Editorial

High-volume hydration for the prevention of acute kidney injury after cardiac surgery

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Comment on: Lim JY, Kang PJ, Jung HS. Effect of high- versus low-volume saline administration on acute kidney injury after cardiac surgery. J Thorac Dis 2018;10:6753-62.

Submitted Feb 05, 2019. Accepted for publication Apr 09, 2019.
doi: 10.21037/jtd.2019.04.45
View this article at: http://dx.doi.org/10.21037/jtd.2019.04.45

Acute kidney injury (AKI) is a serious complication after cardiac surgery, occurring between 5% to 30% of patients, according to the used definition (1-16). In 6% to 20% of patients experiencing AKI, dialysis is required (11,12). Development of AKI leads to an increase in mortality, both at short- and long-term follow-up (1-18). In particular, it has been showed that 12% to 64% of patients experiencing AKI die, as compared to 1% to 5% of patients not developing AKI (11-15). This mortality risk increases also with minor serum creatinine elevations, exceeding 50% in cases requiring hemodialysis (15). Moreover, AKI has a critical impact on non-renal morbidity, as it is associated after cardiac surgery with a higher rate of respiratory insufficiency, infections, sepsis, and gastrointestinal bleeding (1-12).

Several risk factors for post-operative AKI have been recognized, including age, pre-existing chronic kidney disease (CKD), heart failure history, and/or reduced left ventricular ejection fraction (LVEF), diabetes, protracted cardiopulmonary bypass (CPB) time, and recent administration of nephrotoxic agents (1-16). Notably, in patients with CKD, AKI may occur in about 50% of patients after cardiac surgery and it is associated with an almost ten times increased perioperative mortality (16).

Factors contributing to AKI after cardiac surgery include hemodynamic and metabolic alterations, inflammation, exogenous toxins, vasoconstrictors release, and the interactions between blood components and artificial membranes (18). They all contribute to renal vasoconstriction and ischemia. Thus, the unique characteristics of cardiac surgery using CPB markedly increase AKI risk when compared with other clinical and surgical settings (19-21), mainly due to aorta cross-clamping and exogenous blood product transfusion and vasopressors.

As patients at high-AKI risk can be easily identified before cardiac surgery, the best AKI treatment is its prevention, since its management is only supportive in nature, with renal replacement therapy being the mainstay of treatment for severe renal failure. Among prophylactic measures, hydration represents the cornerstone. Indeed, the kidney receives 20% to 25% of total cardiac output and its medullary portion of the nephrons is particularly vulnerable to ischemia. This area is maintained at low oxygen tension, whereas its active sodium transport is associated with high metabolic activity and oxygen requirements. Thus, not adequate circulating volume leads to renal hypoperfusion and elicits neurohumoral responses, promoting further kidney vasoconstriction. On the other hand, vigorous hydration may counteract these detrimental phenomena by optimizing systemic hemodynamics, increasing renal flow, and preserving medullary perfusion (22). Of note, a previous meta-analysis of 4,220 surgical patients showed that perioperative hemodynamic optimization, obtained by fluids and inotropes reduce the incidence of postoperative AKI (21).

The results of the study published in this issue of *Journal of Thoracic Disease* by Lim *et al.* (23) provided a further contribution to the evolving literature on the potential protective role of hydration against AKI in cardiac surgery. The authors addressed whether high-volume saline

administration is associated with a lower AKI incidence in their retrospective registry of 1,740 patients undergoing cardiac surgery with CPB. They found that high-volume saline administration (arbitrarily defined as more than 1 liter infused in the first 48 postoperative hours) was not associated to a significant different AKI risk (9% *vs.* 9%), need for renal replacement therapy (6% *vs.* 5%), or in-hospital mortality (4% *vs.* 4%), when compared to patients receiving low-volume saline (<1 liter/48 hours; mean 0.5 liters). Strengths of this analysis are an appropriate sample size registry with well-characterized data collection. Moreover, the authors aimed at reducing confounding factors in the assessment of the effect of saline after cardiac surgery with propensity score-matched analysis, which confirmed the study results, even after adjustment for major covariates. However, some limitations warrant mention. This was a single-center study, limiting the generalizability of the results due to potentially unique practice patterns at the study site. Moreover, given its retrospective nature, the results of the study should be considered hypothesis generating only.

The neutral conclusions of this study should be examined according to some relevant clinical aspects. First, in this report, as well as in many previous studies, intravenous saline infusion was started after intensive care unit arrival and not before cardiac surgery. When renal function acutely decreases, serum creatinine rises slowly, usually within days and, although AKI typically occurs during CPB, it is usually recognized later. For this reason, creatinine concentration is a delayed measure of kidney dysfunction in the acute setting (24). Therefore, post-operative hydration does not represent a "truly preventive" measure, but it should be considered only a "renal supportive" strategy which, at best, reduces the severity of the ongoing AKI and facilitates kidney function recovery. Second, the mean saline volume administered in the high-volume group was 2 liters over 48 hours, corresponding to an infusion rate of about 40 mL/hour. If we consider that daily water requirement is 2.5–3 liters/day, corresponding to about 100–120 mL/hour, the fluid amount considered in this study cannot be defined as a high-volume hydration. Rather, it represents a "prudential" (safe more than effective) hydration regimen. Thus, whether a preventive and vigorous saline hydration is beneficial against AKI after cardiac surgery remains unclear, thus far. Lastly, another point that needs to be addressed is the inclusion in this registry of patients at low AKI risk. Of note, AKI incidence in this study was 9–11% (by RIFLE and KDIGO criteria, respectively), a figure lower than that observed in most cardiac surgery series (1-16,25) (*Table 1*). This can be explained by the fact that the mean age of the study population was 59 years, mean LVEF and an estimated glomerular filtration rate were normal and the mean aortic cross-clamp time was less than 100 minutes. As advanced age and reduced cardiac and renal function are the most critical risk factors for AKI, patients presenting with these characteristics should be identified before cardiac surgery, and they represent the ideal subset of patients in whom to implement prophylactic measures. Accordingly, in the meta-analysis by Brienza *et al.* (21), postoperative AKI rate was significantly reduced only in studies in which fluids were administered in high-risk patients.

In conclusion, given its detrimental clinical relevance, every effort should be made to prevent AKI after cardiac surgery. Future trials should deal with AKI as main outcome, share the same definition, and should be performed in patients at high AKI risk. In these patients, a preventive strategy based on an early, preoperative, high-volume fluid administration should be evaluated, in terms of AKI incidence and severity, and of potential morbidity and mortality improvement. Taken together all these considerations, the benefits of a prophylactic high-volume hydration in cardiac surgery still warrant investigation.

Table 1 Overview of the most recent studies focusing on AKI and mortality in cardiac surgery

Author (Ref.), year	Study patients (n)	Age (years, mean)	LVEF (%)	CKD (%)	DM (%)	CBP time (mean, min)	AKI definition (sCr increase)	AKI incidence	Mortality (%)	
									No-AKI	AKI
Kuitunen (1), 2006	813						>50%	19.3	0.9	34*
Sisillo (16), 2008	254	72	55	100	20	115	≥25%	46	0.7	7**
Haase (2), 2009	282	>67		25			≥50%	46	0	5**

Table 1 (*continued*)

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Author (Ref.), year	Study patients (n)	Age (years, mean)	LVEF (%)	CKD (%)	DM (%)	CBP time (mean, min)	AKI definition (sCr increase)	AKI incidence	Mortality (%)	
									No-AKI	AKI
Haase (2), 2009	282	>67		25			>0.3 mg/dL	45	0	5**
Robert (3), 2010	24.747	66	53	27	32		>50%	31	1.4	8.6**
Robert (3), 2010	24.747	66	53	27	32		≥0.3 mg/dL	30	1.3	9.1**
Bastin (4), 2013	1.881	66		33		98	≥50%	25	0.4	4**
Bastin (4), 2013	1.881	66		33		98	≥0.3 mg/dL	26	0.3	4**
Xu (7), 2015	3.245	>51			9	>72	≥0.3 mg/dL	40	0.4	6.2**
Howitt (10), 2018	2.267	66				101	≥0.3 mg/dL	36	3.9	7.8***
Gangadharan (9), 2018	400	61			55		≥0.3 mg/dL	9.2	2.8	13.5*
Borracci (25), 2018	418	72		64	20		≥50%	19.6	2.3	9.6**
Borracci (25), 2018	418	72		64	20		≥0.3 mg/dL	19.6	2.3	9.6**
Lim (23), 2019	1.740	59	58	eGFR 76 mL/min/1.73m^2	16	93	≥50%	9	3.7** (overall mortality)	3.7** (overall mortality)
Lim (23), 2019	1.740	59	58	eGFR 76 mL/min/1.73m^2	16	93	≥0.3 mg/dL	11.4	3.7** (overall mortality)	3.7** (overall mortality)

*, mortality at 90 days; **, in-hospital mortality; ***, mortality at 2 years. AKI, acute kidney injury; CKD, chronic kidney disease; CPB, cardiopulmonary bypass; DM, diabetes mellitus; eGFR, estimated glomerular filtration rate; LVEF, left ventricular ejection fraction; sCr, serum creatinine.

Acknowledgements

None.

Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

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Cite this article as: Cardinale D, Cosentino N, Marenzi G, Cipolla CM. High-volume hydration for the prevention of acute kidney injury after cardiac surgery. J Thorac Dis 2019;11(Suppl 9):S1135-S1138. doi: 10.21037/jtd.2019.04.45

