

# Effect of Dexmedetomidine on The Neuroglobin Expression in Elderly Patients With Minimally Invasive Coronary Artery Bypass Graft Surgery

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## ABSTRACT

**Background:** To study the effect of dexmedetomidine (Dex) on the expression of Neuroglobin (Ngb) and postoperative cognitive function in elderly patients undergoing minimally invasive coronary artery bypass surgery.

**Methods:** Forty patients, who underwent elective minimally invasive off-pump coronary artery bypass grafting in our hospital from January 2018 to December 2019, were randomly divided into the Dex group (N = 20) and control group (N = 20). Venous blood samples were taken to determine the expression level of Ngb in both groups. Mini mental status examination (MMSE) was used to detect the cognitive function of patients.

**Results:** The expression level of Ngb in the Dex group was significantly higher than that in the control group at 6h after one-lung ventilation and postoperative 24h ( $P < .01$ ). The MMSE score of the Dex group was significantly higher than the control group at postoperative 7 days and postoperative 30 days ( $P < .01$ ). Although with no statistical significance, the MMSE score of the Dex group was higher than the control group at postoperative 90 days ( $P > .05$ ). The incidence of postoperative cognitive dysfunction (POCD) in the Dex group was significantly lower than that in the control group at postoperative 7 days and postoperative 30 days ( $P < .05$ ).

**Conclusion:** Dex used in elderly patients undergoing minimally invasive coronary artery bypass graft surgery can effectively increase the expression level of Ngb and reduce the incidence of POCD.

## INTRODUCTION

Postoperative cognitive dysfunction (POCD) refers to the condition of neurocognitive decline following surgery in a cognitive and sensory manner [Evered 2018]. POCD has been considered in the anesthetic and surgical literature in isolation

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of cognitive decline, which is common in the elderly within the community and where it is labeled as mild cognitive impairment, neurocognitive disorder, or dementia [Yazit 2020].

Dexmedetomidine (Dex) is a highly selective  $\alpha_2$  receptor agonist with analgesic, sedative, and anti-inflammatory effects that has been shown to reduce the incidence of POCD [Mohite 2019]. Minimally invasive coronary artery bypass graft surgery requires single-lung ventilation, which can cause hypoxemia and affect postoperative cognitive function [Kammerer 2016; Lopez 2017].

Neuroglobin (Ngb) is a globulin that exists in vertebrates and is abundantly expressed in neurons [Gao 2020; Zhang 2019]. It has a high affinity for oxygen, thus increasing the oxygen supply to brain tissue [Zhu 2017]. Ngb is a recently discovered hypoxia-inducible protein, which has a cytoprotective effect in animal models of Alzheimer's disease, stroke, myocardial infarction, and other related diseases [Khan 2006]. Therefore, the purpose of this study was to observe the effect of Dex on the expression of Ngb and postoperative cognitive function in elderly patients with minimally invasive coronary artery bypass graft surgery and to provide clinical references.

## MATERIALS AND METHODS

### Patients

Forty patients, who underwent elective minimally invasive off-pump coronary artery bypass grafting (OPCABG) in our hospital from January 2018 to December 2019, were enrolled. Patients were aged 65-77 years, with weight of 56-75kg.

Inclusion criteria were patients with 1) ASA II or III, and 2) HYHA II or III. Exclusion criteria were patients with 1) dementia and mental history, 2) severe cerebrovascular disease, 3) history of multiple operations, 4) history of severe infection of various systems during the perioperative period, 5) severe perioperative blood loss, severe acid-base balance and electrolyte disturbance, 6) severe abnormal liver and kidney function, 7) no acute myocardial infarction, 8) no history of brain trauma or cerebrovascular accident, 9) no history of diabetes, and 10) no history of mental illness.

With random number tables, the patients were randomly divided into the Dex group (N = 20) and control group (N = 20). This study was approved by the Medical Ethics Committee of the First Affiliated Hospital of Hebei North University (No. K2017001), and all patients signed informed consent forms.

Table 1. General intraoperative information of the two groups

	Dex group (N = 20)	Control group (N = 20)	P
Male, n (%)	9 (45)	10 (50)	.752
Age, years	70.5 ± 4.1	71.4 ± 4.5	.513
Height	166.2 ± 5.3	167.3 ± 5.4	.518
Weight (kg)	68.3 ± 10.1	69.1 ± 9.6	.811
ASA grades, n (%)	-	-	.752
II	10 (50)	11 (55)	
III	10 (50)	9 (45)	
HYHA grades, n (%)	-	-	.749
II	8 (40)	9 (45)	
III	12 (60)	11 (55)	
Number of bypass grafts, n (%)	1 (5)	1 (5)	
Hypertension, n (%)	15 (75)	14 (70)	.732

Age, height, and weight were compared using independent sample t-test. Gender, ASA grades, HYHA grades, and number of bypass grafts were compared using  $\chi^2$  test.

Table 2. Incidence of POCD in the two groups

	Dex group (N = 20)	Control group (N = 20)	P
Postoperative 7 days	2 (10)	8 (40)	.028
Postoperative 30 days	0	4 (20)	.027
Postoperative 90 days	0	2 (10)	.468

POCD, postoperative cognitive dysfunction. Incidence of POCD was compared using  $\chi^2$  test.

### Anesthesia method

The two groups of patients routinely abstained from drinking and fasted for 8 hours before surgery, and no preoperative medication was used. NIBP, ECG and SpO<sub>2</sub> were monitored continuously after entry. The left radial artery was punctured and catheterized under local anesthesia to monitor arterial blood pressure. Anesthesia induction: midazolam 0.04mg/kg, sufentanil 3 $\mu$ g/kg, etomidate 0.2mg/kg, cisatracurium 0.3mg/kg.

After induction, double-lumen endobronchial intubation was performed. During bilateral lung ventilation, tidal volume VT was 7 ~ 8mL/kg, respiratory rate RR was 10-12 beats/min, and inspiratory-expiratory ratio I:E=1:2. During one-lung ventilation, VT=6mL/kg, RR=12-16 times/min, other ventilation parameters remain unchanged, and PETCO<sub>2</sub> is maintained at 35-45mmHg. A four-cavity central venous catheter was inserted into the right internal jugular vein puncture for fluid infusion, CVP monitoring and pumping of vasoactive

Table 3. The hospital stay and postoperative delirium rate in the two groups

	Dex group (N = 20)	Control group (N = 20)	P
ICU stay (h)	35 ± 11	46 ± 12	<.001
Hospital stay (d)	10 ± 1	13 ± 2	<.001
Postoperative 7 days	3 (15)	10 (50)	<.001
Postoperative 30 days	0	5 (25)	<.001
Postoperative 90 days	0	2 (10)	.468

ICU stay and hospital stay were compared using independent sample t-test. Postoperative delirium rate was compared using  $\chi^2$  test.

Table 4. Comparison of Ngb between the two groups

	Dex group (N = 20)	Control group (N = 20)	P
Preoperative 24h (ng/ml)	0.15 ± 0.03	0.16 ± 0.02	.08
6h after one-lung ventilation (ng/ml)	0.28 ± 0.04*	0.19 ± 0.04	<.001
Postoperative 24h (ng/ml)	0.25 ± 0.05*	0.17 ± 0.03	<.001

\*<.01, compared with preoperative 24h. Ngb, neuroglobin. Ngb was compared using independent sample t-test.

drugs. 4-6mg/(kg·h) of propofol and 0.8-1 $\mu$ g/(kg·h) of sufentanil were continuously infused for anesthesia maintenance.

According to the length of operation, 10mg cis-atracurium was injected intermittently to maintain BIS at 40-60. Patients in the Dex group were injected with a loading dose of 0.6 $\mu$ g/kg Dex within 15 minutes before induction of anesthesia, followed by continuous pump injection at a rate of 0.2 $\mu$ g/(kg·h) until the end of the operation; the control group was given the same dose of 0.9% normal saline.

Intraoperative infusion of Ringer's lactate solution, voluven, and autologous blood was performed according to the situation, and vasoactive drugs were used to maintain stable circulation when necessary. At the end of the operation, the infusion of anesthesia was stopped, and the tracheal catheter was returned to the ICU ward. All operations were performed by the same surgeon. After the patient woke up, the postoperative analgesia pump (formula: sufentanil 200 $\mu$ g+ tolansetron 4mg+ normal saline 100ml) was administered at 2ml/h for continuous analgesia for 50h.

### Observation indexes

The primary endpoint is the incidence of POCD. The mini mental status examination (MMSE) was used to detect the cognitive function of patients in the two groups at preoperative 1 day, postoperative 7 days, postoperative 30 days and postoperative 90 days, and the criteria were as follows: a total score of 30, 27-30 as normal, and < 27 as POCD [Yang 2020]. The

Table 5. MMSE comparison of the two groups

	Dex group (N = 20)	Control group (N = 20)	P
Preoperative 1 day	28.5 ± 1.4	28.4 ± 1.3	.745
Postoperative 7 days	24.8 ± 1.3*	20.5 ± 1.4*	<.001
Postoperative 30 days	28.3 ± 1.5†	24.2 ± 1.2*†	<.001
Postoperative 90 days	28.4 ± 1.3†	26.6 ± 1.5†	<.001

\*<0.01, compared with preoperative 1 day; †<0.01, compared with postoperative 7 days. MMSE, mini mental status examination. MMSE was compared using independent sample t-test.

definition of delirium is based on the "Diagnostic and Statistical Manual of Mental Disorders" (DSM IV) [Association AP 1994] criteria: (1) consciousness disorder with reduced ability to focus, sustain, or shift attention; (2) cognitive changes or development of perceptual disorders; (3) acute onset and fluctuating course, and (4) evidence of organic ethological factors. Venous blood samples were taken preoperative 24h, 6h after one-lung ventilation, and postoperative 24h to determine the expression level of serum Ngb in both groups. The incidence of postoperative complications was compared between the two groups.

### Statistical analysis

The trial was powered for tests for two proportions of Dex against normal saline on the incidence of POCD. The sample size calculation was based on the assumption of the incidence of POCD of 0.01% in the Dex group and 16.70% in the control group [Gao 2020]. We estimated that the assignment of 40 patients in a 1:1 ratio to the Dex group versus the control group would provide a power of 64% with a one-sided alpha level of 0.10.

All analyses were performed using SPSS 20.0 software (SPSS, Inc., Chicago, IL, USA). Quantitative data were described as mean ± standard deviation (SD). Normally distributed data, including age, height, weight, ICU stay, hospital stay, Ngb, and MMSE were compared using independent sample t-test. Categorical variables, including gender, ASA grades, HYHA grades, number of bypass grafts, incidence of POCD and postoperative complications were presented as numbers (percentage) and compared using  $\chi^2$  test. Two-tailed probability value of  $P < .05$  was considered as statistically significant.

## RESULTS

There were no significant differences in the general intraoperative information, including gender, age, height, weight, ASA grades, HYHA grades, operation time, number of bypass grafts, and hypertension ( $P > .05$ ) (Table 1).

### POCD

The incidence of POCD in the Dex group was significantly lower than that in the control group at postoperative 7 days and postoperative 30 days ( $P < .05$ ) (Table 2).

Table 6. The incidence of postoperative complications in the two groups

	Dex group (N = 20)	Control group (N = 20)	P
Incision infection	1 (5)	2 (10)	>.999
Ventricular fibrillation	0	0	>.999
Respiratory complications	4 (20)	5 (25)	>.999
Transient renal insufficiency	1 (5)	1 (5)	>.999

Postoperative complications were compared using  $\chi^2$  test.

### Postoperative delirium rate

The ICU stay and hospital stay in the Dex group was significantly lower than the control group. The postoperative delirium rates in the Dex group were significantly lower than that in the control group at postoperative 7 days and postoperative 30 days ( $P < .05$ ) (Table 3).

### Ngb

The expression level of Ngb in the Dex group was significantly higher than that in the control group at 6h after one-lung ventilation and postoperative 24h ( $P < .01$ ). The expression level of Ngb at preoperative 24h was significantly lower than that at 6h after one-lung ventilation and postoperative 24h in the Dex group ( $P < 0.01$ ) (Table 4).

### MMSE score

The MMSE score of Dex group at postoperative 7 days was significantly lower than that at preoperative 1 day ( $P < .01$ ), but the MMSE score at postoperative 30 days and postoperative 90 days were significantly higher than that at postoperative 7 days ( $P < .01$ ). The MMSE score of the Dex group was significantly higher than the control group at postoperative 7 days and postoperative 30 days ( $P < .01$ ). Although with no statistical significance, the MMSE score of the Dex group was higher than the control group at postoperative 90 days ( $P > .05$ ) (Table 5).

### Postoperative complications

There were no significant differences in the incidence of postoperative complications between the two groups ( $P > .05$ ) (Table 6).

## DISCUSSION

Minimally invasive surgery has the advantage of small trauma and quick recovery, which is favored by patients with coronary heart disease. However, bypass of the anterior descending and diagonal branches is suitable for beating-heart coronary artery bypass surgery due to the limited surgical field. In this study, all 40 patients underwent anterior descending coronary artery bypass graft. Beating-heart coronary artery bypass surgery requires single-lung ventilation

[Saha 2019], which is prone to decrease blood oxygen saturation during operation, and its decrease is closely related to the occurrence of POCD [Lopez 2017].

The incidence of POCD in the first week after cardiac surgery has been reported to be as high as 30-60%, which may prolong the length of hospital stay, reduce the quality of life, increase postoperative mortality, and cause a serious burden on individuals and society [Mashour 2015]. Ngb is an oxygen-binding protein that is mainly expressed in nervous tissues where it is considered to be neuroprotective during ischemic brain injury. Therefore, we investigated the relationship between the occurrence of cognitive dysfunction and the expression level of Ngb after minimally invasive coronary artery bypass graft surgery.

Dex can reduce isoflurane-induced neurocognitive damage, acetaminophen-induced liver damage, and myocardial and liver ischemia-reperfusion through a variety of signaling pathways injury [Chou 2019; Geng 2019], it has been clinically proven that Dex can reduce the incidence of delirium and is a better choice for elderly critically ill patients.

Studies have found that Dex can up-regulate the expression level of Ngb and improve the long-term learning and memory ability of rats after hypoxia/reoxygenation injury in the developmental period [Gao 2019]. The results of this study showed that the Ngb expression level of the Dex group significantly increased at 6h after one-lung ventilation and 24h after surgery, while the Ngb expression was not significantly upregulated in the control group, and the Ngb expression level of the Dex group was significantly higher than that of the control group. In addition, the incidence of POCD in the Dex group decreased significantly at postoperative 7 days and 30 days, suggesting that the improvement of POCD by Dex may be related to the increase of Ngb expression level.

MMSE is a POCD screening scale that is simple to operate and has good sensitivity. It is suitable for repeated assessment of cognitive status over time and can reflect the cognitive function status of patients [Myrberg 2020]. Studies have shown that in elderly patients undergoing cardiac surgery, postoperative intravenous acetaminophen combined with intravenous injection of propofol or Dex can reduce postoperative delirium [Subramaniam 2019]. Xu et al [Xu 2017] found that Dex can improve the postoperative cognitive function of elderly patients undergoing laparoscopic ovarian cystectomy under general anesthesia, and effectively reduce the incidence of POCD without obvious or serious adverse reactions. Similarly, the cognitive function status of the control group was significantly lower at postoperative 7 days and 30 days than that before operation, which improved at postoperative 90 days, while Dex can significantly improve the cognitive function at postoperative 7 days and 30 days and has a good preventive effect on the occurrence of postoperative dysfunction in elderly patients.

The limitation of this study was the small sample size, since our hospital is a non-cardiac hospital, and the conclusions remain to be verified by a large randomized controlled study.

## CONCLUSION

Dex used in elderly patients undergoing minimally invasive coronary artery bypass graft surgery can effectively increase the expression level of Ngb and reduce the incidence of POCD.

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