-19 patients who develop acute kidney injury if available, if not the Panel recommends prolonged intermittent renal replacement therapy rather than intermittent hemodialysis [36]. The two earlier modalities are preferred than the later because they do not require a dedicating nurse to oversee the procedure, which helps limit interactions between the infected and the non-infected. Meanwhile, CRRT is more preferred rather than prolonged intermittent renal replacement therapy because dosing is more easily optimized [30,37].

There has not been evidence that CRRT is more superior than intermittent hemodialysis in providing better renal recovery or reducing mortality, however CRRT is associated with more stable hemodynamics in patients with unstable hemodynamics. This advantage is believed due to slower rates of fluid and solute removal [30,37].

3.11. Dosing and initiation timing

Three different modalities in CRRT: continuous venovenous hemodialysis, continuous venovenous hemofiltration, and continuous venovenous hemodiafiltration can be used for COVID-19 patients, however continuous venovenous hemodialysis or continuous venovenous hemodiafiltration are preferable because they have lower risk of circuit clotting (in regard to COVID-19 hypercoagulable state) [30]. CRRT dosing for COVID-19 patients generally follow the same guidelines as non-COVID-19 patients based on Kidney Disease: Improving Global Outcomes. Recommendation for pre-dilution filter is 25—30 mL/kg/h, while for post-dilution filter is 20—25 mL/kg/h. On special occasions, high volume hemofiltration is used to help remove inflammatory mediators, usually in severe sepsis. The recommended clearance dose is > 35 mL/kg/h [25].

It should be noted, however, that there are still conflicting reports regarding the optimum dosing of CRRT for blood purification purposes in severe septic patients. An early prospective randomized trial compared 15 days mortality between three groups of patients with acute renal failure: those assigned ultrafiltration at 20 mL/kg/h (group 1), 35 mL/kg/h (group 2), and 45 mL/kg/h (group 3) [38]. The authors concluded that mortality was significantly higher in group 1 compared to group 2 and group 3, with no significant difference between group 2 and group 3 [38]. Other more recent study, however, reported that there was no significant difference in 90 days mortality between critically ill patients with acute kidney injury and sepsis or at least one other organ failure receiving higher intensity (40 mL/kg/h) and lower intensity (25 mL/kg/h) effluent flow [39]. Another multicenter randomized controlled trial compared the 28-day mortality between 140 critically ill patients with acute kidney injury and septic shock who were assigned to either standard volume hemofiltration (35 mL/kg/h) or high volume hemofiltration (70 mL/kg/h) [40]. They found that high volume hemofiltration did not decrease 28-day mortality [40]. Large, multicenter randomized controlled trial s are necessary to standardize and formulate the optimum dosing for CRRT, especially for severely septic patients who may benefit from inflammatory mediators removal.

Initiation of CRRT is another matter of open debate. A study comparing outcomes of early initiation (within 8 h of diagnosis of acute kidney injury by KDIGO stage 2) versus delayed initiation (within 12 h of stage 3 acute kidney injury or no initiation) of CRRT in 231 patients [41]. The study reported that early initiation of renal replacement therapy decreased 90-days mortality [41]. In contrast, another randomized controlled trial involving 477 patients studied the 90-days mortality between the initiation of CRRT within 12 h of acute kidney injury (early strategy) and a delay of 48 h (delayed strategy) [42]. They concluded that there was no significant difference in overall mortality at 90 days between the two groups [42].

Guidelines for Novel Coronavirus Infection Prevention and Treatment (trial 7th edition) published by the Chinese National Health Commission recommended the use of blood purification therapies to improve the high inflammatory state of severe and critically severe COVID-19 patients [13]. The guideline recommended blood purification system to be initiated in the early or middle stage of cytokine storm, but did not clarify the exact timing any further [13].

It has been suggested that in COVID-19 disease progress there is a window period of 5—7 days between the diagnosis and the onset of multiple organ dysfunction syndromes, while the median time between disease onset and intensive care unit admission is 10.5 days [35,43]. Elevated D-dimer (>0.28 μg/L) and IL-6 (>24.3 pg/mL) levels are excellent predictors of severe pneumonia with 93.3% sensitivity and 96.4% specificity [44]. But even with all these data gathered, the perfect timing to initiate blood purification therapy is still a mystery.

3.12. Membrane for cytokine removal

Initially the rationale behind the extracorporeal blood purification in sepsis patient is to reached the "immune homeostasis". Based on this theory, blood purification technique such as hemofiltration, hemodialysis, and so on, were hoped to be able to control the potential damaged that was induced by the dysregulated immune response. Then this theory leads to a hypothesis, where all the proinflammatory cytokines are being removed at a given rate will cause a cytokine gradient between the blood stream and tissues which will enhance leucocyte trafficking. Other than cytokines removal, the usage of CRRT's membrane in sepsis could also reduce the burden of capillary leaks and adsorbs the amplified cytokine levels. Capillary leaks caused by cytokines storm may induce the global increased permeability syndrome, which could lead to a positive cumulative fluid balance and causing the onset of organ dysfunction.

For inflammatory factors removal, specific filtration membranes need to be evaluated. Inflammatory factors and cytokines such as IL-1, IL-6, and TNF-α are macromolecules, varying in size from 8 to 60 kDa, meanwhile standard filtration membranes only effectively remove molecules within 10—30 kDa. Therefore, high cutoff filters, which membranes have high permeability (pore sizes 60—150 kDa), have been developed for blood purification purposes [45]. In lethal Staphylococcus aureus-induced sepsis animal models, high cutoff filters were reported to be more superior than conventional hemofiltration in improving survival [46]. In human, it was shown to be safely used in septic shock patients in regard to coagulation status and cardiovascular hemodynamics, it was also reported to have high filtration capacity of IL-6, but poor capability in eliminating TNF-α [47]. Even so, a recent double-blind randomized controlled trial involving critically-ill acute kidney injury patients requiring vasopressor compared the use of high cutoff filters and standard hemofiltration and concluded that there was no significant difference in either in-hospital mortality or duration of vasopressor support between the two groups [48].

An in vitro study compared the performance of three single-use blood purification devices which claim to be capable of removing sepsis-associated mediators and endotoxins: oXiris® (Gambro-Hospal, France), CytoSorb® (Cytosorbents, USA), and Toraymyxin® (Toray Industries, Japan) [49]. They reported that oXiris and Cyto-Sorb were able to remove inflammatory mediators in higher rate compared to Toraymyxin, but oXiris and Toraymyxin were superior than CytoSorb in removing endotoxin (lipopolysaccharide) [49]. A prospective case series study with historical controls reported that the use of continuous venovenous haemofiltration using oXiris haemofilter significantly reduced the sequential organ failure assessment (SOFA) score at 48 h post-initiation, although there was no significant difference in mortality between the group treated with oXiris and the historical control group treated using polysulfone-based haemofilter [50]. Another study, though, reported better outcomes of the oXiris treatment, including: lower in-hospital mortality [51], improvement of lactic acid levels and acidosis status [51], and the benefit of not having to use anticoagulation in patients with increased risk of bleeding because of its special heparin-coated column design [52].

3.13. Vascular access

Adapa et al. recommended the site of vascular access for renal replacement therapy in COVID-19 acute kidney injury to be internal jugular or subclavian vein first, with femoral vein as the last alternative, although they did not explain further about the rationale [25]. Kidney Disease: Improving Global Outcomes Clinical Practice Guideline for Acute Kidney Injury, however, recommends the use of right jugular vein as the first choice, followed by femoral vein, left jugular vein, and subclavian vein as the last choice. They explained that subclavian veins are least recommended due to their high risk of catheter-related thrombosis and stenosis. Meanwhile, femoral veins are known for higher risk of infections. Right jugular vein is the most recommended because it has a straight course and therefore catheter inserted should have least contact with vessel wall, and consequently least risk of experiencing thrombosis and stenosis [31].

Catheter length for these veins is adjusted accordingly. Basic guideline of preferred catheter insertion site and catheter length during COVID-19 pandemic is as follow: 15 cm for right internal jugular vein, 20 cm for left internal jugular vein, 15–20 cm for right subclavian vein, 20 cm for left subclavian vein, and 25 cm for femoral vein [32].

3.14. Anticoagulation

Due to hypercoagulable state of COVID-19, systemic anticoagulation should be provided to avoid filter clotting. In patients with normal or hyper-coagulable state, anticoagulation given is based on hospital protocols (can be either heparin or citrate-based anticoagulation) [25]. Although Kidney Disease: Improving Global Outcomes recommends regional citrate anticoagulation rather than heparin if there are no contraindications, citrate-based anticoagulation is not recommended when its protocol is not regularly practiced within the hospital [25]. A meta-analysis comparing the use of heparin and citrate-based anticoagulation for CRRT reported that their efficacy was similar, but citrate-based anticoagulation was associated with significantly lower risk of bleeding, and therefore advised its use in patients with tendencies to bleed who require CRRT [53].

When using unfractionated heparin infusion, the plasma prothrombin time (PPT) target is usually 60–80 s [25]. Patients with thrombocytopenia or international normalized ratio (INR) (INR) > 1.5 are not advised to be given anticoagulation [25]. Some

studies, however, recommends giving argatroban as an alternative in patients with heparin-induced thrombocytopenia. Argatroban, a direct thrombin inhibitor, has been shown to be safe to use in patients with heparin-induced thrombocytopenia undergoing hemodialysis and CRRT [54–56].

3.15. Drug dosing adjustment

Determining the appropriate medication dosage in patient with renal replacement therapy is somehow more complicated. In order to get the correct therapeutic dosages, one must calculate the drug removal from the extracorporeal membrane, residual kidney function, changes in drugs volume distribution and protein binding. These matters are particularly important while treating septic patient with acute kidney injury on CRRT who need antimicrobial treatment.

Antimicrobial drug clearance in CRRT patient depends on its molecular weight, protein binding properties, and volume distribution which may differ for certain type of antibiotics. Other things that should be put in consideration is the type of CRRT modes, duration and intensity which influences the solute clearance. Understanding these methods of drugs clearance is especially needed for narrow therapeutical window antimicrobial such as Amikacin and Vancomycin.

The same thing also applied for the antiviral therapy in COVID-19 patients. Drug removal through CRRT depends on their physiochemical properties and pharmacokinetic variables (such as molecular weight, volume of distribution, and protein binding). Hydrophilic drugs such as favipiravir and remdesivir are easily removed from circulation via CRRT. Remdesivir has low molecular weight, and moderate protein binding, which will make it easier to be removed from the circulation, thus higher dose is needed. Other medication such as favipiravir, has smaller molecular weight, low volume of distribution and low protein binding which should be easily removed by CRRT, but some study showed that elevated favipiravir volume of distribution and elimination rates during CRRT is equal to normal patient. Therefore, dosage adjustment is not recommended. On the other hand, lopinavir/ritonavir and azithromycin has high protein binding property and high volume of distribution which make them difficult to remove by the CRRT [57,58].

Generally, CRRT will clear out almost all the low molecular weight drugs that are non-protein bound depends on the effluent flow. On the other hand, the estimated clearance for the protein bound medication should be measured based on the percentage of the unbound fraction. Medications which blood concentration are measurable, should be adjusted according to their pharmacokinetic property. Meanwhile, medication with observable clinical effects such as analgesics, hypnotic agents, vasopressor and inotropes, doses adjustment should be titrated until the desired effect is reached [58].

4. Conclusion

The incidence of acute kidney injury in critically severe cases of COVID-19 is quite high, and while continuous renal replacement therapy is recommended as the chosen renal replacement therapy, the mortality is still high among patients who eventually received the treatment. Even so, continuous renal replacement therapy has a potentially important role in improving high inflammatory condition in severe cases of COVID-19, which is by removing inflammatory mediators. The most urgent questions that have to be figured out now are the effective standard filtration dosing and the ideal timing to initiate continuous renal replacement therapy to achieve the most optimum result. If we can find the answers to

these, we may be one step closer to finding the key treatment for severe cases of COVID-19 and possibly septic shock caused by other etiologies.

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