

ผลของการป้องกันภาวะไตวายเฉียบพลันโดยการให้ Dexmedetomidine ระหว่างการผ่าตัดทำทางเบี่ยงหลอดเลือดหัวใจ

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The Reno-Protective Effect of Intraoperative Dexmedetomidine Infusion in Elective Coronary Bypass Graft Surgery

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บทนำ: ภาวะไตบาดเจ็บเฉียบพลันเป็นปัญหาที่รุนแรงและพบได้บ่อยจากการผ่าตัดหัวใจทำให้เกิดภาวะทุพพลภาพและเสียชีวิตภายหลังการผ่าตัด ยา dexmedetomidine ออกฤทธิ์ยับยั้งการตอบสนองของระบบประสาท sympathetic และลดการตอบสนองของร่างกายต่อความเครียดจากการผ่าตัด ผู้ทำการศึกษาต้องการทดสอบสมมติฐานที่ว่า dexmedetomidine สามารถป้องกันภาวะไตบาดเจ็บเฉียบพลันในผู้ป่วยที่เข้ารับการผ่าตัดทำทางเบี่ยงหลอดเลือดหัวใจแบบไม่ฉุกเฉิน

วิธีการศึกษา: เป็นการศึกษาแบบ double-blinded, randomized controlled trial ผู้ป่วยที่เข้ารับการผ่าตัดทำทางเบี่ยงหลอดเลือดหัวใจแบบไม่ฉุกเฉินที่มีการทำงานของไตปกติจะถูกแบ่งออกเป็นสองกลุ่มคือกลุ่มที่ได้รับ dexmedetomidine (กลุ่ม dexmed) ขนาด 0.5 ไมโครกรัม/กิโลกรัม เป็นเวลา 20 นาที และได้รับยาต่อเนื่องในขนาด 0.4 ไมโครกรัม/กิโลกรัม จนกระทั่งผ่าตัดเสร็จ ส่วนกลุ่มควบคุมจะได้รับ normal saline การระบุความรู้สึกระหว่างผ่าตัดของทั้งสองกลุ่มไม่แตกต่างกัน เก็บตัวอย่างเพื่อตรวจค่า creatinine และ NGAL ในเลือดและค่า NGAL ในปัสสาวะในช่วงก่อนเริ่มผ่าตัดและภายหลังการผ่าตัดที่ 6 และ 24 ชั่วโมง ค่า $p < 0.05$ มีนัยสำคัญทางสถิติ

Background: Acute kidney injury (AKI) is a common and serious complication after cardiac surgery which increases morbidity and mortality. Dexmedetomidine has significant sympatholytic properties and ameliorating stress response. We hypothesized that dexmedetomidine can prevent acute kidney injury in patients undergoing elective CABG.

Methods: This study was double-blinded, randomized controlled trial. Elective CABG patients with normal renal function were allocated to intravenous dexmedetomidine or placebo group. The drugs were bolus 0.5mcg/kg in 20 minutes then 0.4 mcg/kg/hr was infused until the end of the operation. Anesthetic and surgical technique was similar in both groups. Serum creatinine, plasma NGAL and urine NGAL were collected and compared at 0,6,24 hours. P value < 0.05 was considered statistically significant.

Results: Total of 20 patients were enrolled and randomized into dexmedetomidine group (n=10) and control group (n=10). There were no differences in patient characteristic data. Serum creatinine and urinary NGAL at 6 and 24 hours were not significantly different between groups. Plasma NGAL in dexmedetomidine group was significantly less than control group at 6 and 24 hours (149.5 vs 291.4;

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ผลการศึกษา: ผู้ป่วยกลุ่มละ 10 โดยทั้งสองกลุ่ม ระดับ creatinine ในเลือด และ NGAL ในปัสสาวะ ที่ 6 และ 24 ชั่วโมง ไม่มีความแตกต่างกันอย่างมีนัยสำคัญ ในกลุ่ม dexmedetomidine มีระดับ NGAL ในเลือดที่ 6 และ 24 ชั่วโมงน้อยกว่ากลุ่มควบคุมอย่างมีนัยสำคัญทางสถิติ (149.5 vs 291.4; $p=0.016$ และ 118.5 vs 201.5; $p=0.004$) กลุ่ม dexmedetomidine มีปริมาณปัสสาวะระหว่างการผ่าตัดมากกว่ากลุ่มควบคุมอย่างมีนัยสำคัญ (4.5 vs 2.4 ml/kg/hr.; $p=0.011$) และยังพบผู้ป่วยที่มีภาวะไตวายเฉียบพลันในกลุ่มควบคุม 3 ราย แต่ไม่พบในกลุ่ม dexmedetomidine เลย ($p=0.06$)

สรุป: Dexmedetomidine ลดการเกิดภาวะไตวายเฉียบพลันได้ในผู้ป่วยที่เข้ารับการผ่าตัดทางเบี่ยงหลอดเลือดหัวใจแบบไม่ฉุกเฉินที่มีการทำงานของไตปกติโดยวัดจากระดับ NGAL ในเลือด นอกจากนี้ยังกล่าวถึงช่วยเพิ่มปริมาณปัสสาวะระหว่างการผ่าตัดอีกด้วย

คำสำคัญ: การป้องกันการบาดเจ็บต่อไต, การผ่าตัดทางเบี่ยงหลอดเลือดหัวใจ, ภาวะไตวายเฉียบพลัน, dexmedetomidine

$p=0.016$ and 118.5 vs 201.5; $p=0.004$). Moreover, dexmedetomidine group had significantly higher urine output throughout the operation (4.5 vs 2.4 ml/kg/hr.; $p=0.011$). At 24 hours, we found AKI in 3 patients in the control group but none in the dexmedetomidine group ($p=0.06$).

Conclusion: We demonstrated that dexmedetomidine reduced AKI in elective CABG patients when using plasma NGAL as a biomarker. We also found that dexmedetomidine helps promoting intraoperative urine output.

Keywords: acute kidney injury, dexmedetomidine, coronary artery bypass graft, renal protection, cardiopulmonary bypass

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Introduction

Acute kidney injury (AKI) is a common and serious complication after cardiac surgery and is associated with increase mortality; increase length of hospital stays and more resource utilization. Depending on the preoperative kidney function status, the rate of postoperative AKI can be as high as 20% in cardiac surgery patients.¹ Acute kidney injury is characterized by a progressive worsening course, being the consequence of different pathophysiologic mechanisms, with patient-related factors and cardiopulmonary bypass as major causes involving hemodynamic, inflammatory and ischemic and reperfusion injury.² During and after CABG, changes in perfusion pressure, sympathetic tone, hematocrit, body temperature, hemolysis, embolism, blood product transfusion, inflammation and sepsis compromise kidney function. Prevention of AKI after cardiac surgery is important and has been investigated such as promoting renal perfusion, antioxidant utilization or reducing blood

transfusion. No single pharmacological regimen has conclusively proved its efficacy in preventing AKI.

Dexmedetomidine is a selective alpha-2 agonist that provides anxiolysis and analgesia without respiratory depression. It has clinically significant sympatholytic properties and decreases the stress response to surgery and intensive care procedures.³⁻⁶ In animal models involving general anesthesia, dexmedetomidine increases urinary output, suggesting that it reverses a prerenal antidiuretic response.⁷ In a large multicenter study of intensive care unit (ICU) sedation after coronary artery bypass graft surgery, dexmedetomidine increased diuresis and decreased the incidence of high serum creatinine values.⁸

Clinical risk factors associated with AKI after cardiac surgery have been identified. Diagnosis of acute kidney injury using serum creatinine level and urine output are still lack of diagnostic sensitivity in the early postoperative period and become abnormal several hours or days later. These could potentially delay

diagnosis and appropriate prompt treatment of renal injury. Neutrophil gelatinase-associated lipocalin (NGAL) appears to be a novel biomarker for the early diagnosis of AKI.⁹ Earlier studies suggest that plasma and urine NGAL levels can be used as an early biomarker for the detection of AKI following cardiac surgery using CPB.¹⁰⁻¹²

This study aims to compare acute kidney injury after coronary bypass graft surgery between dexmedetomidine group and control group to test the hypothesis that dexmedetomidine could protect kidney function in patients undergoing cardiopulmonary bypass machine facilitated CABG by using plasma and urine NGAL to predict renal function after CABG surgery.

Material & Methods

Patients

After institutional review board approval from ethic committee at Faculty of Medicine, Chulalongkorn University. Written informed consent was obtained from all patients. Patients scheduled for elective coronary artery bypass graft (CABG) surgery was enrolled to the study. Inclusion criteria were age more than 18 years-old with normal preoperative renal function serum creatinine of less than 1.5 mg/dL in female and less than 2.0 in male. Patients had allergy to studied regimen, left ventricular ejection fraction (LVEF) less than 30% and body mass index (BMI) more than 35 were excluded from study as well as those underwent combined surgery. There were 20 patients in this study that were randomly allocated into dexmedetomidine and control group by computer-based randomization. Patients, surgeons and anesthesiologists were blinded to the study groups.

Anesthetic techniques & regimen

General anesthesia was induced with intravenously midazolam 0.1-0.2 mg/kg and fentanyl 5-10 mcg/kg or thiopental 3-5 mg/kg or propofol 2 mg/kg. Patients are intubated with pancuronium 1 mg/kg or rocuronium 0.6-1 mg/kg. Anesthesia was maintained with nitrous oxide in oxygen, isoflurane, fentanyl, and pancuronium

or rocuronium as required. Standard monitoring was provided including an indwelling radial artery catheter and central venous catheter.

After skin incision, the dexmedetomidine group received a loading dose of 0.5 mcg/kg of dexmedetomidine for 20 minutes followed by a continuous intravenous infusion at 0.4 mcg/kg/hr. until the end of operation. The control group received a loading dose and continuous IV infusion of normal saline at the same rate.

During the cardiopulmonary bypass, mean arterial pressure was maintained at 60-80 mmHg or 20% from baseline. If hypertension was detected, nicardipine 0.2 mg was given intravenously. Ephedrine 6 mg or norepinephrine 4 mcg were given within 5 minutes and repeated every 5 minutes if hypotension was presented. Atropine 0.6 mg was administered for bradycardia (heart rate less than 50 beats per minute). After the operation, patients were remained intubated and transferred to Cardio-thoracic intensive care unit.

Sampling & outcome measurement

Blood and urine sampling was collected at the time of skin incision, 6 and 24 hours later for serum creatinine, plasma NGAL and urine NGAL. NGAL level was determined by using quantitative enzyme-linked immunosorbent assay (ELISA). Zhou, et al. reported overall pooled sensitivity of NGAL for the diagnosis of AKI was 0.68 and specificity was 0.79. The overall pooled positive likelihood ratio and negative likelihood ratio were 3.98 and 0.33, respectively, with a diagnostic odds ratio of 13.05.¹³

Perioperative data included urine output, aortic cross clamp time, cardiopulmonary bypass time, operative time, blood products, inotropic/vasopressor drugs, anesthetic agents used, length of ICU stay, and length of hospital stay were documented. AKI was defined as an increase in serum creatinine level by either more than 50% or more than 0.3 mg/dL (compared with preoperative values) after surgery. This definition of AKI has been suggested by the Kidney Disease Improving Outcomes.¹⁴ As from our institute

laboratory reference value, plasma and urine NGAL level higher than 100 ng/ml would be considered as acute kidney injury.

Statistical analysis

Sample size calculation referred from incidence of acute kidney injury after CABG from Wagener's previous study, which is about 20%.^{15,16} Using different between peak level of serum creatinine between AKI and non-AKI group with type I error of 0.05 and type II error of 0.2, total of 10 patients in each group or 20 patients in study were required.

Continuous data were reported as mean/SD and analyzed with student's t-test. Mann-Whitney U test was used to analyze continuous data without normal distribution. Categorical variables were reported as proportions and analyzed using Chi-squared test or Fisher's exact test when an expected value was less than 5. P-value of less than 0.05 indicated a statistically significant difference. Outcome measures were expressed with 95% confidence interval (CI) when appropriate. All analyses were performed with the use of SPSS software version 21 (IBM).

Results

There were 20 patients in this study randomized to dexmedetomidine groups (10 patients) and control groups (10 patients). All the patients enrolled in the study completed it. Patients in both groups were similar in age, sex, body weight, height, BMI, underlying disease, left ventricular function (Table 1). After induction of general anesthesia, dexmedetomidine or normal saline was infused following the protocol. Intraoperative parameters such as operative time, aortic cross clamp time, CPB time, used of vasoactive drugs or amount of blood transfusion were no significant difference (Table 2).

Table 1 Patients characteristics and preoperative status

Parameter	Control (N=10)	Dexmedetomidine (N=10)
Age (years)	66 ± 7	65.5 ± 8.4
Sex (%M)	80%	60%
Body weight (kg)	68.7 ± 12.9	63 ± 13.5
BMI	26.3 ± 5.8	25.2 ± 4.7
ASA II /III	2 / 8	0 / 10
Pre-op LVEF	60.9 ± 13.1	58.6 ± 15.5
Coexisting diseases		
- Diabetics	60%	30%
- Hypertension	70%	90%
- Peripheral vascular disease	0%	0%
- Carotid stenosis	0%	0%
- Cerebrovascular disease	0%	10%
Preop serum Cr (mg/dL)	1.1 ± 0.3	1 ± 0.3

Table 2 Intraoperative parameters

	Control (N=10)	Dexmedetomidine (N=10)	p-value
Number of artery bypass graft(s)			0.675
x1	1	1	
x2	7	5	
x3	2	3	
x4	0	0	
x5	0	1	
x6			
Timeliness (min)			
Operative time	383.5 ± 91.9	370.5 ± 74.2	0.732
Aortic cross clamp time	100.8 ± 23.4	107.5 ± 33.7	0.613
CPB time	137.6 ± 33.3	140 ± 41.7	0.889
Number of Inotropics used			0.607
0	0	0	
1	5	3	
2	3	5	
3	2	2	
Fluids administered (ml)			
Crystalloid	800 ± 434	940 ± 266.5	0.398
Colloid	90 ± 191.2	140 ± 309.8	0.67
Blood products (units)			
PRC	2.2 ± 1.2	1.4 ± 0.7	0.095
FFP	2.1 ± 1.4	1.7 ± 1.2	0.49
Platelets	7 ± 4.8	6.1 ± 5	0.688
Intraoperative urine output (ml/kg/hr)	2.4 ± 1.2	4.5 ± 1.9	0.011*

* indicated p < 0.05

There was no significant difference between groups in baseline serum creatinine at the time of skin incision, 6 and 24 hours later. At first 24 hours, we found the AKI of 3 patients (30%) in the control group but none in the dexmedetomidine group ($p=0.06$) (Table 3). Plasma NGAL baseline were shown no significant difference in both groups. But at 6 and 24 hours later, the dexmedetomidine group was significantly less than the control group (149.5 vs 291.4; $p=0.016$ and 118.5 vs 201.5; $p=0.004$). Moreover, dexmedetomidine group

had significantly higher urine output throughout the operation (4.5 vs 2.4 ml/kg/hr.; $p=0.011$). However, there was no significant difference in urine NGAL at any time point between. Although there was no difference in the length of ICU stay but we found that the dexmedetomidine group had shorten hospital stay but no statistical significance (6.6 vs 9.9 days, $p=0.182$) and none in both groups received the renal replacement therapy. No other postoperative complications were found.

Table 3 Study outcomes

		Control (N=10)	Dexmedetomidine (N=10)	p-value
Serum creatinine (mg/dl)	Time	(mean $\pm$ SD)		
	0 h	1.1 $\pm$ 0.3	1 $\pm$ 0.3	0.401
	6 h	1.1 $\pm$ 0.3	0.9 $\pm$ 0.3	0.208
	24 h	1.2 $\pm$ 0.4	0.9 $\pm$ 0.3	0.053
	48 h	1.2 $\pm$ 0.3	1 $\pm$ 0.3	0.079
Plasma NGAL (ng/ml)	Time	(mean $\pm$ SD)		
	0 h	104.3 $\pm$ 35.5	81 $\pm$ 19.7	0.091
	6 h	291.4 $\pm$ 149.9	149.5 $\pm$ 45.5	0.016*
	24 h	201.5 $\pm$ 69.3	118.5 $\pm$ 29.6	0.004*
Urine NGAL (ng/ml)	Time	(median(range))		
	0 h	29.1 (7.3-211.5)	16.8 (2.8-183.5)	0.656
	6 h	96.2(28.5-6613.0)	25.2(2.4-110)	0.370
	24 h	131.7(21-226.6)	80(11.5-176.2)	0.656
AKI (case)	Time	(Number)		
	6 h	0 (0%)	0 (0%)	-
	24 h	3 (30%)	0 (0%)	0.060
	48 h	3 (30%)	1 (10%)	0.264
Length of ICU stay (days)	(mean $\pm$ SD)	1.4 $\pm$ 0.7	1.3 $\pm$ 0.5	0.715
Length of hospital stay (days)	(mean $\pm$ SD)	9.9 $\pm$ 7.2	6.6 $\pm$ 0.7	0.182
Renal replacement Therapy (case)	(Number)	0	0	-

* indicated $p < 0.05$

Discussion

We observed a significant association between intraoperative dexmedetomidine infusion and lower incidence of postoperative AKI by using plasma NGAL as a biomarker, as well as urine flow rate. Although we were not found the significant difference in the occurrence of AKI as evaluated with serum creatinine, we demonstrated the significant lower level of plasma NGAL when using dexmedetomidine infusion

intraoperatively. However, there was no clinical significant in term of length of ICU stay, length of hospital stays and the rate of renal replacement therapy.

There were significant differences between plasma NGAL between groups but not urine NGAL. McIlroy, et al. found higher urinary NGAL in all postoperative time points in patients who developed in adult cardiac patients with normal renal function.¹⁷ Bennett, et al. found mean urine NGAL level increased 15-fold within

2 h and by 25-fold at 4 and 6 h after cardiopulmonary bypass in pediatric open cardiac surgical patient.¹⁰

We use plasma and urine NGAL for predict renal function after CABG because they are reliable biomarkers for early detecting AKI after cardiac surgery and might result in prompt therapeutic intervention to limit associated morbidity. Recent findings suggest that plasma and urinary NGAL is a sensitive and specific marker of kidney injury in both adult and pediatric patients undergoing cardiac surgery with CPB.⁹⁻¹³

Renal dysfunction after coronary artery bypass grafting is common and is associated with increased morbidity and mortality. Cardiac surgery is associated with activation of sympathetic nervous system, hemodynamics, sympathetic nervous system activity and renal function are closely interrelated. Dexmedetomidine-induced sympatholytic might attenuate catecholamine stress induced complication resulting in prevention of AKI.¹⁸ Earlier study has shown that plasma norepinephrine was reduced at various time points during the infusion of dexmedetomidine.¹⁹ The reno-protective effects of dexmedetomidine including inhibition of renin release, increased glomerular filtration and increased secretion of sodium and water.^{20,21} This can explain increasing intraoperative urine output in our study. Leino, et al. found increase in mean urinary output during first 24 hours in elective low-risk CABG patients receiving dexmedetomidine compare to placebo.²²

Our study had some limitations. We could not demonstrate clinical significant in AKI patient. We followed plasma, urine NGAL and serum level for diagnosis of AKI only until 24 hours after surgery. These levels may increase after 24 hours thus impact on diagnosis of AKI after cardiac surgery. Furthermore, our study included only normal baseline kidney function patients not in reduced kidney function patient. Further study is warranted to study the effect of dexmedetomidine in higher risk cardiac patients along with appropriate dose and duration of infusion.

Conclusions

Our study demonstrated the use of intraoperative dexmedetomidine infusion lowered incidence of AKI in low risk elective CABG patients. Moreover, it associated with an increase in urinary output as compared to placebo. There was no difference in renal replacement therapy, length of ICU and hospital stay.

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