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# Preventive Effects of Dexmedetomidine on Renal Dysfunction and Hemodynamic Stability in Malignant Obstructive Jaundice Patients During Peri-Operative Period

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Statistical Analysis C  
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**Background:** This study aimed to investigate effects of intra-operative administration with dexmedetomidine (Dex) on hemodynamics and renal function in patients with malignant obstructive jaundice.





**Material/Methods:** Our randomized, double-blinded, placebo-controlled study was conducted among 40 patients with malignant obstructive jaundice between August 2009 and March 2011 in The Affiliated Hospital of Inner Mongolia Medical University. The 40 patients were randomly divided into 2 groups: the Dex group (receiving Dex 0.5 µg/kg 10-minutes before induction and then a 0.5 µg/kg/hour maintenance infusion until end of operation 30 minutes) and the Control group (receiving normal saline of same amount and at same rate). The adverse events, including incidence of cardiovascular complications and nausea and vomiting, and length of hospital stay were determined. The level of cystatin C (CysC), retinol-binding protein (RBP), creatinine (Scr), and blood urea nitrogen (BUN) were also evaluated.

**Results:** Dexmedetomidine administration significantly decreased heart rate (HR) and stroke volume variation (SVV) and significantly increased capital venous pressure (CVP) and mean arterial pressure (MAP) values compared to that in the Control group ( $P<0.05$ ). Dexmedetomidine administration significantly upregulated urine volume and significantly downregulated atropine levels compared to the Control group ( $P<0.05$ ). Dexmedetomidine administration significantly improved renal functions, by modulating CysC, RBP, Scr and BUN levels compared to the Control group ( $P<0.05$ ). Dexmedetomidine administration demonstrated no additional side-effects. Dexmedetomidine administration significantly shortened length of hospitalization in the Dex group compared to the Control group ( $P<0.05$ ).

**Conclusions:** Dexmedetomidine plays preventive effects on renal dysfunction and hemodynamic stability in malignant obstructive jaundice patients during peri-operative period.

**MeSH Keywords:** **Dexmedetomidine • Hemodynamics • Jaundice, Obstructive • Pituitary-Adrenal Function Tests**

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## Background

Hemodynamic fluctuations are frequently observed during operation on malignant obstructive jaundice patients. These fluctuations commonly lead to insufficient perfusion of important organs including the heart, brain, and kidney. The kidney is extremely sensitive to ischemia and hypoxia, and prone to post-operative renal dysfunction or even renal failure. Dexmedetomidine has sedative, analgesic effects. It can maintain hemodynamic stability, as well as provide protective effects on vital organs [2–4]. Studies show that the clearance of Dex is not affected by severe impairment of renal function [5,6]. It can also be used safely for patients with biliary malignant tumors. The obstructive jaundice patients always occur the bradyarrhythmia [7], however, the dexmedetomidine could cause a side-effect of bradyarrhythmia [8].

There is currently no relevant literature about the effects of Dex on hemodynamics and renal function in malignant obstructive jaundice patients during peri-operative period. This randomized clinical study was designed to investigate these effects of Dex.

## Material and Methods

### Patients

This study was approved by the ethics committee of The Affiliated Hospital of Inner Mongolia Medical University (Approval No. 03106019). Written informed consent was obtained from each patient. The participants were selected from patients with malignant obstructive jaundice undergoing surgeries from November 2016 to January 2018. A total of 40 participants were enrolled, and they were divided randomly into 2 groups each containing 20 participants. The present interventional RCT design has been registered in Chinese Clinical Trial Registry (ChiCTR) and progress appropriately.

Inclusion criteria: 1) age 18–65 years, 2) ASA class I–III, 3) body mass index (BMI) 18–24 kg/m<sup>2</sup>, 4) cutaneous or sclera icterus, 5) total bilirubin (TBil) >170 µmol/L, 6) surgery performed: cholangiojejunostomy or radical resection of tumor, and 7) no history of renal disease and normal renal function before operation.

Exclusion criteria: 1) neuropsychiatric disorders or unable to cooperate for other reasons, 2) hypotensive or bradycardic, and 3) anaphylactic reaction to anesthetics.

### Anesthesia performance

Participants fasted 6 hours prior to the experiment and avoided drinking 4 hours prior. Catheters were placed in the radial artery and internal jugular vein of all participants. Monitoring of heart rate (HR), invasive arterial pressure (ABP), mean arterial pressure (MAP), blood oxygen saturation (SPO<sub>2</sub>), stroke volume variation (SVV), central venous pressure (CVP), and bispectral index (BIS) was done on all patients. Patients in the Dex group were pre-medicated with dexmedetomidine (0.5 µg/kg, intravenous) 10 minutes before induction of anesthesia, and then given a continuous infusion at 0.5 µg/kg/hour until 30 minutes before the end of operation. In the Control group, the same amount of normal saline was infused at the same time intervals and rate as the Dex group. General anesthesia was induced with sufentanil 0.2–0.3 µg/kg, etomidate 0.1–0.2 mg/kg, and rocuronium 0.6 mg/kg. After endotracheal intubation, ventilation was controlled to maintain the end-tidal CO<sub>2</sub> pressure at 35–45 mm Hg. Anesthesia was maintained with Propofol 4–8 mg/kg/hour, remifentanyl 0.1–0.15 µg/kg/minute, and rocuronium intermittently according to operative needs in order to achieve SVV ≤13%, CVP 5–12 cmH<sub>2</sub>O, and BIS 40–60 during operation. After the operation, the tracheal catheter was removed when the patient met the extubation indications.

### Endpoint

The primary endpoints mainly included hemodynamic changes and the levels of cystatin C (CysC), retinol-binding protein (RBP), creatinine (Scr), and blood urea nitrogen (BUN). Hemodynamic changes (HR, SVV, CVP, MAP) and the dosage of ephedrine and atropine during operation were recorded at the following times: before pump dexmedetomidine (D1), after pump dexmedetomidine (D2), before operation (D3), and post-operative (D4). The level of CysC, RBP, Scr, and BUN were recorded at following the times: pre-operative (T1), immediately post-operative (T2), 24 hours post-operative (T3), and 72 hours post-operative (T4). The secondary endpoints, including cardiovascular complications, incidence of nausea and vomiting, and length of hospital stay, were also recorded in this study.

### Statistical analysis

Statistical analysis was performed with SPSS18.0 software (SPSS, Inc., Chicago, IL, USA). All data are presented as the mean ± standard deviation (SD). Differences within groups were evaluated using paired Student's *t*-test, and clinical variables differences between 2 groups were evaluated using unpaired Student's *t*-test. *P* value less than 0.05 was considered statistically significant.

**Table 1.** Participant demographics (n=20,  $\bar{x}\pm s$ ).

Group	Ages	Sex (Male/Female)	BMI (kg/m <sup>2</sup> )	ASA (I/II)	Operation times (min)	Surgery (c/r*)
Control	54.85±4.96	13/7	22.15±1.23	8/12	212.35±49.89	17/3
Dex	55.00±5.07	12/8	22.07±1.16	10/10	221.35±48.16	18/2
<i>p</i>	0.925	0.744	0.833	0.525	0.065	0.892

\* Cholangiojejunostomy or radical resection.

**Table 2.** Perioperative hemodynamic parameters (n=20,  $\bar{x}\pm s$ ).

Group	Time	HR (beats/min)	MAP (mmHg)	SVV (%)	CVP (cmH <sub>2</sub> O)
Control	D1	74±6.02	75.37±5.66	10.25±2.18	8.75±2.96
	D2	73.62±6.29	72.25±6.89	10.5±2.45	8.25±2.69
	D3	76.62±4.96	67.87±5.46	15.87±2.23	7.6±2.26
	D4	78.2±3.75	69.24±4.32	16.02±2.31	7.2 ±2.08
	D5	79.12±3.68	68.75±6.55	13.25±2.05	6.5±2.46
Dex	D1	74.87±5.51	74.87±7.1	10.25±1.98	9±1.77
	D2	69.62±5.26 <sup>#</sup>	77.87±5.11	10.5±2.45	9.25±1.0
	D3	71±5.5*	73.37±3.85*	10.75±1.58*	9±1.27*
	D4	73±6.3*	72.95±4.6*	10.02±1.67*	8.28±1.56*
	D5	77±4.98*	74.37±6.55*	9.87±1.81*	9.5±1.83*
<i>p</i>		0.0341	0.010	0.047	0.07

Compared with control group, \*  $p<0.05$ ; Compared with D1, <sup>#</sup>  $p<0.05$ .

**Table 3.** Transfusion volume and vasoactive agent in two group (n=20,  $\bar{x}\pm s$ ).

Group	Input (ml)	Output (ml)	Urine volume (ml)	Ephedrine (mg)	Atropine (mg)
Control	2130.00±365.77	761.00±137.00	617.00±131.00	5.4±0.50	0.52±0.31
Dex	2062.50±399.96	868.50±153.79	733.50±130.44*	5.3±0.78	0.28±0.21*
<i>p</i>	0.581	0.697	0.045	0.968	0.010

Compared with control group, \*  $p<0.05$ .

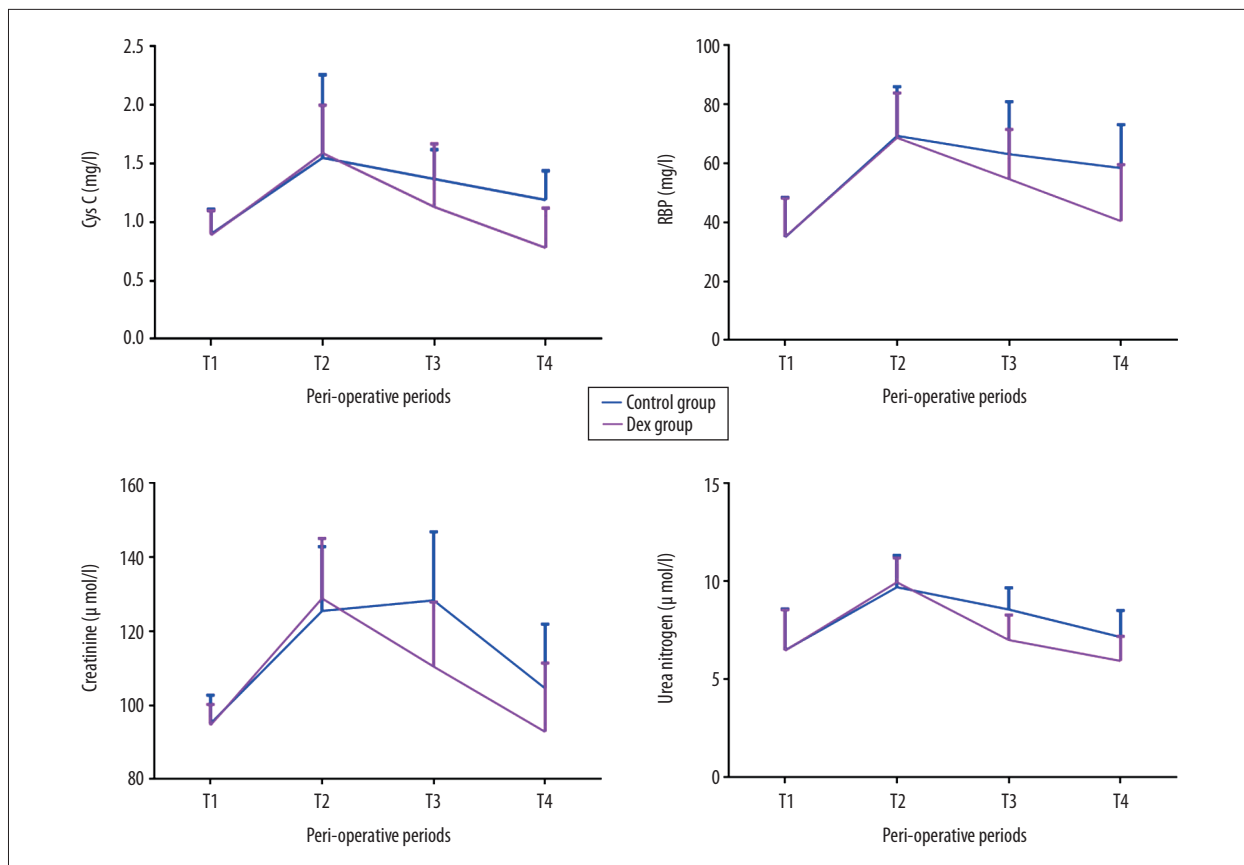
## Results

### Demographics of the patients

A total of 40 patients were included in the study, with 20 individuals in the Dex group and 20 individuals in the Control group. Demographic data are summarized in Table 1. There were no significant differences between the 2 groups.

### Dexmedetomidine administration decreased HR and SVV and increased CVP and MAP values

Compared with the Control group, the HR and SVV values of patients in the Dex group were significantly decreased at D3, D4, and D5, respectively (Table 2,  $P<0.05$ ). Meanwhile, the CVP and MAP values were also significantly increased compared to that in the Control group (Table 2,  $P<0.05$ ). Moreover, the HR at D2 was significantly decreased compared to that at D1 (Table 2,  $P<0.05$ ).



**Figure 1.** Comparison of peri-operative renal indicators.

### Dexmedetomidine administration upregulated urine volume and downregulated atropine levels

The results indicated that the urine volume levels were significantly upregulated in the Dex group compared to that in the Control group (Table 3,  $P < 0.05$ ). Meanwhile, the atropine levels in the Dex group were also decreased significantly compared to that in the Control group (Table 3,  $P < 0.05$ ). However, there were no significant differences for the input/output levels and ephedrine levels between the 2 groups (Table 3,  $P < 0.05$ ).

### Dexmedetomidine administration improved the renal functions

In order to evaluate the renal functions, the associated parameters, including CysC, RBP, Scr, and BUN were examined in this study. The results showed that compared with the Control group, the levels of CysC, RBP, Scr, and BUN were significantly reduced in the Dex group at peri-operative periods of T2, T3, and T4 (Figure 1, Table 4,  $P < 0.05$ ). Meanwhile, in the Dex group, the levels of CysC, RBP, Scr, and BUN were also increased following with the peri-operative periods (Figure 1, Table 4,  $P < 0.05$ ).

### Dexmedetomidine administration demonstrated no other side-effects

In our study, the common side-effects, including hypotension, bradyarrhythmia, nausea and vomiting, were evaluated. The results showed that there were no significant differences for the aforementioned side-effects between the Control group and the Dex group (Table 5,  $P > 0.05$ ). This result suggested that the dexmedetomidine administration was safe.

### Dexmedetomidine administration shortened the hospitalization time

The hospital study time could reflect the efficacy of the dexmedetomidine administration; therefore, we evaluated the length of hospitalization. The result indicated that the length of hospitalization was significantly shortened in the Dex group compared to that in the Control group (Table 5,  $P < 0.05$ ).

## Discussion

In this study, participants in the dexmedetomidine (Dex) and the Control groups had no significant differences in general

**Table 4.** Parameters of peri-operative renal function (n=20,  $\bar{x}\pm s$ ).

Group	Time	Cys C (mg/L)	RBP (mg/L)	Scr ( $\mu$ mol/L)	Bun (mmol/L)
Control	T1	0.90 $\pm$ 0.21	34.95 $\pm$ 13.5	95.06 $\pm$ 7.69	6.5 $\pm$ 2.11
	T2	1.55 $\pm$ 0.31#	69.4 $\pm$ 16.71#	125.5 $\pm$ 17.41#	9.72 $\pm$ 1.62#
	T3	1.37 $\pm$ 0.25#	63.15 $\pm$ 17.85#	128.4 $\pm$ 18.51#	8.58 $\pm$ 1.10#
	T4	1.19 $\pm$ 0.25#	58.45 $\pm$ 14.72#	104.6 $\pm$ 17.35#	7.17 $\pm$ 1.36#
Dex	T1	0.89 $\pm$ 0.21	35.11 $\pm$ 13.15	94.65 $\pm$ 5.6	6.48 $\pm$ 2.09
	T2	1.59 $\pm$ 0.41**	68.7 $\pm$ 15.24**	128.9 $\pm$ 16.2**	9.97 $\pm$ 1.25**
	T3	1.13 $\pm$ 0.54**	54.7 $\pm$ 16.83**	110.45 $\pm$ 17.46**	7.02 $\pm$ 1.28**
	T4	0.78 $\pm$ 0.34**	40.4 $\pm$ 19.26**	92.85 $\pm$ 18.56**	5.95 $\pm$ 1.26**
<i>p</i>		0.045	0.011	0.034	0.049

Compared with T1 in control group, #  $p < 0.05$ ; compared with control group, \*  $p < 0.05$ .

**Table 5.** Primary and secondary outcome variables.

Group	Hypotension	Bradycardia	Nausea and vomiting	Length of hospitalization
Control	2	0	3	18.80 $\pm$ 6.28
Dex	3	1	1	16.55 $\pm$ 5.87*
<i>p</i>	0.079	0.098	0.080	0.021

Compared with control group, \*  $p < 0.05$ .

demographics or intra-operative fluid input. The CVP of patients in the Control group after the operation (D4) showed a significant decrease compared with that before the operation (D3). SVV showed an increasing trend, which was closely related to the insufficiency of effective blood volume before the operation, as well as the inhibitory effects of narcotic drugs on the circulatory system. However, SVV of patients in the Dex group at various time points fluctuated less with CVP, which correlated with the loading dose of dexmedetomidine given before operation and the maintenance infusion given during the operation. It was also demonstrated that dexmedetomidine could reduce the influence of hemodynamic fluctuations on renal dysfunction. The heart rate of patients in the Dex group was lower than that of patients before infusing dexmedetomidine, due to the drug's action on central alpha 2 receptors which reduces sympathetic excitability. Additionally, patients with malignant obstructive jaundice had higher inhibition of vagus nerve tension, which made them more prone to bradycardia. After injection of atropine, these patients quickly return to normal without irreversible circulatory fluctuations or organ function damage.

At present, Scr and BUN are commonly used in the clinic to predict post-operative renal function damage 24 hours after surgery. These 2 indicators are easily influenced by many factors,

and exhibit hysteresis, so they cannot be used as sensitive indicators of renal dysfunction [9]. However, this study showed that CysC was more sensitive in early diagnosis of renal dysfunction than Scr and BUN, and has many advantages in early diagnosis of renal dysfunction. CysC is removed by the kidney and can freely pass through the glomerulus [10]. The renal tubules do not secrete or excrete CysC, so the blood content remains relatively constant. Other benefits include lack of tissue specificity, constant expression, and fewer influencing factors. As shown in Table 5, CysC in the Dex group increased significantly within 24 hours after operation compared to the Control group, which indicates that trauma and anesthesia operation damaged renal function to different extents, and gradually decreased after 24 to 72 hours. Additionally, we found that dexmedetomidine improves glomerular filtration rate and increases urine volume, and reduces renal tubular damage. When RBP value increases in serum, it indicates the renal proximal tubule is damaged, so it is regarded as a sensitive diagnostic indicator of subclinical renal function damage. In this study, urine RBP [11] in the Dex group was significantly lower than that in the Control group at 24 hours post-operative (T3) and 72 hours post-operative (T4). This reveals that dexmedetomidine may increase the re-absorption rate of RBP in renal proximal tubules and reduce the occurrence of renal tubular injury in the peri-operative state.

Dexmedetomidine can reduce the dosage of narcotic drugs and other sedatives, and correspondingly reduce the side effects of these drugs, especially in larger trauma surgery setting [12,13]. In this experiment, the nausea and vomiting and hospitalization time in the Dex group were significantly shorter than those in the Control group, which may be related to the aforementioned factors. There was no statistical difference in the number of post-operative cardiovascular complications between the 2 groups. The combined effects of dexmedetomidine action at the alpha 2 receptor inhibit sympathetic nerve tension and hyperfunctioning vagus nerve in patients with malignant obstructive jaundice lead to hypotension and bradycardia, but short-term application during the operations did not lead to increased post-operative cardiovascular complications. At the same time, the hospitalization time in the Dex group was shorter than that in the Control group which reduced the hospitalization expense.

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## Conclusions

Intra-operative infusion of dexmedetomidine can prevent renal dysfunction of patients with malignant obstructive jaundice, reduce adverse reactions, accelerate post-operative rehabilitation, and reduce medical expenses.