Research Paper

Efficacy of Dexmedetomidine and Droperidol in Preventing and Treating Carboprost Tromethamine-Induced Side Effects in Cesarean Section

YINLAN QIU, ZHICHAO GONG, HONG LI, MINMIN LI, PEIPEI LIU[1], H. S. MA AND XIAOHONG ZHAO[2]*

Department of Anesthesiology, [1]Department of Infectious Diseases, [2]Department of Anesthesia and Resuscitation, Dongying People's Hospital, Dongying, Shandong 257091, China

The main objective of this study is to explore the role of dexmedetomidine combined with droperidol in preventing and treating carboprost tromethamine-induced side effects in cesarean section. 240 patients undergoing cesarean section were enrolled in this study and grouped them into the four groups (n=60 for each). Group D treated with dexmedetomidine, group F intervened by droperidol, group DF treated with dexmedetomidine+droperidol and group C given an equal amount of normal saline. The administration dose and rate were the same in all four groups. Pulse oxygen saturation and heart rate were recorded intraoperatively and mean arterial pressure was monitored every 5 min. Monitoring was performed at the time of entering the operating room (T0), before (T1) and 10 min after intrauterine carboprost tromethamine injection (T2), and at the end of surgery (T3). Side effects, blood pressure, heart rate changes, and Ramsay sedation scores were also analyzed. Group DF showed markedly higher Ramsay sedation scores than groups C and F. Along with that group DF showed lower incidence rates of nausea and vomiting, chest tightness, chills, blood pressure drop and tachycardia than group C, with relatively stable hemodynamics. Low-dose dexmedetomidine+droperidol shows promising results in preventing and treating carboprost tromethamine-induced side effects during cesarean section, with superior efficacy, low adverse event rate and high safety, making it safe for clinical use.

Key words: Dexmedetomidine, carboprost tromethamine, droperidol, cesarean section

Currently, postpartum hemorrhage[1], uterine inertia, cicatricial uterus, placenta previa, multiple pregnancies, macrosomia and uterine fibroids are the main causes of maternal death in China, with uterine inertia accounting for 70 %-90 %. Carboprost Tromethamine (CBT) is a compound composed of prostaglandin F2 alpha (α) derivatives, which binds to prostaglandin receptors in uterine smooth muscle cells[2], thus reducing postpartum hemorrhage. It not only takes effect quickly, but also lasts for a long time, allowing the uterine smooth muscles to contract vigorously and harmoniously[3]. Furthermore, CBT can promote the cervical dilatation of the uterine body and facilitate the rapid expulsion of the placenta, thus effectively preventing postpartum massive bleeding[4]. At present, CBT is known to be effective in preventing postpartum hemorrhage, but it can also produce serious side effects, especially nausea and vomiting[5]. This is because the active ingredient of CBT is similar to those of prostaglandin. While the use of such a drug in the event of uterine inertia can cause the uterine smooth muscle to contract and reduce bleeding, it can also induce contractions of the smooth muscle of digestive tract and bronchus, resulting in nausea, vomiting, chest distress and other side effects. Moreover, it induces vascular smooth muscle contractions, resulting in increased Blood Pressure (BP) and tachycardia. Absorption of the active ingredients of CBT in blood can also lead to many adverse reactions in pregnant women, such as chills and tremors during surgery.

Dexmedetomidine (DEX) is an α_2 adrenergic receptor agonist with good specificity[6] and has

***Address for correspondence**
E-mail: qiuqiu851220@163.com

sedative and analgesic effects while exerting only a slight effect on the respiratory system, which can effectively reduce various cardiovascular system manifestations, such as tachycardia, elevated BP and inhibit adverse reactions such as shivering during intraspinal anesthesia[7,8].

Droperidol (DRO) is indicated for adjunctive sedation in intravertebral anesthesia[9]. It reduces activity of dopamine in stimulating the vomiting center of the brain and is mainly used in clinical treatment of vertigo and migraine. It can also be used to treat nausea, vomiting and other diseases caused by opioid use[10]. In addition, DRO acts on postoperative nausea and vomiting, mainly by acting on α adrenergic receptors[11].

Based on the limited research literature on the prevention and treatment of CBT-induced side effects, this study explores the safety, effectiveness and patient satisfaction of DEX, DRO in preventing and treating side effects caused by CBT, providing a research basis for the rational clinical application of DEX and DRO.

MATERIALS AND METHODS

General information:

According to the inclusion criteria, 240 out of the 300 women with full-term pregnancy who underwent elective Cesarean Section (CS) from February 2020 to February 2022 were selected for this study. The pregnant women were randomly assigned to four groups as DEX group (group D), DRO group (group F), DEX+DRO group (group DF) and control group (group C) with 60 patients in each group. This study was carried out after being reviewed and approved by the Ethics Committee of Dongying People's Hospital.

Inclusion criteria:

37-41 w of pregnancy; age range was (22-40) y; height range was 150-170 cm; weight range was 55-95 kg; American Society of Anesthesiologists (ASA) classification[12] was grade II/III; patients who experienced intraoperative uterine inertia and received intrauterine injection of CBT to prevent and treat postpartum hemorrhage and patients with no allergies to any of the three drugs used in this study are included in the study.

Exclusion criteria:

Patients in which intraspinal anesthesia cannot be performed due to personal factors or diseases; occurrence of other adverse reactions before intrauterine injection of CBT; diseases of nervous system, blood clotting system, respiratory system, etc.; pregnant women with hypertensive disease or pregnancy-induced hypertension syndrome and patients with repeated application of CBT are excluded from the study. The related experimental drugs used in this study are shown in Table 1 and related instruments and equipment's used are shown in Table 2.

TABLE 1: RELATED DRUGS USED IN THIS STUDY

S. No	Drug name	Manufacturer	Specification (model)	SFDA Approval No.
1	Ropivacaine hydrochloride injection	Shijiazhuang No. 4 Pharmaceutical Co., Ltd.	10 ml:100 mg	H20203107
2	Norepinephrine bitartrate injection	Xi'an Lijun Pharmaceutical Co., Ltd.	1 ml:10 mg	H61021666
3	Atropine sulfate injection	Tianjin Jinyao Pharmaceutical Co., Ltd.	1 ml:0.5 mg	H12020383
4	DEX hydrochloride injection	Yangtze River Pharmaceutical Group	2 ml:0.2 mg	H21090931
5	DRO injection	Shandong Hualu Pharmaceutical Co., Ltd.	2 ml:5 mg	H37022102
6	Tropisetron hydrochloride for injection	Shangdong Luoxin Pharmaceutical Group Stock Co., Ltd.	Freeze-dried powder injection:5 mg	H20061061

7	CBT	Changzhou Siyao Pharmaceutical Co., Ltd.	1 ml:250 μg	H20094183
8	Ephedrine hydrochloride injection	Northeast Pharmaceutical Group Shenyang No.1 Pharmaceutical Co., Ltd.	1 ml:30 mg	H21022412
9	Normal saline (0.9 % sodium chloride injection)	Sichuan Kelun Pharmaceutical Co., Ltd.	100 ml:0.9 g	H51021156

TABLE 2: RELEVANT INSTRUMENTS AND EQUIPMENT USED IN THIS STUDY

S. No	Equipment and instrument	Manufacturer	Specification (model)	National Machinery Registration No.
1	Single-use puncture set for local anesthesia	Zhejiang Sujia Medical Instrument Co., Ltd.	AS-E/SII	20163080426
2	Patient monitor	Philips Medizin Systeme Boblingen GmbH	PHILIPS-M8003A	
3	Anesthesia machine	Shenzhen Mindray Bio-Medical Electronics Co., Ltd.	WATO EX-65 Pro	2016354253

Preoperative education and preparation:

Preoperative education: Before surgery, medical staff fully communicated with pregnant women and their families to inform them of anesthesia related risks and reduce their psychological burden.

Preoperative pre-rehabilitation: The nutrition of pregnant women was enhanced before surgery.

Preoperative fasting: The pregnant women were subjected to 8 h of preoperative fasting and 2 h of water deprivation.

Research methods:

The temperature and humidity of the operating room were controlled within the normal range (temperature: 22°-24° and humidity: 50 %-60 %). After entering the operating room, the peripheral venous access of the mother was routinely opened and 500-1500 ml of sodium lactate Ringer's solution was continuously injected intravenously during the operation. BP, Heart Rate (HR) and percutaneous Saturation of Peripheral Oxygen (SpO_2) were monitored. Pure oxygen inhalation was administered through the mask at 5-6 l/min. All pregnant women in the four groups underwent combined spinal-epidural anesthesia at L2-L3 (the lumbar anesthesia solution was 2.3-2.7 ml of 0.5 % liquid specific gravity of ropivacaine). A median puncture was performed and completed by the same experienced anesthesiologist. The intraoperative plane of anesthesia was maintained at T6-S5.

All the four groups underwent low transverse CS. During CS, 10 units of oxytocin were routinely injected into the uterus after the delivery of the fetus. When uterine inertia was found, the mother was given 250 μg CBT *via* intrauterine injection and the corresponding drugs were immediately pumped through intravenous injection to prevent adverse reactions. The drugs used were 0.4 μg/kg DEX in group D, 2.5 mg DRO in group F, 0.2 μg/kg DEX+1.25 mg DRO in group DF and the same amount of normal saline in group C. The pumping time of the four groups was 10 min. Treatment and remedial measures for serious intraoperative complications are follows as intravenous injection of 5 mg tropisetron were given for severe nausea and vomiting; intermittent intravenous administration of ephedrine (6-10 mg) or norepinephrine (4-8 μg) were given for non-invasive BP drop by >20 % before the preoperative level; intermittent intravenous infusion of nitroglycerin or urapidil were given for non-invasive BP elevation by 30 % after the preoperative level; intermittent drip of atropine were given for HR below 60 beats/min and oxygen administration through pressured oxygen mask were given for chest distress and shortness of breath.

Outcome measures:

BP, HR and percutaneous SpO_2 were monitored and recorded at four time points which includes time point upon entry into the operating room (T0), before intrauterine CBT injection (T1), 10 min after intrauterine CBT injection (T2) and at the end of surgery (T3).

Nausea and vomiting grading criteria was grade 0 indicates no stomach discomfort or nausea; grade 1 (mild) indicates temporary stomach discomfort, occasional nausea and no vomiting; grade 2 (moderate) indicates obvious nausea, stomach discomfort and no vomiting and grade 3 (severe) indicates severe nausea and vomiting.

The occurrence of nausea and vomiting in the four groups of pregnant women along with the scores and grades of related scoring scales were recorded. Chills scores and chills onset frequency in four groups of pregnant women were recorded. Respiratory adverse events like chest distress and cardiovascular adverse events such as BP and HR changes were recorded, and Ramsay sedation scores were determined.

Statistical analysis:

The data involved in this study were processed by Statistical Package for the Social Sciences (SPSS) version 23.0 software, in which the measured data were represented by mean±standard deviation ($\bar{x}\pm s$). Count data were analyzed by the Chi-square (χ^2) test. Repeated measures one-way Analysis of Variance (ANOVA) and two independent samples t-test were used for intra-group and inter-group comparisons of measured data, respectively. While the Bonferroni post-hoc test was used for pairwise comparisons between different time points within the group.

RESULTS AND DISCUSSION

Basic characteristics were compared between the four groups of patients undergoing CS as shown in Table 3. The four groups of patients showed no evident difference in age, height, weight, gestational age and ASA classification (all $p>0.05$).

Operation conditions were compared between the four groups of patients as shown in Table 4. No statistical significance was identified among the four groups of patients in terms of operation time, intraoperative bleeding and intraoperative infusion volume ($p>0.05$).

Intraoperative Ramsay sedation scores were compared among the four groups of patients as shown in Table 5. Groups D and DF had higher Ramsay sedation scores than groups C and F ($p<0.05$).

TABLE 3: COMPARISON OF AGE, HEIGHT, WEIGHT, GESTATIONAL AGE AND ASA CLASSIFICATION OF PREGNANT WOMEN AMONG FOUR GROUPS

Groups	n	Age (y)	Height (cm)	Weight (kg)	Gestational weeks (w)	ASA II/III (%)
D	60	30.41±5.76	161.3±5.1	75.2±9.4	39.3±1.1	39 (65.0 %)/21 (35.0 %)
F	60	31.60±5.17	160.2±5.0	74.7±8.8	39.2±0.8	38 (63.3 %)/22 (36.7 %)
DF	60	30.16±5.26	160.1±4.7	75.6±9.6	39.4±10	42 (70.0 %)/18 (30.0 %)
C	60	30.92±5.45	161.5±5.0	73.1±9.4	39.2±0.8	40 (66.7 %)/20 (33.3 %)
F	-	0.841	0.733	0.966	0.998	0.297
p	-	0.472	0.523	0.412	0.475	0.586

TABLE 4: COMPARISON OF OPERATION TIME, INTRAOPERATIVE BLEEDING AND INTRAOPERATIVE INFUSION VOLUME AMONG FOUR GROUPS OF PREGNANT WOMEN

Groups	n	Operation time (min)	Intraoperative bleeding (ml)	Intraoperative infusion volume (ml)
D	60	42±4	262.0±43.6	1,061.0±148.6
F	60	42±6	251.0±28.2	1,044.8±139.4
DF	60	42±6	257.2±41.4	1,045.6±152.2
C	60	41±6	258.1±25.3	1,042.4±134.4
F	-	0.684	0.974	0.167
p	-	0.849	0.404	0.918

TABLE 5: COMPARISON OF INTRAOPERATIVE RAMSAY SEDATION SCORES AMONG FOUR GROUPS OF PREGNANT WOMEN

Group	n	Ramsay sedation score n (%)				
		1 point	2 points	3 points	4 points	Mean
D	60	2 (3.3 %)	33 (55.0 %)	25 (41.7 %)	0 (0.0 %)	2.4±0.6*#
F	60	16 (26.7 %)	44 (73.3 %)	0 (0.0 %)	0 (0.0 %)	1.7±0.4
DF	60	4 (6.7 %)	17 (28.3 %)	38 (63.3 %)	1 (1.7 %)	2.6±0.6*#
C	60	45 (75.0 %)	15 (25.0 %)	0 (0.0 %)	0 (0.0 %)	1.3±0.4

Note: *p<0.05 *vs.* group C and #p<0.05 *vs.* group F

Incidence of side effects like nausea and vomiting were compared between the four groups of patients as shown in Table 6. Groups F and DF showed a markedly lower incidence of moderate to severe nausea and vomiting's than groups D and C (p<0.05).

Other side effects such as BP drop, tachycardia and chills were compared between the four groups of patients as shown in Table 7. Group DF had a statistically lower incidence of BP drop than groups C and D and an obviously reduced incidence of tachycardia than groups C and F (p<0.05); the incidence of chills in group DF was significantly lower compared with group C (p<0.05); while the incidence of bradycardia in group F was lower than group C and DF (p<0.05).

Side effects occurred in 15 patients (25 %) in group DF, 28 patients (46 %) in group D, 29 patients (48.3 %) in group F and 43 patients (71.7 %) in group C. There was a significant difference in the incidence of side effects between groups DF and C (χ^2=26.162, p<0.05).

At T1 and T0, four groups showed no significant difference (p>0.05) in SpO_2, HR and Mean Arterial Pressure (MAP). Compared with T0, there were significant differences in SpO_2, HR and MAP in groups C, D and F at T2 (p<0.05). There were significant differences in SpO_2 and MAP in group DF between T2 and T0 (p<0.05).

In group DF, there was a significant difference in MAP between T0 and T3 (p<0.05); MAP and HR at T3 in group D were also significantly different (p<0.05). Statistical significance was also identified in SpO_2, HR and MAP in group F (p<0.05) and SpO_2 and MAP in group C (p<0.05).

At T2, statistically significant differences in MAP and HR were found between group C and DF (p<0.05). There was significant difference in HR between group C and D (p<0.05) and a statistical significance was also determined in MAP between group C and F (p<0.05). Group DF was statistically different from group D and F in HR (p<0.05).

At T3, group C showed significant difference in SpO_2 and HR levels than groups DF and D (p<0.05). Compared with pregnant women in group DF, HR and MAP in group D and HR and SpO_2 in group F were significantly different (p<0.05) (Table 8).

CBT is an F2α derivative, belonging to the amino butanol salt solution. It has been shown to cause uterine smooth muscle contraction, thus preventing postpartum hemorrhage and reducing clinical blood transfusion rate[13]. CBT not only acts on the human uterine smooth muscle, when absorbed into the blood it can also affects the smooth muscle in other areas of the body[14]. In the digestive system, CBT induces gastrointestinal smooth muscle contraction, affects gastric acid secretion and regulates gastric juice and gastric motility, leading to nausea and vomiting[15]. In the respiratory system, CBT will cause bronchial smooth muscle contraction, chest distress and even dyspnea and other side effects[16]. As for the cardiovascular system, it causes the contraction of smooth muscle of the cardiovascular system, causing side effects such as tachycardia and elevated BP. As this prostaglandin-like effect can also cause side effects such as chills and muscle pain, it will bring great discomfort and pain to pregnant women during the operation. But CBT has good application value in the treatment of postpartum hemorrhage during CS.

In this study, the incidence of nausea and vomiting in pregnant women in group C after intrauterine injection of CBT was as high as 20 % and the incidence of chest distress, chills, BP elevation and tachycardia were all high (71.7 %), indicating great side effects induced by CBT alone. Currently, clinicians usually use these side effects as an indicator to confirm the body's response to CBT

injection. However, the resulting side effects and maternal psychological stress are enormous. Anesthesiologists mostly use drugs to reduce the discomfort of pregnant women during surgery, so as to increase surgical comfort.

DEX and DRO, alone and in combination, were used in this study to alleviate the nausea and vomiting caused by the application of CBT in pregnant women and the clinical effects of three medication methods were compared. DRO has a strong antiemetic effect, mainly by inhibiting dopamine D_2 receptors in the vomiting center and promoting the biotransformation of dopamine in the central nervous system, thus producing a potent antiemetic effect[17]. It has been reported that DRO effectively reduces nausea and vomiting in patients within at least 24 h after surgery[18].

TABLE 6: COMPARISON OF THE INCIDENCE OF NAUSEA AND VOMITING AMONG FOUR GROUPS OF PREGNANT WOMEN

Group	Number of cases (n)	Nausea and vomiting (n)	Grade 0, n (%)	Grade 1, n (%)	Grade 2, n (%)	Grade 3, n (%)
D	60	14 (23.3 %)	0 (0.0 %)	2 (3.3 %)	2 (3.3 %)	10 (16.7 %)
F	60	3 (5.0 %)*#	1 (1.7 %)	1 (1.7 %)	0 (0.0 %)	1 (1.7 %)
DF	60	5 (8.3 %)*#	1 (1.7 %)	0 (0.0 %)	3 (5.0 %)	1 (1.7 %)
C	60	21 (35.0 %)	0 (0.0 %)	1 (1.7 %)	5 (8.3 %)	15 (25.0 %)

Note: *p<0.05 *vs.* group C and #p<0.05 *vs.* group D

TABLE 7: COMPARISON OF OTHER SIDE EFFECTS IN FOUR GROUPS OF PREGNANT WOMEN

Group	n	Chest distress, n (%)	Chills, n (%)	Adverse cardiovascular events			
				BP elevation, n (%)	BP drop, n (%)	Tachycardia, n (%)	Bradycardia, n (%)
D	60	5 (8.3 %)	2 (3.3 %)	5 (8.3 %)	2 (3.3 %)*#	1(1.7 %)*$	5 (8.3 %)
F	60	6 (10.0 %)	1 (1.7 %)	6 (10.0 %)	10 (16.7 %)	14 (23.3 %)	0 (0.0 %)#&
DF	60	3 (5.0 %)*	0 (0.0 %)*	2 (3.3 %)	3 (5.0 %)*#	2 (3.3 %)*$	5 (8.3 %)
C	60	12 (20.0 %)	10 (16.7 %)	2 (3.3 %)	16 (26.7 %)	15 (25.0 %)	2 (3.3 %)

Note: *p<0.05 *vs.* group C; #p<0.05 *vs.* group D; $p<0.05 *vs.* group F and &p<0.05 *vs.* group DF

TABLE 8: COMPARISON OF SPO_2, HR AND MAP AMONG FOUR GROUPS OF PREGNANT WOMEN AT DIFFERENT TIME POINTS

Group	n	Monitoring indexes	T0	T1	T2	T3
		SpO_2	97.9±1.4	97.9±1.1	97.0±1.4	97.8±1.1*
D	60	HR	86.4±8.1	88.3±4.6	73.5±5.8*#	82.8±4.7*#
		MAP	84.8±4.1	83.7±3.5	74.5±3.5	73.5±2.6#
		SpO_2	97.4±1.5	97.8±0.8	96.0±1.7	96.7±1.2#
F	60	HR	81.3±9.6	84.6±5.1	95.8±3.3#	86.9±4.6#
		MAP	84.2±3.6	83.3±3.2	78.2±2.7*	81.9±3.2
		SpO_2	97.3±1.6	97.7±0.8	96.4±1.4	97.3±1.5*
DF	60	HR	79.0±8.8	80.9±4.7	80.0±8.2*	76.2±7.6*
		MAP	84.7±3.7	83.8±2.3	75.2±2.8*	74.8±2.3
		SpO_2	97.0±1.6	97.4±0.8	96.2±1.3	96.3±1.0
C	60	HR	81.6±8.3	84.0±5.4	95.3±9.9	90.5±3.9
		MAP	85.3±3.5	84.3±2.2	77.0±2.9	81.2±2.6

Note: *p<0.05 *vs.* group C and #p<0.05 *vs.* group DF

In this research, the incidence of nausea and vomiting in group C was as high as 35 %, which was the highest among the four groups *vs.* 23.3 % in group D and 5 % in group F. And the incidence rates of moderate to severe nausea and vomiting were significantly lower in group DF compared with groups D and C. But no notable difference was identified between groups DF and F in the incidence of nausea and vomiting. The above results suggest that compared with DEX monotherapy, DRO alone has a stronger preventive and therapeutic effect on nausea and vomiting induced by intraoperative application of CBT in patients undergoing CS, while DEX+DRO has comparable effects to DRO monotherapy in reducing the incidence of nausea and vomiting.

Both DEX and DRO have strong sedative effects, but their mechanisms of action are different. DEX mainly binds to the presynaptic α_2 receptor located in the locus coeruleus of the central nervous system, which promotes intracellular potassium efflux and leads to cell hyperpolarization, resulting in a negative feedback effect by reducing norepinephrine release and decreasing plasma catecholamine content, and ultimately leading to central sedation. Various studies have shown that DEX makes it possible to awaken patients from anesthesia at any time, with a slight impact on breathing and a high safety profile[19]. The main function of DRO is to bind to the dopamine receptors located in the central system, thus inhibiting the reticular activation system in the brain and achieving strong nerve stability and sedation[20]. While comparing the Ramsay sedation scores in this study, groups DF and D had significantly higher sedation scores than group C and group F. It shows that DEX alone and its combination with DRO have stronger sedative effects than DRO monotherapy, mainly due to the high specificity of DEX in stimulating α_2 adrenergic receptors.

It has been reported in the literature that DEX has a relatively high safety profile and an obvious inhibitory effect on shivering caused by intraspinal anesthesia[21-23]. The incidence of chills were lower in Group F than group C, suggesting that DRO is effective in preventing and treating chills caused by CBT in CS patients. In this study, the incidence of chills was statistically lower in group DF *vs.* group C, while no significant difference was determined between group DF, group D and group F. It shows that for CBT-induced chills, both DEX and DRO have certain inhibitory effects. But their combined medication was found to be no better than that of DEX and DRO alone, without statistical significance.

The application of CBT in CS can produce cardio-cerebrovascular effects such as increased BP and accelerated HR. DEX acts as a negative feedback by interacting with α_2 receptors in the central presynaptic membrane, thus reducing blood catecholamine concentration, BP and HR[24]. In addition, DEX acts on the cardiovascular system, leading to hypotension and bradycardia, mainly because of the increased activity of its postsynaptic α_2-adrenergic receptors[25]. DRO blocks α adrenergic receptors and thus relaxes vascular smooth muscle, but the effect is weak. Intravenous DRO can induce a certain decrease in BP and a compensatory increase in HR, which may be related to its dosage, drug concentration and rate of injection[26]. Intravenous DRO administration is more likely to cause hypotension if it is administered too quickly or a large dose is administered, and its sympathetic inhibitory effect is weak[27].

In this study, the incidence of tachycardia in group C was significantly higher than that in group DF and D, but no significant difference was found in the incidence of hypertension among the four groups, which may be related to peripheral vascular dilatation under intraspinal anesthesia.

In this study, the incidence of BP drop in pregnant women in group F (10 %) was statistically lower than group C (16.7 %). The incidence of bradycardia in group D (5 %) was markedly reduced compared to group C (2 %). Intraspinal anesthesia during CS will dilate the peripheral blood vessels of the body, which will lead to relative insufficient blood volume and reduced BP. Therefore, intraoperative application of CBT can cause an increase in BP. However, the incidence of BP reduction in the control group was still higher than that in group F. The anti-sympathetic effect of DEX[24] lowers BP while acting on α receptors in the heart, which slows the HR[21,28,29]. DEX also has a dose-dependent effect on the cardiovascular system. It has been suggested that DEX also has a certain excitatory effect on α_1 receptors, which may also cause a transient increase in BP[30]. In this study, a 5 % incidence of BP elevation was recorded in

group D, lower compared with group C, which may be related to the dose dependence of DEX on BP increase. At the same time, the application of low-dose DEX has little effect on postoperative lactation. Therefore, the use of intravenous DEX to prevent and treat the side effects induced by CBT during CS has a certain theoretical basis.

The incidence of BP drop was significantly higher in group F *vs.* group C, while no significant difference was determined between them in the incidence of tachycardia. The results of this study suggest that intravenous DRO can induce a certain reduction in BP.

Group DF showed markedly lower incidence rates of BP drop and tachycardia than groups F and C. When low-dose DRO was used in combination with DEX, the reduced drug and the small effect of DRO on the cardiovascular system play a synergistic role in avoiding the occurrence of hypotension caused by peripheral vasodilation under intraspinal anesthesia, thus maintaining hemodynamic stability.

The incidence of chest distress in group D was significantly lower compared with group C. DEX acts on α receptors of bronchial smooth muscle in the respiratory system to dilate bronchus and increase effective ventilation in the lungs, thus alleviating respiratory discomfort such as chest distress caused by CBT[26]. Among the four groups of pregnant women, the incidence of chest distress in group DF was significantly lower than that in group C, indicating that DEX has a certain preventive and therapeutic effects on chest distress caused by the application of CBT in CS.

Although DRO has a good effect on preventing postoperative restlessness during anesthesia recovery, as well as postoperative delirium, nausea, vomiting and pain, it can also cause extravertebral reaction and even respiratory depression and other adverse consequences in severe cases. In addition, DRO can prolong QT interval and induce many adverse reactions such as Torsade de Pointes[27]. Hence, attention should be paid to observation in routine clinical application, and long-term Electrocardiogram (ECG) monitoring is needed to prevent the occurrence of arrhythmia[17]. DRO-induced extrapyramidal reactions are positively correlated with the dosage administered. Studies have shown that intravenous administration of 0.6-1.25 mg DRO contributes to a low incidence of adverse reactions[31] and rarely causes QT interval prolongation. In this study, there were extrapyramidal reactions in neither group F nor group DF, and the dosage of DRO in group DF was 1.25 mg due to the dose correlation, which was relatively safer.

Changes in patients' vital signs were also closely observed during the operation. Through the comparison of SpO_2, MAP and HR at four time points among the four groups of pregnant women, it was found that SpO_2 and MAP of all the four groups decreased at T2 and T0. This is mainly related to the side effects such as chest distress and BP drop in patients after using CBT. Significantly increased HR was observed in groups C, D and F, while the HR of group DF did not change significantly, indicating that the combination of the two drugs can better control hemodynamics and stabilize HR.

In group DF, the MAP at T3 was statistically lower than that at T0, but no significant differences were identified in HR and SpO_2 between the two time points. At T2, MAP in group DF decreased and HR accelerated compared with group C. At T3, group DF had non-significantly lower MAP than group C, while HR was still significantly different between groups. It is suggested that the corresponding drugs used in the operation have a short onset time and a lasting action against CBT-induced adverse events. DEX+DRO can effectively reduce the probability of adverse cardiovascular reactions in patients, stabilize hemodynamics, and increase intraoperative and postoperative patient satisfaction.

At T2, group DF showed statistically different HR levels than groups D and F. And compared with group DF, the HR and MAP in group D and HR and SpO_2 in group F were significantly different at T3. It shows that DEX or DRO alone can alleviate CBT-induced side effects while still causing adverse reactions in patients during and after CS, due to side effects that induced by the drugs themselves. On the contrary, their combination lowers the dosage of the corresponding drugs, thus reducing the adverse reactions of the drugs themselves and synergistically exerting the curative effect against the side effects caused by CBT.

Therefore, low-dose DEX combined with DRO is effective in preventing and treating CBT-induced side effects in patients undergoing CS,

while reducing the incidence of side effects caused by those drugs. Due to the limitations of this study, the number of patients included in the study is relatively small. In addition, the time for evaluating the effect after intervention is relatively short resulting in no significant difference in the comparison of the incidence of BP increase and tachycardia among the four groups of pregnant women.

After the fetus delivery during CS, CBT should be injected into the uterus immediately in case of uterine inertia. At this time, intravenous administration of low-dose DEX and DRO can prevent CBT-induced side effects and maintain hemodynamic stability. Moreover, the combination therapy has sedative and tranquilizing effects, which is more potent than their single use. And in addition to the above benefits, DEX plus DRO therapy has a higher safety profile, which can be popularized and applied in clinical practice.

Conflict of interests:

The authors declared no conflict of interests.

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