Int J Clin Exp Med 2020;13(1):56-64
www.ijcem.com /ISSN:1940-5901/IJCEM0103358

Original Article

Effect of dexmedetomidine on myocardial protection in pregnant patients with hypertensive disorders in caesarean section and its impact on changes of homocysteine and D-dimer

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Received October 10, 2019; Accepted December 9, 2019; Epub January 15, 2020; Published January 30, 2020

Abstract: Objective: This study aimed to investigate the effect of dexmedetomidine on pregnant patients with hypertensive disorders in caesarean section and on changes of homocysteine and D-dimer. Methods: In total, 78 pregnant patients with hypertensive disorders and caesarean section were selected for a random and double-blind study. Pregnant women with myocardial protection by normal saline injection were enrolled in group A, while pregnant women with myocardial protection by dexmedetomidine injection were enrolled in group B; with 39 women in each group. The changes of related indicators of cardiac injury (creatine kinase isoenzyme (CK-MB), heart fatty acid binding protein (hFABP) and heart rate) were compared between the two groups before operation (T0), at the beginning of anesthesia induction (T1), at the end of operation (T2), and at one day after operation (T3). The levels of homocysteine (Hcy) and D-dimer (D-D) at T0, T1, T2 and T3 were compared between the two groups. Results: The level of CK-MB, hFABP, Hcy l and D-D at T1, T2 and T3 in group B were significantly lower than that in group A ($P < 0.001$). The heart rate at T1 and T2 in group B was significantly lower than that in group A ($P < 0.001$). The operation time, postoperative hospital stay, intraoperative bleeding volume, automatic respiratory recovery time and extubation time in group B were less than those in group A. The incidence of chills, hypotension, bradycardia and respiratory depression complications in group B were significantly lower than those in group A ($P < 0.05$). Conclusion: Dexmedetomidine has more effective myocardial protection in patients with pregnant hypertensive disorders in caesarean section, and it has better effect on down-regulating the surgical indicators of Hcy and D-D, better recovery and safety; which is worthy of wide clinical promotion.

Keywords: Dexmedetomidine, pregnant hypertensive disorders in caesarean section, myocardial protection, homocysteine, D-dimer

Introduction

Pregnancy-induced hypertension is a common gynecologic and obstetric disease. It is common in clinical pregnancy after 20 weeks of gestation. The incidence of pregnancy-induced hypertension is high [1, 2]. With the change of social environment in recent years, the incidence of pregnancy-induced hypertension has been increasing year by year due to living habits and dietary structure [3, 4]. Acute myocardial injury and cardiovascular complications are induced during cesarean section in patients with pregnancy-induced hypertension, and the severe cases can cause death. It is a threat to maternal and infant health [5]. It has been reported that creatine kinase isoenzymes (CK-MB) and heart-type fatty acid binding protein (hFABP) are important indicators of myocardial function [6]. Reducing the degree of myocardial injury in pregnant women during cesarean section is a hotspot for clinicians [7]. In view of the duration, trauma and inflammation of cesarean section [8], choosing the appropriate anesthesia method can reduce the injury of various organs in pregnant women to a certain extent, and reduce the inflammation, stress reaction and blood hypercoagulability during the operation [9]. Dexmedetomidine, as a highly effective α2 adrenergic receptor agonist, is a common

Table 1. General clinical data of two groups of patients

Group	Group A (n=39)	Group B (n=39)	t/X^2	P
Age	25.70 ± 6.28	25.38 ± 6.44	0.222	0.825
Body mass index (kg/m^2)	18.25 ± 2.92	18.19 ± 2.75	0.093	0.96
Alcohol intake			0.000	1.000
Yes	0 (0.00)	0 (0.00)		
No	39 (100.00)	39 (100.00)		
Smoking situation			0.000	1.000
Yes	0 (0.00)	0 (0.00)		
No	39 (100.00)	39 (100.00)		
Thyroid function test				
FT3 (pmmol/L)	4.16 ± 0.83	5.78 ± 0.53	10.270	<0.001
FT4 (pmmo/L)	10.38 ± 2.62	11.48 ± 4.74	1.268	0.209
TSH (μIU/m L)	1.92 ± 0.35	2.65 ± 0.71	5.759	<0.001
Blood routine				
Hb (gm/dl)	9.33 ± 1.21	10.92 ± 2.85	3.207	0.002
RBC (×10^{12}/L)	4.04 ± 0.10	4.34 ± 0.36	5.014	<0.001
PLT (×10^9/L)	137.01 ± 15.20	120.15 ± 19.72	4.229	<0.001
liver function				
ALT (U/L)	21.03 ± 9.02	19.34 ± 8.44	0.854	0.396
AST (U/L)	18.12 ± 7.54	17.42 ± 7.68	0.406	0.686

anesthetic drug and has been widely used in clinic [10]. Relevant studies have found that dexmedetomidine is effective in alleviating inflammation and hypercoagulability [11, 12]. It has been suggested that the increase of homocysteine (Hcy) and D-dimer (D-D) is closely related to inflammation, stress reactions and hypercoagulability during operation [13, 14]. This study aims to explore the effect of dexmedetomidine on myocardial protection in pregnant patients with hypertensive disorders in caesarean section and its impact on changes of homocysteine and D-dimer.

Materials and methods

Case data

In total, 78 pregnant patients with hypertensive disorders and caesarean section admitted to our hospital from April 2017 to February 2018 were selected for a random and double-blind study. Pregnant women with myocardial protection by normal saline injection were enrolled in group A, while the pregnant women with myocardial protection by dexmedetomidine injection were enrolled in group B; with 39 cases in each group. The age range of group A was (22-39) years, with an average age of (25.70 ± 6.28) years; while the age range of group B was (23-38) years, with an average age of (25.38 ± 6.44) (**Table 1**).

Inclusion and exclusion criteria: (1) Only patients with pregnancy-induced hypertension in our hospital were included in this study [15]. There were no abortions caused by chromosomes, anatomy, endocrine abnormalities, reproductive system infections and autoimmune diseases, etc. (2) This study excluded patients with hypertension, hepatitis B virus, gallstones, AIDS and various blood diseases, and pregnant women with abnormal pregnancy history. The participants and their families signed informed consent in advance, and this study was approved by the Gansu Maternal and Child Health Hospital Obstetrics and Gynecology Ethics Committee.

Treatment methods

The venous access was established immediately after entering the operating room in both groups, and the bispectral index was detected at the same time (the interval was maintained between 40 and 50). General anesthesia with tracheal intubation was carried out in group A and group B. The induction schemes were as follows: midazolam 0.1 mg/kg, vecuronium 0.1 mg/kg (Medicine H19991172, Shanghai Hengrui Pharmaceutical Co., Ltd.), sufentanil 0.5 μg/kg (Medicine H20054172, Yichang Humanwell Pharmaceutical Co., Ltd.) and etomidate 0.4 mg/kg (Medicine H32022999, Jiangsu Ehwa Pharmaceutical Co., Ltd.) were injected intrave-

nously at first. After induction, tracheal intubation and mechanical ventilation were performed. Sufentanil 0.6 μg 2 $kg^{-1}·h^{-1}$ (Medicine H20054172, Yichang Humanwell Pharmaceutical Co., Ltd.) and propofol 5-10 $mg.kg^{-1}.h^{-1}$ (Medicine H20010368, Xi'an Libang Pharmaceutical Co., Ltd.) were injected by constant-speed pump.

Myocardial protection of pregnant women in group A was performed by normal saline injection. The normal saline was pumped at a constant rate 15 minutes before induction of anesthesia. The dosage of normal saline was 1 $μg·kg^{-1}·h^{-1}$. The normal saline was injected during induction of anesthesia (the dose was halved compared with that before induction) until the end of operation. Myocardial protection of pregnant women in group B was performed by dexmedetomidine injection (Medicine H20130027, Xcisen Pharmaceutical Co., Ltd.). Dexmedetomidine was pumped at a constant rate 15 minutes before induction of anesthesia. The dosage standard was the same as the normal saline. At the beginning of anesthesia, the dosage of dexmedetomidine was reduced by half. During the induction of anesthesia, dexmedetomidine was pumped at a constant rate until the end of the operation.

Outcome measures

The general clinical data of the two groups were compared. The changes of related indicators of cardiac injury (creatine kinase isoenzyme (CK-MB), heart fatty acid binding protein (hFABP) and heart rate) were compared between the two groups before operation (T0), at the beginning of anesthesia induction (T1), at the end of operation (T2), and at one day after operation (T3). The levels of homocysteine (Hcy) and D-dimer (D-D) at T0, T1, T2 and T3 were compared between the two groups. The operative indicators (operation time, postoperative hospital stay, and intraoperative bleeding volume) and recovery (automatic respiratory recovery time and extubation time) of the two groups were compared. The complications (chills, hypotension, bradycardia and respiratory depression) of group A and group B were compared.

Observation indexes

The two groups were compared for general clinical materials, changes in indexes associated with myocardial damage at different time points, including CK-MB, hFABP (ELISA) and heart rate, Hcy and D-D levels at various time points (preoperative (T0), at the beginning of anesthesia induction (T1), upon completion of the operation, (T2), 1d after operation (T3)) by ELISA, surgical indexes (operation time, postoperative length of stage (LOS), intraoperative amount of bleeding), and recovery (time required to recover autonomous respiration, and time for extubation), and complications (shivering, hypotension, bradycardia and respiratory depression).

ELISA

Venous blood was sampled at various time points, centrifuged at 3500 r/min, stored in a refrigerator of -20°C, and tested for levels of Hcy, D-D, CK-MB and hFABP by ELISA in strict accordance with its instructions on the test kit (Shanghai Tongwei Industry Co., Ltd.) and following steps: 100 ml standard solution, sample, negative and positive control solutions from reaction wells were taken and added with 100 ml antibody solution for biological reaction. Then, the solution was covered and left to stand for 40 min before mixing. Next was the addition of 100 ml streptavidin into each reaction well, covered with film, and rested for 40 min. Solution in the reaction wells was then discarded, reaction substrates A and B were added at an amount of 100 μl, covered with film and placed in a dark environment for 5 min. After addition of 100 μL stop buffer into each reaction well, an enzyme labeling analyzer was used to measure the OD of each well at the wavelength of 450 nm, and calculate the levels of Hcy, D-D, CK-MB and hFABP.

Statistical methods

SPSS 17.0 (Beijing Bi Insight Information Technology Co., Ltd.) software system was applied for statistical analysis. The enumeration data were expressed by [n (%)]. The enumeration data between the two groups were tested by chi-squared test. The measurement data were tested by ($x \pm s$). The comparison between the two groups was detected by independent sample t test. The comparison at different time points in the group was corrected by Bonifacio method, and expressed by F test. $P < 0.05$ indicates the difference was statistically significant.

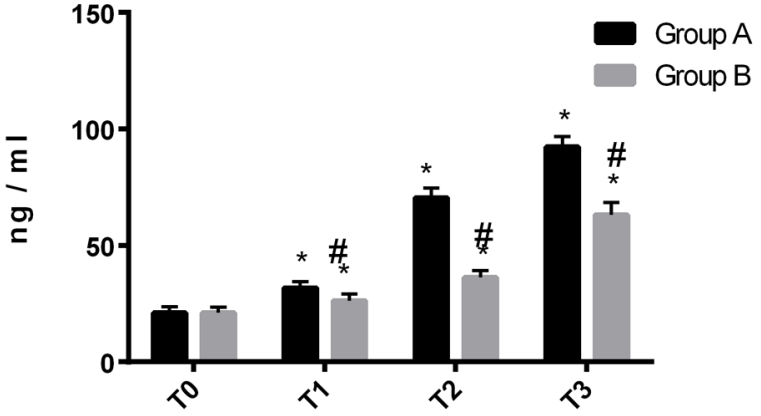

Figure 1. Changes of CK-MB levels in group A and group B at different time points. * indicates that the CK-MB levels of group A and group B at T0-T3 were up-regulated (P < 0.001). # indicates that the CK-MB levels of group B at T1, T2 and T3 were lower than those of group A (P < 0.001).

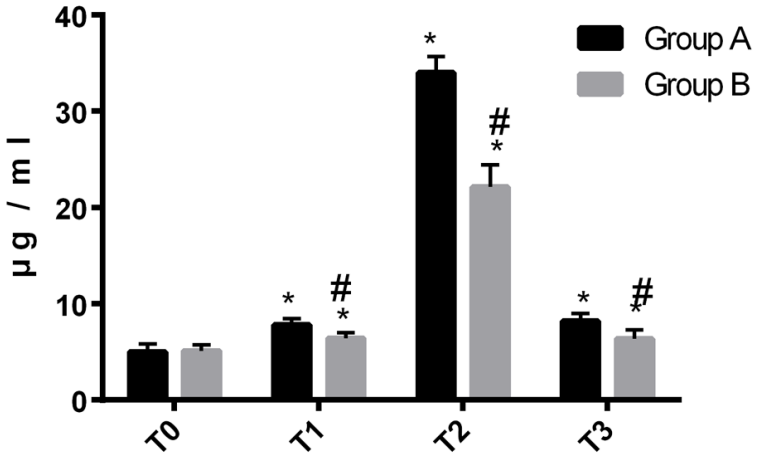

Figure 2. Changes of hFABP levels in group A and group B at different time points. * indicates that the hFABP levels of group A and group B at T0-T2 were up-regulated, and down-regulated after reaching the peak at T2 (P < 0.001). # indicates that the hFABP levels of group B at T1, T2 and T3 were lower than those of group A (P < 0.001).

Results

No differences in baseline data between the two groups

There was no clear difference in baseline data, such as age, BMI, alcohol intake, smoking habits between the two groups (P > 0.05).

Dexmedetomidine significantly decreased CK-MB levels in group B

The CK-MB levels at T0-T3 in group A were (21.04 ± 2.59) ng/ml, (31.77 ± 2.64) ng/ml, (70.43 ± 4.29) ng/ml, and (92.27 ± 4.49) ng/ml, respectively. The CK-MB levels at T0-T3 in group B were (21.12 ± 2.28) ng/ml, (26.34 ± 2.81) ng/ml, (36.28 ± 3.08) ng/ml, and (63.20 ± 5.24) ng/ml, respectively. The CK-MB levels in the two groups at T0-T3 were up-regulated. The differences at different time points were statistically significant (P < 0.001). There was no remarkable difference in CK-MB level between group A and group B at T0 (P > 0.05), while the CK-MB levels at T1, T2 and T3 in group B significantly were lower than those in group A (P < 0.001) (**Figure 1**).

Dexmedetomidine significantly decreased hFABP levels in group B

The hFABP levels of group A at T0-T3 were (5.02 ± 0.78) μg/ml, (7.82 ± 0.62) μg/ml, (34.02 ± 1.66) μg/ml, and (8.23 ± 0.75) μg/ml, respectively. The hFABP levels of group B at T0-T3 were (5.11 ± 0.65) μg/ml, (6.42 ± 0.58) μg/ml, (22.14 ± 2.32) μg/ml, and (6.37 ± 0.95) μg/ml, respectively. The levels of hFABP in the two groups were increased at T0-T2, and decreased after the peak at T2. The differences at different time points were statistically significant (P < 0.001). There was no remarkable difference in the level of hFABP between group A and group B at T0 (P > 0.05), while the level of hFABP at T1, T2 and T3 in group B was significantly lower than that in group A (P < 0.001) (**Figure 2**).

Dexmedetomidine significantly decreased heart rate in group B

The heart rates of group A at T0-T3 were (92.15 ± 1.23) times/min, (91.24 ± 1.52) times/min, (85.32 ± 1.26) times/min, and (91.78 ± 1.24) times/min, respectively. The heart rates of group B at T0-T3 were (92.02 ± 1.19) times/min, (80.16 ± 1.52) times/min,

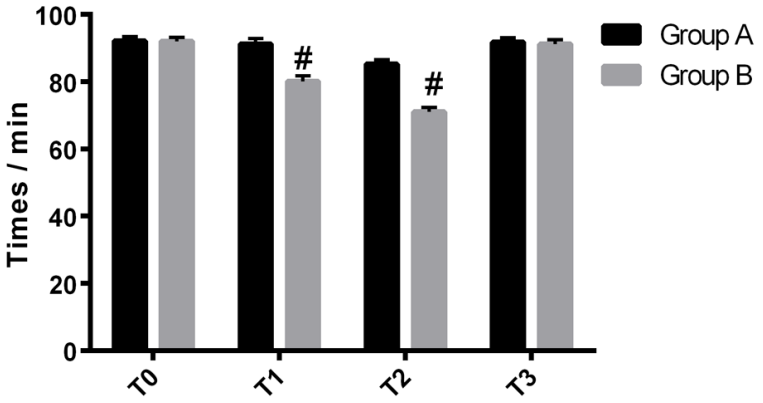

Figure 3. Changes of heart rate in group A and group B at different time points. # indicates that the heart rates of group B at T1 and T2 were lower than those of group A (P < 0.001).

(71.03 ± 1.37) times/min, and (91.23 ± 1.20) times/min, respectively. The heart rates in group A at T0-T2 were down-regulated, increased after reaching the lowest value at T2, and returned to T0 level at T3. There was significant difference between T2 and other time points in group A (P < 0.001). The heart rates in group B at T0-T2 were down-regulated, increased after reaching the lowest value at T2, and returned to T0 levels at T3. There was a significant difference between T2 and other time points in group B (P < 0.001).

There was no significant difference in heart rate between group A and group B at T0 and T3 (P > 0.05). The heart rate at T1 and T2 in group B was significantly lower than that in group A (P < 0.001) (**Figure 3**).

Dexmedetomidine significantly decreased Hcy levels in group B

The Hcy levels of group A at T0 to T3 were (2.65 ± 0.38) μg/ml, (11.48 ± 0.63) μg/ml, (16.52 ± 1.45) μg/ml, and (23.18 ± 2.73) μg/ml, respectively. The Hcy levels of group A at T0 to T3 were (2.63 ± 0.35) μg/ml, (9.91 ± 0.54) μg/ml, (11.05 ± 1.37) μg/ml, and (12.17 ± 1.82) μg/ml, respectively. The HCY levels in the two groups at T0-T3 were up-regulated. The differences at different time points were statistically significant (P < 0.001). There was no remarkable difference in HCY level between group A and group B at T0 (P > 0.05), while the HCY levels at T1, T2 and T3 in group B were significantly lower than those in group A (P < 0.001) (**Figure 4**).

Dexmedetomidine significantly decreased D-D level in group B

The D-D levels of group A at T0 to T3 were (8.12 ± 0.36) μg/ml, (11.48 ± 0.63) μg/ml, (16.52 ± 1.45) μg/ml, and (23.18 ± 2.73) μg/ml, respectively. The D-D levels of group A at T0 to T3 were (8.03 ± 0.42) μg/ml, (9.91 ± 0.54) μg/ml, (11.05 ± 1.37) μg/ml, and (12.17 ± 1.82) μg/ml, respectively. The D-D levels in the two groups at T0-T3 were up-regulated. The differences at different time points were statistically significant (P < 0.001). There was no remarkable difference in D-D level between group A and group B at T0 (P > 0.05), while the D-D levels at T1, T2 and T3 in group B were significantly lower than those in group A (P < 0.001) (**Figure 5**).

Dexmedetomidine significantly improved operative indicators and recovery in group B

The operation time, postoperative hospital stay, intraoperative bleeding volume, automatic respiratory recovery time and extubation time in group B were significantly less than those in group A (P < 0.001) (**Table 2**).

Dexmedetomidine significantly decreased complications in group B

The incidences of chills, hypotension, bradycardia and respiratory depression complications in group B were significantly lower than those in group A (P < 0.05). See **Table 3**.

Discussion

In this study, the changes of CK-MB and hFABP in the two groups were analyzed. It was found that the levels of CK-MB and hFABP in group A and group B were up-regulated from T0 to T3. At T0, there was no clear difference in CK-MB and hFABP levels between group A and group B. The level of hFABP in group A and group B was decreased after reaching the peak at T2, and the difference at different time points was statistically significant. The levels of CK-MB and hFABP in group B at T1, T2 and T3 were lower than those in group A.

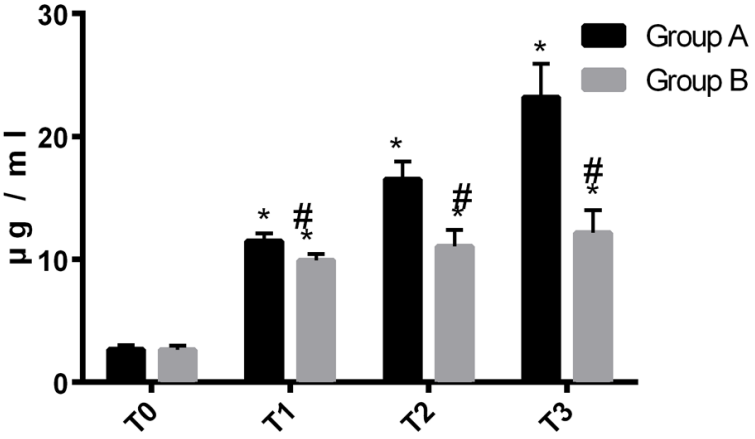

Figure 4. Changes of Hcy levels in group A and group B at different time points. * indicates that the Hcy levels of group A and group B at T0-T3 were up-regulated (P < 0.001). # indicates that the Hcy levels of group B at T1, T2 and T3 were lower than those of group A (P < 0.001).

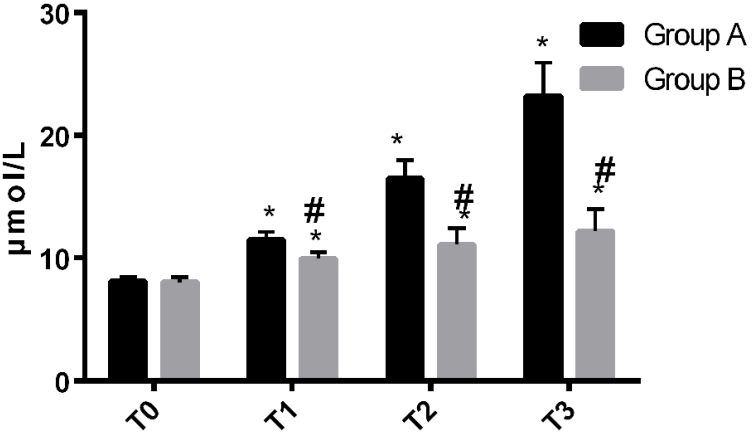

Figure 5. Changes of D-D levels in group A and group B at different time points. * indicates that the D-D levels of group A and group B at T0-T3 were up-regulated (P < 0.001). # indicates that the D-D levels of group B at T1, T2 and T3 were lower than those of group A (P < 0.001).

A large number of studies have confirmed that hFABP and CK-MB are important myocardial markers [16, 17]. hFABP is a small cytoplasmic protein in the heart. At present, some studies suggested that the expression of hFABP in the myocardium can be utilized as a biomarker for early myocardial injury [18]. CK-MB often enters plasma and urine after early myocardial injury, suggesting the changes in myocardial function [19]. The relevant reports showed that the serum levels of hFABP and CK-MB were increased when myocardial infarction, muscle atrophy and other myocardial diseases [20]. Therefore, it was considered that dexmedetomidine can inhibit the increase of CK-MB and hFABP levels in pregnant patients with hypertensive disorders and caesarean section, which is better for improving the protection of myocardial function for patients with pregnancy-induced hypertension during cesarean section. Similar studies also found this result [21]. At the same time, by comparing the changes of heart rate at different time points in group A and group B, it was found that the heart rates in group A and group B at T0-T2 were down-regulated, and then up-regulated after reaching the lowest value at T2, and returned to T0 levels at T3. There was also significant difference between T2 and other time points in group A and group B. The heart rate at T1 and T2 in group B was lower than that in group A.

Heart rate, as a common cardiac indicator, exerts an important role in monitoring the hemodynamic fluctuations of patients during operation. Some studies have shown that excessive fluctuations of hemodynamics during operation reflected the poor anesthetic and sedation effect of patients. Therefore, it was believed that the stabilization effect of dexmedetomidine for hemodynamics of pregnant patients with hypertensive disorders and caesarean section was better. Then, by observing the changes of Hcy and D-D levels in two groups, it was found that Hcy and D-D levels in group A and group B at T0-T3 were up-regulated. There was no remarkable difference in Hcy and D-D levels between group A and group B at T0, while the Hcy and D-D levels at T1, T2 and T3 in group B were lower than those in group A. The oxygen stress reaction often occurs during operation due to an imbalance of the auto-redox system [22]. Some studies have shown that Hcy was up-regulated with inflammation and stress reaction during operation [23]. The serum D-D level in patients with pregnancy-induced hypertension was higher than

Table 2. Comparison of operative indicators and recovery between the two groups of patients

Group	Group A (n=39)	Group B (n=39)	t	P
Operation time (min)	63.28 ± 7.25	62.01 ± 6.82	0.169	0.866
Postoperative hospital stay (d)	8.24 ± 0.52	8.01 ± 0.83	1.467	0.147
Intraoperative bleeding Volume (mL)	295.12 ± 32.55	293.32 ± 31.76	0.247	0.805
Automatic respiratory Recovery time (min)	20.16 ± 1.74	13.82 ± 1.04	19.530	<0.001
Extubation time (min)	29.45 ± 6.20	21.42 ± 4.18	6.706	<0.001

Table 3. Comparison of the incidence of complications in the two groups of patients

Group	Group A (n=39)	Group B (n=39)	X^2	P
Chill	12 (30.77)	2 (5.13)	-	-
Hypotension	3 (7.69)	0 (0.00)	-	-
Bradycardia	2 (5.13)	0 (0.00)	-	-
Respiratory depression	0 (0.00)	0 (0.00)	-	-
Total	17 (43.59)	2 (5.13)	15.660	<0.001

that in healthy pregnant women due to hypercoagulability, but the abnormal increase of D-D levels in pregnant women during childbirth will affect the physical recovery after childbirth [24]. Relevant clinical studies have demonstrated Dexmedetomidine's preferable suppression of serum Hcy and D-D in patients with angiocardiopathies such as hypertension and CHD [25]. Therefore, it is believed that dexmedetomidine can better reduce the levels of Hcy and D-D in pregnant patients with hypertensive disorders and caesarean section, which can better improve the stress reaction and hypercoagulability. Finally, the operative indicators, recovery and the incidence of complications were compared between the two groups. It was found that the operation time, hospital stay, postoperative hospital stay, intraoperative bleeding volume, automatic respiratory recovery time, and extubation time in group B were less than those in group A. The incidence of chills, hypotension, bradycardia and respiratory depression complications in group B was lower than those in group A. A large number of similar studies have also shown that dexmedetomidine was more effective in preventing complications in pregnant patients with hypertensive disorders and caesarean section [25]. Therefore, it was concluded that dexmedetomidine was more effective in adjusting the operative indicators, recovery and the incidence of complications in pregnant patients with hypertensive disorders and caesarean section.

While the impact of Dexmedetomidine on myocardial preservation, Hcy and D-D was studied in pregnant patients with hypertensive disorders and caesarean section, the study is limited as it fails to ascertain the specific mechanism how Dexmedetomidine affects Hcy and D-D, making it necessary to further study its ability to affect changes in Hcy and D-D directly or indirectly through other channels. Therefore, it is expected that the future studies can be oriented towards the effect mechanisms of Dexmedetomidine to provide more references for our experiments.

In conclusion, dexmedetomidine is a more effective myocardial protection for pregnant patients with hypertensive disorders and caesarean section, and it has better effect on downregulating the surgical indicators of Hcy and D-D, better recovery and safety, which is worthy of wide clinical promotion.

Disclosure of conflict of interest

None.

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