Perioperative dexmedetomidine reduces the incidence and severity of acute kidney injury following valvular heart surgery

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Acute kidney injury (AKI) following cardiac surgery is closely interrelated with hemodynamic instability and sympathetic activity, and adversely influences prognosis. Here, we investigated in a randomized placebo-controlled trial whether dexmedetomidine, an α2 adrenoreceptor agonist, could prevent AKI after valvular heart surgery. Two hundred patients undergoing valvular heart surgery were randomly assigned to equal placebo or treatment groups. Dexmedetomidine was infused at a rate of 0.4 μg/kg/h starting immediately after anesthetic induction and continuing for 24 h after surgery. We then assessed the incidence of AKI during the first 48 postoperative hours, hemodynamic variables, and a composite of major morbidity end points. The incidence of AKI, based on Acute Kidney Injury Network criteria, was significantly lower in the treatment group compared with the control group (14 vs. 33%). The dexmedetomidine group exhibited a significantly lower incidence of a composite of major morbidity end points (21 vs. 38%) and a significantly shorter length of intensive care unit stay (3 (2, 3) days vs. 3 (2, 4) days) compared with the control group. Thus, perioperative infusion of dexmedetomidine effectively reduced both the incidence and severity of AKI, and improved outcome in patients undergoing valvular heart surgery without untoward hemodynamic side effects.

Kidney International advance online publication, 7 October 2015; doi:10.1038/ki.2015.306

KEYWORDS: acute kidney injury; cardiac surgery; cardiopulmonary bypass; dexmedetomidine

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Received 7 April 2015; revised 25 June 2015; accepted 2 July 2015

Acute kidney injury (AKI) following cardiac surgery is a frequent complication exerting an adverse influence on patient prognosis.[1] As yet, no definite strategy for preventing AKI after cardiac surgery exists. Various factors including ischemia-reperfusion injury, renal hypoperfusion, systemic inflammation, and embolic events, especially in association with cardiopulmonary bypass (CPB), have been thought to be responsible for the development of AKI after cardiac surgery.[1–3]

Renal function is tightly interrelated with hemodynamic stability and sympathetic activity. Surgical stress-induced sympathetic hyperactivation increases catecholamine release resulting in unstable hemodynamics and renal artery vasoconstriction, which is detrimental to renal function.[2] Consequently, sympatholytic action through α2 adrenoreceptors has been thought to be helpful for hemodynamic stability[4,5] and for mitigating renal ischemia/perfusion injury.[6] Activation of α2 adrenoreceptors in the renal vasculature and tubules also inhibits renin secretion, and increases glomerular filtration and secretion of sodium and water.[7]

Dexmedetomidine, a highly selective α2 adrenoreceptor agonist, has theoretical advantages for reducing renal injury, and animal studies have demonstrated the renoprotective efficacy of dexmedetomidine under various conditions.[6,8] However, only a limited number of prospective studies have been conducted in that regard in cardiac surgical patients. Of interest, dexmedetomidine was administered postoperatively and not preemptively in most previous clinical studies,[9,10] whereas the preventive use of dexmedetomidine before renal insult could exert a greater protective effect than when used afterwards.[6]

The aim of this prospective, randomized, and placebo-controlled trial was to investigate the effect of 24-h dexmedetomidine infusion starting immediately after anesthetic induction on the development of AKI after valvular heart surgery.

RESULTS

Patient characteristics, including the Cleveland Clinic score for acute renal failure and the type of surgery performed, were similar between groups (Table 1).

Table 1 | Demographic and perioperative clinical data

	Control group ($n=100$)	Dexmedetomidine group ($n=100$)	*P*-value
Age (years)	62 ± 13	64 ± 12	0.258
Sex (M:F)	51:49	45:55	0.396
Body mass index (kg/m^2)	23.3 ± 3.6	23.4 ± 3.3	0.873
Hypertension	41	50	0.201
Diabetes mellitus	17	22	0.372
Congestive heart failure	12	12	>0.999
MI within 1 month	3	1	0.312
Cerebrovascular disease	13	12	0.831
COPD	2	3	0.651
Medications			
ACEi/ ARB	26/28	35/38	0.167/0.133
β-blockers	38	28	0.133
Calcium channel blockers	29	26	0.635
Diuretics	61	56	0.473
Operation			
Aortic valve replacement	29	34	0.447
Mitral valve replacement	31	35	0.547
Double valve operation	12	6	0.138
Valve + CABG	10	12	0.651
Valve + aorta	18	13	0.329
Preoperative ejection fraction (%)	60 ± 12	63 ± 10	0.053
EuroSCORE	5.4 ± 3.3	4.8 ± 2.8	0.236
Cleveland Clinic Score[a]	2.5 ± 1.3	2.5 ± 1.3	0.873

Abbreviations: ACEi, angiotensin converting enzyme inhibitors; ARB, angiotensin receptor blockers; CABG, coronary artery bypass graft; COPD, chronic obstructive lung disease; MI, myocardial infarction.
Values are mean ± standard deviation or number of patients.
[a]Cleveland Clinic Foundation Acute Renal Failure Scoring System (minimum score = 0; maximum score = 17).

No patient, except those who received renal replacement therapy showed oliguria (<0.5 ml/kg/h) for more than 6 h, fulfilled the definition of AKI according to urine output-based Acute Kidney Injury Network (AKIN) criteria. In addition, patients who received renal replacement therapy all met the serum creatinine criteria for stage 3 of the AKIN criteria. Therefore, both serum creatinine-based AKIN and total AKIN criteria yielded the same results in terms of the diagnosis of AKI in our study. The incidence of AKI was significantly lower in the dexmedetomidine group compared with the control group (14 vs. 33%, $P=0.002$). Fourteen patients (14%) in the control group were diagnosed with stage 2 or 3 AKI, and 5 of these patients received renal replacement therapy. By contrast, only one patient in the dexmedetomidine group was diagnosed with stage 3 AKI ($P=0.003$) and received renal replacement therapy ($P=0.097$) (Figure 1). Overall, dexmedetomidine administration was able to reduce the incidence of AKI with an odds ratio of 0.331 (95% confidence interval; 0.164–0.667, $P=0.002$). Ordinal logistic regression analysis revealed that dexmedetomidine administration would prevent the progression of AKIN stage with an odds ratio of 0.307 (95% confidence interval; 0.152–0.620, $P=0.001$). The group × time interactions on serum creatinine level and estimated glomerular filtration rate (GFR) were not statistically significant between groups in the linear mixed-model analysis (data not shown).

Intraoperative data including fluid balance, transfusion, and the use of vasopressors were not significantly different between groups (Table 2). Heart rate ($P=0.003$) and mean pulmonary artery pressure ($P=0.006$) were significantly lower in the dexmedetomidine group compared with the control group throughout the study period, whereas other hemodynamic variables were comparable between groups (Figure 2). After adjusting for intraoperative parameters as covariates (CPB time, transfusion requirement, and number of patients requiring vasopressin), logistic regression analysis revealed that dexmedetomidine administration was still effective in reducing the incidence of AKI with an odds ratio of 0.307 (95% confidence interval; 0.142–0.662, $P=0.003$).

Postoperative data including fluid balance, transfusion, and the use of vasopressors during the first 48 h after surgery were similar between groups except that the amount of blood loss during the first postoperative 24 h was significantly less in the dexmedetomidine group than in the control group ($P=0.036$) (Table 3). White blood cell and neutrophil counts, c-reactive protein levels, and glucose levels were comparable between groups throughout the study period (data not shown).

The amount of sufentanil infused during the intraoperative period was less in the dexmedetomidine group than in the control group (298 ± 34 vs. 313 ± 41 μg, $P=0.006$). Postoperatively, the number of patients requiring remifentanil infusion (40 vs. 59, $P=0.004$) and its infusion rate (4.2 ± 1.9 vs. 5.7 ± 2.6 μg/kg/h, $P=0.002$) and duration (10 ± 15 vs. 25 ± 38 h, $P=0.009$) were significantly lower and shorter in the dexmedetomidine group than in the control group. The