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Editorial

Renal Support for Pediatric Patients With Acute Kidney Injury After Cardiac Surgery. What Do We Know Now?

Terapia de apoyo renal en pacientes pediátricos con lesión renal aguda tras cirugía cardiaca. Estado actual de los conocimientos

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Acute kidney injury (AKI) is common in children undergoing complex cardiac surgery (CS) for congenital heart disease. Depending on the patient's age, RACHS (Risk Adjusted classification for Congenital Heart Surgery) score, time on cardiopulmonary bypass (CPB), need for extracorporeal life support (ECLS) and definition of AKI, the incidence of AKI can be as high as 42%, with an incidence of 1%-17% for dialysis and a mortality rate of 20%-100%.[1–6] In their article published in *Revista Española de Cardiología*, Santiago et al.[7] reviewed their 14 years of experience in 81 children with a mean age of 50-54 months who received continuous renal replacement therapy (CRRT) after CS. These children had a higher mortality rate (43%) than those who received CRRT for noncardiac causes (4%). There were 14 patients on ECLS with 3 of them having the CRRT circuit directly connecting to the ECLS circuit. CRRT was initiated when the fluid balance was positive and there was oliguria, or a serum creatinine concentration double that of normal levels for age. Compared with patients receiving CRRT for other causes, those with CS had a higher incidence of CRRT, lower blood pressure, a longer duration of CRRT, and more frequent need for mechanical ventilation. Risk factors associated with mortality were hypotension at the start of CRRT, Pediatric Risk of Mortality Score≥21, and the use of hemofiltration.

AKI after CS can develop as a result of CPB in children. Risk factors for AKI from CPB include young age, CPB duration, surgical complexity, cardiac arrest time, and hypotension. Postoperative factors after CPB contributing to the development of AKI are young age, sepsis, multiorgan failure syndrome, circulatory arrest, ventilator support, low cardiac output, and thrombocytopenia. Children who developed AKI after CS had a higher mortality than those without AKI.[1] Although there seems to be a trend toward decreasing mortality in AKI after CS in the past decade (summarized by Pederson et al.[1]), mortality remains high at 20%-67%. Similarly, the mortality in children who required ECLS after CS was 32%-40%[5,6] but rose to 77%-100% if they required dialysis therapy.[2,5,6] These findings indicate that the need for ECLS increases mortality in children undergoing CS and that the presence of AKI significantly increases mortality in those with or without ECLS.

Common indications for dialysis after CS are fluid overload, AKI, and/or hyperkalemia. Depending on the institution's preference, need for dialysis efficiency, and availability of access, dialysis therapy can be either peritoneal dialysis (PD) or CRRT. Intermittent hemodialysis is not a desirable modality in children after CS due to its impact on systemic hemodynamics. PD is a common technique due to its lower hemodynamic strain, especially in earlier studies and in children not on ECLS. With advances in pediatric CRRT protocols and technology, CRRT has been used more frequently in the past decade. For children on ECLS, CRRT is commonly performed by placing a hemofilter in-line with the ECLS circuit, using a separate vascular access for the CRRT machine, or connecting the CRRT machine directly to the ECLS circuit.[5] Mortality in children who received PD after CS ranged from 20%-57%.[3,8,9] Jander et al.[10] reported a mortality rate of 76% in 25 children who received CRRT after CS. None of these patients required ECLS. While this mortality rate was higher than the 43% reported by Santiago et al.[7] in *Revista Española de Cardiología*, patients in that study were younger (mean 26 months) and had a higher RACHS score, which is usually associated with greater mortality. Another possible explanation for the lower mortality rate in Santiago et al.'s study was he earlier initiation of CRRT. However, the percentage of fluid overload at which CRRT was indicated is not clear in their article. In both studies, low cardiac output and multiorgan failure syndrome were associated with the mortality.

So far, there is no consensus on which dialysis modality, PD or CRRT, should be considered first in children requiring dialysis after CS. Study of this question is still lacking. PD is hemodynamically friendly with few complications such as hyperglycemia, electrolyte imbalance, or leakage. However, it has a lower dialysis efficiency and is subject to the influence of systemic hemodynamic status. In contrast, CRRT is a slower form of hemodialysis that allows for faster removal of fluid and solutes when desired. However, it requires a double lumen vascular access of at least 7 F, which can sometimes be a problem in small infants. Its complications include bleeding, hypothermia, thrombocytopenia, electrolytes and acid-base imbalance, immune activation, altered drug delivery, nutritional loss, and blood loss as a result of circuit clotting. In

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small infants, initiation of CRRT can pose a risk of hypotension due to a relatively large circuit volume.

CRRT can be performed as hemofiltration that has enhanced convective transport and middle molecule clearance or as hemodiafiltration that provides mainly diffusive transport for small molecule clearance. Which technique is preferable for AKI after CS is unknown. In the study by Santiago et al.,[7] the use of hemofiltration predicted mortality. However, it is not clear whether this was secondary to the severity of AKI and/or an electrolyte and acid-base imbalance, which are frequently observed with this technique.

In children who require ECLS after CS, the way in which CRRT is performed may affect the outcome. Although placement of an in-line hemofilter is relatively easy, its blood flow is not controllable and the fluid removal by intravenous pump is subject to error. In addition, it significantly enhances the hemolysis from ECLS.[5] The hemolysis *per se* can be associated with the development of hemoglobulinuria nephropathy. The increased free hemoglobin level from hemolysis can reduce cardiac output and induce coronary vasoconstriction through a nitric oxide scavenging effect.[11] Indeed, the degree of hemolysis was associated with mortality in infants on ECLS who received CRRT through an in-line hemofilter.[5]

Using a separate vascular access for the CRRT machine may not be a feasible option in small children. In addition, it may also enhance hemolysis, as demonstrated in patients with ventricular assist device and a separate CRRT access.[12] Although it remains to be determined, connecting the CRRT machine directly to the ECLS circuit may also enhance hemolysis: CRRT *per se* can induce a mild degree of hemolysis[13] and further injury to red blood cells can occur where relatively smaller CRRT tubings connect to a larger ECLS circuit. So far, no study has compared outcomes among children with different CRRT methods in ECLS. Regarding the dose of CRRT, randomized studies in adults[14] or the observational pediatric CRRT registry[15] did not show an improved outcome with a high-dose CRRT.

In the pediatric CRRT registry, children with a fluid overload of >20% (volume-based method) had higher mortality (65.6%) than those with <20% overload (43.1%). For each 1% fluid overload, mortality increased by 3%.[16] Hayes et al.[17] also reported that a fluid overload of >20% (volume-based method) was a risk factor for non-survival in children undergoing CRRT. These findings are in line with reports that early initiation of PD to reduce fluid overload after CS surgery in infants reduced mortality by 20%-26%.[8,9] In addition, Santiago et al.[7] reported that they initiated CRRT whenever there was a positive fluid balance, which could have been one of the reasons why their patients had lower mortality than those in the study by Jander et al.[10] However, a prospective randomized study that compared early and late initiation of hemofiltration in adults with oliguric AKI failed to show a significant difference in 28-day mortality between the groups.[18] Importantly, the volume-based method (sum of daily [fluid in–fluid out]/intensive care unit or hospital admission weight) used in most studies overestimates fluid overload by not considering the daily insensible loss. For example, the insensible loss for a 10-kg infant is 150 mL due to skin loss. To maintain euvolemia, this infant should have a positive fluid balance of 150 mL/10 kg=1.5% each day. However, according to the volume-based method, this infant would have a 10.5% positive fluid balance at day 7 when the infant is actually euvolemic.

The cause-effect relationship between the degree of fluid overload and CRRT mortality remains to be clarified. Animal studies have demonstrated the "cross-talk" between ischemic renal injury and dysfunction of the brain, lung, heart, liver, and neurons.[19] This "cross-talk" between ischemic renal injury and dysfunction of other organs may explain why there is an increased mortality in patients who develop AKI after cardiac injury and why multiorgan failure syndrome is consistently found to be a mortality factor in these patients. Therefore, fluid overload may simply be a consequence of AKI, and the lower mortality with early initiation of CRRT is due to the interruption of this "cross-talk" between the kidneys and other organs by removal of the proinflammatory cytokines and chemokines involved in the "cross-talk".

In contrast, fluid overload *per se* may exert an adverse effect on organ function. For example, cellular swelling can affect the function, metabolism, and gene expression of renal tubular cells, hepatocytes, and astrocytes.[20] Fluid overload can theoretically cause interstitial edema and compression of tubules and congestive heart failure, which further damages the kidney.

CONCLUSIONS

Despite improvement in surgical techniques and renal support in recent decades, mortality in children who develop AKI after CS remains highly elevated. Many aspects of renal support in these children are still controversial and there is no consensus among centers on how renal support should be provided. Since CPB time is related to the incidence and severity of AKI, as well as to the complexity of CS, one approach to eliminate controversies is to stratify multicenter studies according to RACHS classifications. This way, for each RACHS categoryof, the variables that affect outcome can be reduced, allowing more straightforward data analysis and subsequently the development of practice guidelines to reduce mortality.

CONFLICTS OF INTEREST

None declared.

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