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Sufentanil for carboprost-induced adverse reactions during cesarean delivery under combined spinal-epidural anesthesia

Short title: Sufentanil for carboprost-induced adverse reactions

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ABSTRACT

Objectives: Carboprost plays an important role in managing refractory uterine atony and severe postpartum hemorrhage. However, it is associated with challenging adverse reactions. We aimed to evaluate the clinical effects of low dose sufentanil on the prevention of adverse events associated with carboprost during cesarean delivery.

Material and methods: Patients were randomly divided into two groups: a placebo control group (group C, n = 15) that received an intravenous infusion of 1 mL of normal saline 2 min before carboprost and a sufentanil group (group S, n = 15) that received 5 μg of sufentanil. The primary outcome was the incidence of nausea and vomiting following carboprost administration.

Results: The incidence of nausea, vomiting, and gastrointestinal discomfort was significantly lower in group S than in group C ($p < 0.05$).

Conclusions: The prophylactic use of low dose sufentanil reduces the incidence of gastrointestinal side effects caused by carboprost administration during cesarean section.

Key words: cesarean delivery; sufentanil; opioids; carboprost; side effects; nausea and vomiting

INTRODUCTION

Globally, almost one-quarter of all maternal deaths are associated with postpartum hemorrhage (PPH), which is the primary cause of maternal mortality, affecting about 5% of all women following parturition [1]. PPH is defined as the loss of at least 500 mL of blood following vaginal delivery or the loss of at least 1.000 mL following cesarean delivery within 24 h after birth [2, 3]. The leading cause of PPH-related death among women worldwide is uterine atony [1]. This uterine atony-associated PPH can be prevented using prophylactic uterotonics during the third stage of labor, which is recommended by the World Health Organization for all labors [4]. Oxytocin is used as a first line uterotonic pharmacological intervention; it is a low-cost treatment widely available in all settings and confers substantial clinical benefits with minimal side-effects. However, owing to its short half-life (4–10 min), oxytocin requires continuous or repeated administration [5]. Furthermore, the saturation of uterine receptors may limit its maximum effect, and excessive dosages may result in water toxicity owing to its antidiuretic effect [5].

Carboprost, a prostaglandin F2a analog, first emerged as an efficacious treatment for PPH in the early 1980s [6]. It is currently used as a second-line treatment for uterine atony and has an important role in the management of refractory uterine atony and severe PPH [7, 8]. Carboprost induces uterine smooth muscle contraction after the first or second dose in approximately 95% of cases [9]. However, a number of adverse reactions have been reported, including nausea, vomiting, and diarrhea [9]. Flushing, pyrexia, moderate increases in blood pressure, and hypoxia have also been reported [7, 10]. Although these adverse events are usually moderate and non-fatal, they are unpleasant for parturient patients who have undergone cesarean delivery with spinal-epidural anesthesia [10]. Additionally, there is currently no standard treatment for adverse events associated with carboprost, other than symptomatic relief [11].

As an opioid, sufentanil is widely used in obstetric anesthesia owing to its strong analgesic effect, wide safety margins, long-lasting anesthetic effect, lack of accumulation, and favorable safety profile (*Sufentanil and Cesarean Section.Pdf*, n.d.). In addition to analgesia, studies have shown that opioids possess other pharmacological effects, such as: 1) inhibition of gastrointestinal motility [12]; 2) increased threshold of visceral pain perception [13]; 3) inhibition of airway smooth muscle contraction [14]; and 4) dilation of blood vessels and reduced peripheral resistance [15]. Therefore, in addition to reducing the occurrence of gastrointestinal adverse events associated with carboprost, sufentanil may relieve respiratory and circulatory adverse events, such as bronchospasm and hypertension. Therefore, we conducted a prospective, randomized controlled trial to further investigate the effects of an intravenous infusion of low dose sufentanil on the adverse events induced by carboprost during cesarean delivery under combined spinal-epidural anesthesia. To the best of our knowledge, this was the first study to investigate the effect of sufentanil on the adverse events induced by carboprost administration.

MATERIAL AND METHODS

Study design

This prospective randomized controlled study was conducted at the West China Second University Hospital. The Ethical Committee of West China Second University Hospital approved the study protocol in May 2018 (K2017035). Written informed consent was provided by each patient on the day prior to surgery.

Patients

Patients with American Society of Anesthesiologists physical status I or II, aged from 18 to 45 years, with a gestational age ≥ 37 weeks, who had also received oxytocin and carboprost during the cesarean delivery owing to multiple gestation, hydramnios, or macrosomia, were enrolled in our study. Patients with contraindications for combined spinal-epidural anesthesia, and those with neuraxial anesthesia failure or anesthesia spread level lower than T6, were excluded. Other exclusion criteria were as follows: 1) body mass index > 35 kg/m^2; 2) contraindication to prostaglandin, such as asthma or glaucoma; 3) history of allergy to carboprost, opioids, or bupivacaine; 4) severe pulmonary infection; 5) concomitant disease known to cause nausea, vomiting-like Meniere's syndrome, vestibular neuritis, or acute gastroenteritis; 6) those who could not cooperate with the study due to disease or language barrier, such as individuals with mental illness, belonging to ethnic minorities, or deafness; and 7) use of anticholinergic drugs, antispasmodic drugs, or other drugs that affect gastrointestinal motility within 72 h of birth.

Randomization

Using the random number table method, patients were randomly divided into two groups of 15 patients, as follows: a control or placebo group (group C) that received 1 mL of 0.9% normal saline and a study group (sufentanil group, group S) that received 5 μg of sufentanil (diluted to 1 mL with normal saline and used within 1 min).

Using the random number table, the researchers randomly divided 30 pregnant females into two groups, and the group allocations were placed in sealed envelopes. The drugs for both groups were allocated by an anesthesiologist. The pharmacists were blind to the randomization. On the day of the trial, the dispenser randomly selected one sealed envelope. Then, the dispenser allocated the drug and labeled the syringe according to the group allocation within the envelope. Additionally, the syringe number, drug, and patient name were recorded in the record book. Sufentanil and normal saline were prepared in 1 mL and administered to the patients 1–2 min prior to the administration of carboprost. Another anesthesiologist was responsible for observing and recording vital signs and adverse events following the administration of carboprost. Prior to the procedure, the patient was advised that they should immediately inform the observer if they experienced nausea, vomiting, chest distress, gastrointestinal discomfort, or any other discomfort. The observer and recorder

would then consult the patient once every five minutes to assess if there was any discomfort. At the end of the procedure, the pharmacist added the name and dose of the drug on the anesthesia record sheet and supplemented the observation record results on the experimental observation record sheet. The patient was blinded to the procedures.

Standard protocol

All patients fasted for at least 8 h and were given no drinking for at least 2 h before the procedure and no preoperative medication was administered. Upon entry, compound sodium lactate Ringer's solution (10–20 mL/kg/h) was infused into the superficial forearm vein. Basic vital signs, including electrocardiogram, pulse oxygen saturation (SpO_2), and noninvasive blood pressure (BP), were monitored. The basic vital signs were measured three times to determine the occurrence of arrhythmia. Patients in both groups were then anesthetized with combined spinal and epidural anesthesia as per the routine protocol. With the patient in the left lateral position, a lumbar puncture was performed at the third lumbar interspace(L3-4) using a midline approach. An 18-gauge epidural needle was introduced using loss of resistance to air, and the dura was punctured with a 27-gauge spinal needle using the needle-through needle technique. After confirming the subarachnoid space with aspiration of cerebrospinal fluid, 0.5% hyperbaric bupivacaine 12–15 mg was administered. After withdrawal of the spinal needle, a 20-gauge epidural catheter was inserted through the epidural needle 3–4 cm into the epidural space to cover the event of an inadequate spinal block or unexpected prolonged surgery After the epidural needle had been removed, the catheter was firmly fixed. Patients were then placed in the supine position. Sensory block was checked using pin-prick and the highest block level was controlled from T6 to T4. Those with significantly decreased blood pressure (systolic BP (SBP) lower than 80% or 90 mmHg) were treated with 0.05 mg of norepinephrine. Atropine (0.25 mg) was administered intravenously to patients with significantly decreased heart rate (HR, lower than 60 beats/min). If SpO_2 was less than 90%, oxygen was provided through a mask to assist breathing. In case of severe nausea or vomiting, sufentanil (5 μg) was administered intravenously.

Following delivery, all patients received routine oxytocin (10 units) in 500 mL of lactate Ringer's solution, via an intravenous drip at 100–150 mL/h, and 10 units of oxytocin was intramuscularly injected according to the protocol. Obstetricians judged the intensity of uterine contractions according to uterine stiffness and bleeding volume and administered carboprost (250 μg, intramuscular or upper arm deltoid muscle injection) if necessary.

Data collection

The primary outcome was the incidence of carboprost-related adverse reactions, such as nausea, vomiting, chest distress, facial flushing, gastrointestinal discomfort, hypoxemia, and hypertension. SBP, diastolic BP (DBP), mean BP (MBP), HR, and SpO_2 were recorded before initiating anesthesia (pre-anesthesia), 1–2 min before carboprost injection (pre-H), and every 3 min after carboprost injection for up to 30 min (post-H). The demographic characteristics of all patients, including age, height, weight, gestational week, parity, and medical history, were recorded. The highest block level, duration of the procedure, intraoperative infusion volume, estimated blood loss, urine volume, intraoperative use of phenylephrine (pre- and post-delivery), need to perform uterine externalization, abdominal exploration, and application of atropine were also recorded.

Statistical analysis

The sample was calculated as follows: $n \approx \frac{(\mu_\alpha+\mu_\beta)^2 \cdot 1+\frac{1}{k} \cdot p(1-p)}{(p_e-p_c)^2}$, $p = \frac{p_e+k\,p_c}{1+k}$, p_e and p_c are the positive rates of nausea and vomiting for group S and group C, according to our preliminary result and pe = 0.5, pc = 0.15. The sample was the same in both groups, k = 1, α = 0.05, and β = 0.1.

The numerical variables are expressed as the mean ± standard deviation (χ ± s), medians (quartile), or numbers (%), as shown in tables. The baseline data and intraoperative observation indices between the groups were compared by independent t-tests. Differences in vital signs between the groups at the same time point were analyzed using multivariate analysis of variance. Differences in vital signs within groups at each time point were analyzed using repeated measured analysis of variance, and pairwise comparisons were conducted using the LSD method. Categorical variables were analyzed using Pearson Chi-square test or Fisher exact test. Data were managed and analyzed using SPSS 25 (SPSS Institute). Two-sided p-values of less than 0.05 were considered to indicate statistical significance.

RESULTS

A total of 30 patients were enrolled and randomized, with 15 patients in each group (Fig. 1). No differences were found between the groups regarding the maternal and neonatal baseline characteristics or intraoperative variables (p > 0.05; Tab. 1).

During the procedure, nausea and vomiting occurred in 17/30 (56.7%) patients; 13/15 (86.7%) patients in group C and 4/15 (26.7%) patients in group S. All incidences of vomiting occurred in group C following treatment with carboprost (11/15, 73.3% vs 0/15, 0%, p = 0.000, Tab. 2). The total incidence of nausea was 43.3%, with nine cases in group C and four cases in group S. One patient in group S complained of nausea before receiving carboprost and was therefore excluded from the analysis. The incidence of nausea in group S was significantly lower than that in group C (20% vs 60%, p = 0.025, Tab. 2). The incidence of gastrointestinal discomfort following carboprost administration in group C was higher than that in group S (73.3% vs 26.7%, p = 0.011). The incidence of other adverse reactions, such as chest congestion, facial flushing, and SpO_2 lower than 90%, was similar between the groups (p > 0.05, Tab. 2).

The vital signs recorded for each group are presented in Figures 1–3. The trends in SBP, DBP, and MBP over time were similar between groups C and S. The SBP, DBP, and MBP of the two groups at the pre-H point were all lower than the pre-anesthesia values; however, there was a significant difference only between SBP and DBP in group C (p < 0.05). There were no significant differences in SBP, DBP, and MBP within or between the groups 3–30 min post-H (p > 0.05), except in one case of transient hypertension that occurred in group S 6 min post-H with a BP of 142/101 (113) mmHg. The BP of patients in the two groups remained within the normal range. A similar trend was observed in HR change over time in both groups (Fig. 4). The HR of patients in each group at the pre-H time point was slightly lower than that recorded pre-anesthesia; however, a significant difference was only observed in group S (p < 0.05). The HR 15- and 18-min post-H was higher than that pre-H in group S. There were no other significant differences in HR between the groups 3–30 min post-H (p > 0.05) or at any time point (p > 0.05), except for three min post-H. In group C, SpO_2 increased slightly at the pre-H time point and three min post-H and decreased gradually thereafter. In group S, there was a slight elevation in SpO_2 at the pre-H time point that decreased gradually from 3–30 min post-H. SpO_2 in group S was lower than that in group C 3–15 and 21 min post-H (p < 0.05; Fig. 5).

DISCUSSION

Intraoperative nausea and vomiting are common complications faced by patients, as observed by anesthesiologists and obstetricians, during cesarean delivery. These symptoms cause discomfort to the parturient patient and can interfere with the procedure. In addition to uterotonics, patient age, gender, smoking history, kinetosis, history of postoperative nausea and vomiting, hypotension, visceral pain, uterine extraction, anesthesia, and surgical

procedure can cause intraoperative nausea and vomiting [16]. Herein, we found no significant differences in these factors between the groups. Furthermore, drugs, such as haloperidol, propofol, midazolam, and glucocorticoids, have been shown to influence the occurrence of intraoperative nausea and vomiting [16, 17]. Therefore, the use of those drugs was avoided in our study. Atropine was administered to two bradycardic patients in each group. Although atropine is an anticholinergic drug with some antiemetic activity, the baseline data, intraoperative procedure, and anesthesia remained comparable between the groups, and there was no statistical difference in the use of atropine between them.

As a second line uterotonic, it is recommended that a single dose of 250 μg of carboprost is administered intramuscularly or intramyometrially, repeated every 15–30 min, up to a maximum of eight times (2 mg) [18]. The stimulation of smooth muscle in the gastrointestinal tract after carboprost injection is associated with side effects, such as nausea and vomiting, which are reported in 60% and 73.3 % of patients, respectively [19].

In the present study, the incidence of vomiting and nausea was lower in parturient patients who received sufentanil following carboprost administration than in those who received placebo. Sufentanil is a potent opioid analgesic that functions as a specific μ-opioid receptor agonist. Opioids act on the central nervous system (CNS) as well as on μ-opioid receptors in the enteric nervous system, thereby delaying gastrointestinal transmission and inhibiting intestinal fluid secretion [20]. Thorent et al. studied the effects of opioids on gastrointestinal peristalsis in healthy volunteers and showed that the intradural administration of morphine slows gastric emptying and the transport of contents through the small intestine [21]. In 1997, Gunnar et al.[20] showed that the addition of an intrathecal adjuvant of sufentanil, fentanyl, to patients undergoing cesarean delivery significantly reduces the need for antiemetic agents during the procedure compared with the saline group. Consistent with the results of previous studies, we showed that a low dose of sufentanil could significantly reduce the incidence of nausea and vomiting following carboprost administration during cesarean delivery. However, sufentanil itself can also cause nausea and vomiting through direct excitation of the central chemoreceptor trigger zone (CTZ), inhibition of gastrointestinal motility, and stimulation of the vestibular organs [22]. This may be explained as follows. First, sufentanil slows down normal gastrointestinal peristalsis, thereby increasing pressure in the gastrointestinal tract, resulting in nausea and vomiting. In the present study, carboprost induced nausea and vomiting by increasing gastrointestinal peristalsis, while sufentanil was able to reduce the incidence of nausea and vomiting by inhibiting this effect. Second, the route of administration

and dose of sufentanil may also have an influence [23]. The low dose of sufentanil used in this study and the slow intravenous infusion may reduce the possibility of sufentanil acting directly on CTZ or vestibular organs [24]. Studies have shown that opioids can reduce visceral pain through central and peripheral pathways [25, 26]. Wilder-Smith et al. compared tramadol with morphine for the treatment of chronic pancreatitis pain, and they showed that morphine increases the overall and visceral pain threshold by acting on μ opioid receptors in the CNS [25]. Consistent with the results of Wilder-Smith et al., our study demonstrated that sufentanil can significantly reduce the incidence of gastrointestinal discomfort following the use of carboprost.

In addition to the gastrointestinal tract, carboprost acts on the respiratory system. Patients may complain of chest distress owing to a decrease in SpO_2 [27]. In our study, the incidence of $SpO_2 < 90\%$ was 20% in both groups. Hankins et al. reported decreased SpO_2 in five patients with PPH following treatment with 15-methylprostaglandin F2 α [28]. Their results showed that arterial oxygen saturation decreases by 10.4% ± 5.4 %, primarily within 7 ± 2.5 min following 15-methylprostaglandin F2 α injection, while the pulmonary shunt increases by 20.7% ± 5.9%. They concluded that decreased arterial oxygen saturation is secondary to a decrease in the ventilation/blood flow ratio and increased intrapulmonary shunt [28]. Evidence from animal studies has shown that opioids can inhibit the contraction of airway smooth muscle [14, 29, 30]. Baroffio et al. [14] isolated calf tracheal smooth muscle to study the effect of opioids on the contraction of airway smooth muscle and showed that opioids significantly reduce the contraction of airway smooth muscle compared with the blank control group under the same electrical stimulation intensity. This may be caused by opioids acting on opioid receptors on the presynaptic membrane of neuromuscular junctions, inhibiting the secretion of acetylcholine via cholinergic nerves in the airway smooth muscle via negative feedback, thereby inhibiting the contraction of airway smooth muscle [14]. In our study, the incidence of $SpO_2 < 90\%$ and the incidence of chest distress in group S were not significantly different compared with those in group C, which contrasted with the conclusion reached by Baroffio et al. [14]. This contradiction may be explained as follows. First, the low doses of sufentanil used in our study led to insufficient sufentanil concentrations in the lung, which were not high enough to alleviate the contraction of bronchial smooth muscle. Second, isolated calf tracheal smooth muscle tissue was used by Baroffio et al. [14] to exclude the effects of sufentanil on the CNS and other hormones or substances in circulation on airway

resistance. Third, there are species differences in the distribution of opioid receptors in the airway [30].

The results of our study showed that SpO_2 in group S began to decrease 3 min earlier than that in group C and was significantly lower in group S than in group C from 3 to 15 min following carboprost administration. It then gradually recovered to the same level as that in group C after approximately 18 min. Therefore, sufentanil was unable to alleviate the hypoxemia induced by carboprost and temporarily increased the degree of hypoxemia. This result was consistent with that of Yasuda et al. [31], who studied the effects of morphine and fentanyl on the tension of tracheal smooth muscle in 38 patients. Tracheal smooth muscle tension is indirectly reflected by the cuff pressure of the airway catheter. The results showed that morphine and fentanyl induce tracheal contraction. As pretreatment with droperidol can antagonize fentanyl-induced tracheal contraction, it was speculated that the mechanism of tracheal contraction induced by fentanyl may be related to the activation of α-adrenergic receptors [31]. In addition, fentanyl may induce chest wall stiffness and increase airway resistance [32].

In our study, hemodynamic indices in the two groups fluctuated within the normal range, and only one patient in group S experienced transient hypertension. It has been previously reported that 4% of patients receiving carboprost treatment may experience hypertension as a side effect [19]. In the present study, the incidence of hypertension was 3.3%. The mechanism of carboprost-induced hypertension may be through the action of prostaglandin F2-α on thromboxane A2 receptors on vascular smooth muscle cells, leading to vasoconstriction by increasing the Ca^{2+} concentration in vascular smooth muscle cells [33]. Topozada et al. reported 16 cases of maternal PPH treated with 15-methylprostaglandin F2-α [34]. Among these 16 patients, three developed hypertensions, with the highest blood pressure reported to be 210/120 mmHg. The incidence of hypertension in their study was 18.8%, significantly higher than 3.3%. It is speculated that the total dose of 15-methylprostaglandin F2-α (437.5 μg) in their study was higher than the 250-μg dose used in our study.

Opioids have inhibitory effects on the cardiovascular system and can lead to bradycardia and hypotension [13]. The mechanism underlying this effect might be explained as follows. First, vagus nucleus activation through the CNS reduces sympathetic tension in the spinal cord [35]. Second, the direct dilation of blood vessels reduces peripheral resistance. In 2005, Ebert et al. administered low dose sufentanil via continuous infusion through the brachial artery to 10

healthy volunteers. The results showed that the brachial artery blood flow in the arm on the 978 side that is infused is significantly higher than that in the arm that is not infused; however, the HR and BP of the healthy volunteers do not change. We demonstrated that continuous infusion of low dose sufentanil can directly induce vasodilation through local effects and systemically regulate the autonomic nervous system via the CNS [15]. Like Ebert et al., we used a low dose of sufentanil, which was administered by slow intravenous infusion. The effect of sufentanil on systemic vascular resistance may not be significant, and its effect on hypertension induced by carboprost is limited.

Another study has shown that remifentanil, which has a short half-life of only 5–10 min, alleviates the adverse effects of carboprost administration during cesarean section [11]. Sufentanil has a lower influence on hemodynamics than remifentanil. Therefore, a future study should be conducted to determine whether remifentanil or sufentanil is superior for alleviating the adverse effects of carboprost administration during cesarean section. In addition, there are some limitations to the present study. For example, the study population was small; thus, some complications caused by sufentanil may not have been observed. Furthermore, we used only a target effect-site sufentanil concentration; thus, whether the concentration of sufentanil used in our study (5 μg/mL) is the most suitable dose is unknown.

As for the impact of sufentanil on the baby safety in early breastfeeding, the half-life of sufentanil is about 30 minutes. According to the law of drug metabolism, the blood drug concentration is negligible after 5 half-life (150 min); The drug is passively transported between maternal blood and milk, and the drug concentration in milk will not exceed that in maternal blood; Moreover, the milk secretion in the first three days of postpartum is very small, and the newborn's food intake is also very small. The drugs in the milk are absorbed into the blood through the neonatal digestive system. After the first pass metabolism of the liver, the amount entering the nervous system is further reduced, so there is almost no respiratory depression, and respiratory depression is not observed clinically.

In this study, although the prophylactic use of low dose sufentanil reduced the incidence of nausea, vomiting, stomach pain, and other gastrointestinal side effects following the administration of carboprost during cesarean section, it was unable to alleviate the hypoxemia caused by carboprost and may temporarily aggravate the severity of hypoxemia.

Statement of ethics

The authors have no ethical conflicts to disclose.

Author contributions

HFL and LZ conceptualized and designed the study. QH and JG conducted of the study. QH, PB, XX analyzed the data, assisted by TH and PY. QH wrote the manuscript. All authors agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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Conflict of interest

The authors declare that they have no conflict of interest.

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Table 1. The characteristics and intraoperative variables

	Group C	Group S	p-value
Age [years]	30.93 ± 4.59	32.40 ± 4.53	0.386
Height [cm]	161.5 ± 4.02	159.20 ± 3.59	0.105

Weight [kg]	70.33 ± 10.6	69.83 ± 8.16	0.886
Gestational age [weeks]	38.14 ± 1.18	38.13 ± 1.30	1.000
Gravida [n]	2.67 ± 1.72	2.67 ± 1.59	0.514
Para [n]	0.4 ± 0.63	0.27 ± 0.46	0.562
Primipara	10 (66.7)	11 (73.3)	1.000
Twin pregnancy	1 (6.7)	2 (13.3)	1.000
Smoking	0 (0)	1 (6.6)	1.000
Kinetosis	5 (33.3)	3 (20)	0.682
Post-operative nausea and vomiting history	1 (6.7)	0 (0)	1.000
Operation duration	45.93 ± 6.88	44.73 ± 11	0.723
Intraoperative infusion volume	833.3 ± 154	866.67 ± 209	0.623
Intraoperative urine volume	126.7 ± 86.2	157.67 ± 156	0.505
Intraoperative blood loss	392 ± 98.8	426 ± 168	0.504
Intraoperative norepinephrine dosage [µg]	90 ± 107.2	138.4 ± 104.4	0.237
Intraoperative atropine use n (%)	3 (20)	3 (20)	1.000
uterine extraction n (%)	2 (13.3)	0 (0)	0.483

Intraoperative abdominal exploration n (%)	2 (13.3□	2 (13.3)	1.000
Block level (T4/T6)	8/7	7/8	0.715

Table 2. The adverse reaction between the two groups

	Group C (n = 15)	Group S (n = 15)	p-value
Nausea			
Pre- Hemabate	0 (0)	1 (6.7)	1.000
Post- Hemabate	9 (60)	3 (20)	0.025*
Total	9 (60)	4 (26.7)	0.065
Vomiting	11 (73.3)	0 (0)	0.000*
IONV	13 (86.7)	4 (26.7)	0.001*
Chest distress	4 (26.7)	4 (26.7)	1.000
Facial flushing	1 (6.7)	5 (33.3)	0.169
Stomachache	11 (73.3)	4 (26.7)	0.011*
SpO_2 < 90%	3 (20)	3 (20)	1.000

IONV — Intraoperative nausea and vomiting; *stand for p < 0.05

Table 3. The vital signs between the two groups

groups	Pre-A	Pre-H	Post-H								
			3min	6min	9min	12min	15min	18min	21min	24min	27min	30min

SBP (mmHg)	S	118.5 ± 12.5	115± 13.1	113.6 ± 14.9	116.8 ± 12.4	115± 10.4	116.4 ± 9.8	115.2 ± 10.8	114.5 ± 12.4	112.9 ± 13.6	113.5 ± 11.3	115.4 ± 9.8	114.2 ± 9.7
	C	121.3 ± 6.1	114.7 ± 11.8*	112.9 ± 10.7*	115.4 ± 10.4	114.8 ± 12.7	114.7 ± 12.9	116.3 ± 11.5	117.6 ± 11.0	118.6 ± 10.3	118.4 ± 10.1	117.9 ± 10.5	116.7 ± 10.3*
DBP (mmHg)	S	72.3 ± 9.8	70.3 ± 11	69.6 ± 14	73.2 ± 11.7	68.4 ± 9.6	66.1 ± 8.3	64.3 ± 7.5*	64.3 ± 10.5*	64.7 ± 11*	66.1 ± 11.1	66.3 ± 12	67.7 ± 8.7
	C	76.8 ± 5.1	68.8 ± 11.6*	66.6 ± 9.8*	68.2 ± 7.9*	62.7 ± 7.5*	61.1 ± 10.3*	60.7 ± 10.8*	63.1 ± 9.0*	62.7 ± 7.9*	64.9 ± 7.4*	62.6 ± 7.7*	65.1 ± 7.5*
MBP	S	87.4 ± 10.1	85.9 ± 13.9	85.6 ± 14.1	87.4 ± 11.8	85.1 ± 9.71	83.8 ± 7.52	80.9 ± 8.4*	80.9 ± 9.2*	79.7 ± 10.8*	80.9 ± 10.7*	81.9 ± 10.2	82.1 ± 9.1
	C	92.3 ± 5.1	84.8 ± 14.1	81.3 ± 8.8*	82.7 ± 8.5*	79.2 ± 7.0*	77.9 ± 10.4*	78.1 ± 11.0*	78.7 ± 7.7*	80.4 ± 7.8*	81.3 ± 8.1*	80.5 ± 6.7*	79.7 ± 6.8*
HR	S	91.5 ± 13.8	85.5 ± 10.7*	87.5 ± 12.1$	94.5 ± 14.1	94.5 ± 15.5	95.0 ± 16.0	95.3 ± 13.5#	95.8 ± 13.9#	95.0 ± 15.3	93.5 ± 15.7	94.8 ± 15.8	92.9 ± 15.1

	C	96.1 ± 12.6	94.0 ± 14.2	97.1 ± 13.0	96.5 ± 9.4	97.5 ± 12.4	99.9 ± 13.2	100.8 ± 12.5	97.7 ± 10.3	95.1 ± 6.4	94.1 ± 7.7	93.2 ± 8.9	92.5 ± 8.6
SpO_2 (%)	S	97.8 ± 1.0	98.7 ± 1.22*	98.1 ± 1.4#$	97.3 ± 1.8#$	95.9 ± 1.4*#$	95.6 ± 1.6*#$	94.2 ± 1.9*#$	94.3 ± 1.6*#	94.1 ± 1.7*#$	94.7 ± 1.8*#	94.6 ± 1.6*#	95.2 ± 1.8*#
	C	98.3 ± 0.8	99.1 ± 0.9*	99.1 ± 0.9*	98.9 ± 1.2	98.2 ± 1.7#	97.4 ± 2.1#	96.5 ± 3.0*#	95.9 ± 3.5*#	96.1 ± 3.1*#	95.7 ± 2.7*#	95.8 ± 2.5*#	96.0 ± 2.5*#

post-H — post-Hemabate; pre-A — pre-anaesthesia; pre-H — pre-Hemabate; *stand for comparing with pre-A, $p < 0.05$ # stand for comparing with pre-C, $p < 0.05$ $ stand for comparing with group O, $p < 0.05$

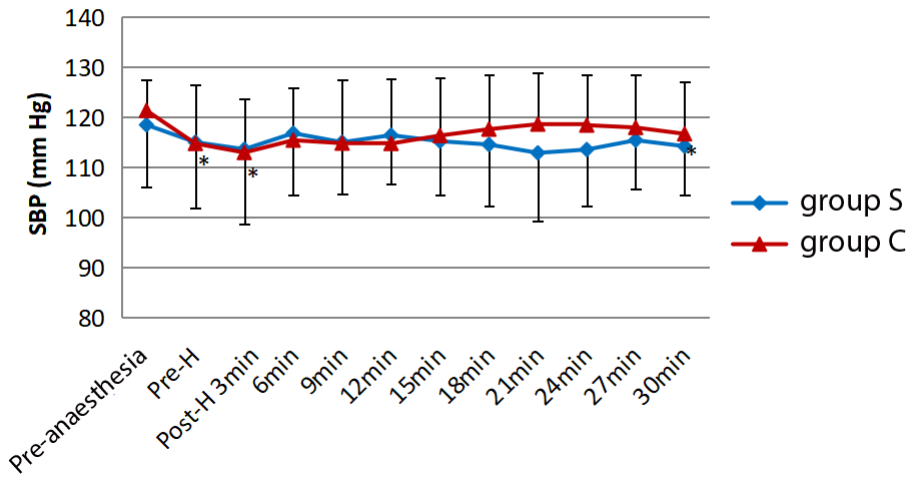

Figure 1. The systolic blood pressure tread over time between the two groups. Generally, the systolic blood pressure of the patients in two groups was stable and within normal range at each study point, and no statistically difference was found between the two groups at any post-H point; Post-H — post-Carboprost administration; Pre-H — Pre-Carboprost

administration; SBP — systolic blood pressure;*means p < 0.05 compared with pre-anaesthesia

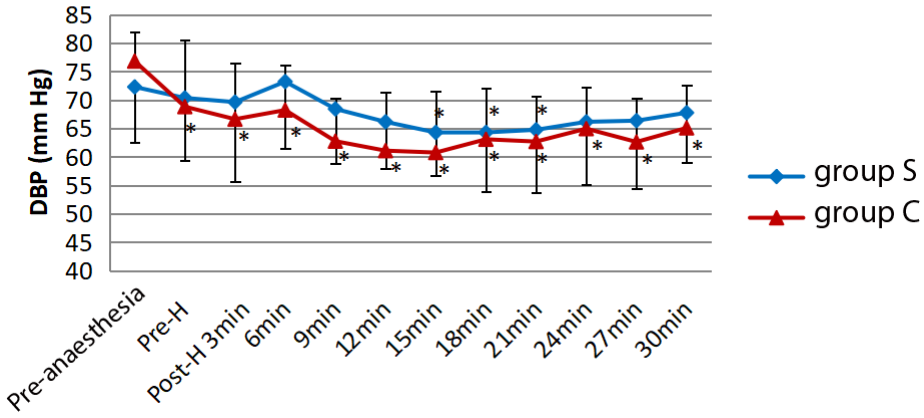

Figure 2. The diastolic blood pressure tread over time between the two groups. Generally, the diastolic blood pressure of the patients in two groups was stable and within normal range at each study point, and no statistically difference was found between the two groups at any post-H point; DBP — diastolic blood pressure; Post-H — post-Carboprost administration; Pre-H — Pre-Carboprost administration; *means p < 0.05 compared with pre-anaesthesia

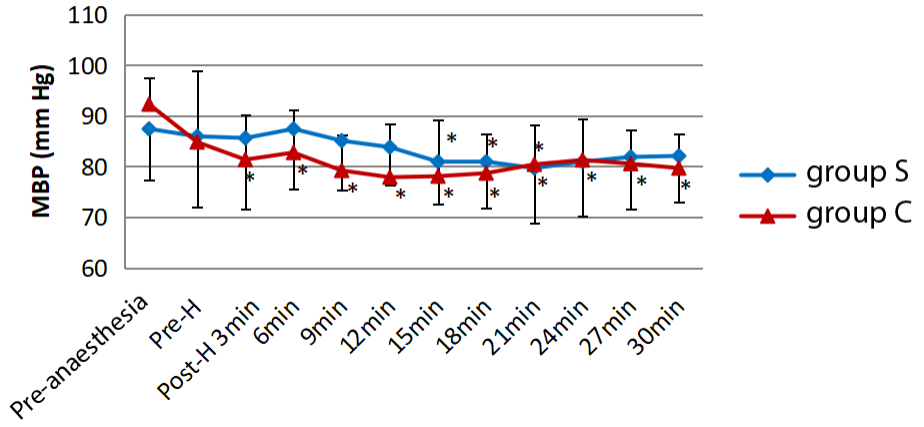

Figure 3. The mean blood pressure tread over time between the two groups. Generally, the mean blood pressure of the patients in two groups was stable and within in normal range at each study point, and no statistically difference was found between the two groups at any

post-H point; MBP — mean blood pressure; Post-H — post-Carboprost administration; Pre-H — Pre-Carboprost administration; *means p < 0.05 compared with pre-anaesthesia

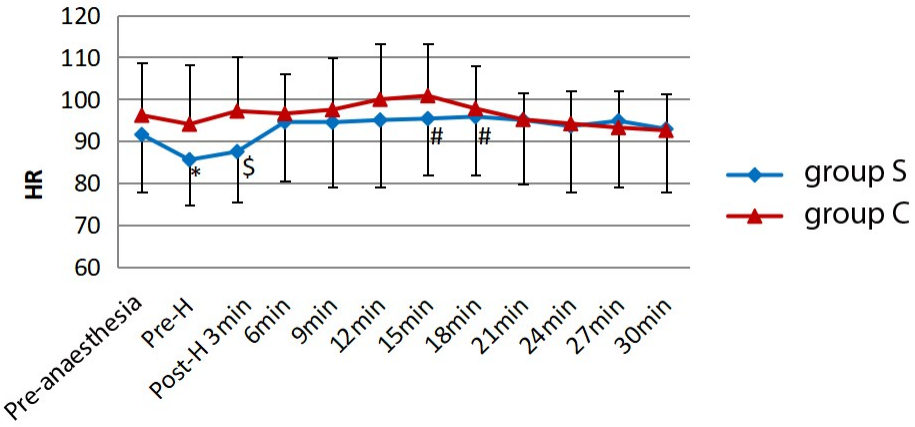

Figure 4 The heart rate tread over time between the two groups. Generally, the heart rate of the patients in two groups was stable and within in normal range at each study point, and no statistically difference was found between the two groups at any post-H point except the Post-H 3-minute point. The heart rate of Group S was obviously lower than that of Group C; HR — heart rate; Post-H — post-Carboprost administration; Pre-H — Pre-Carboprost administration; *means p < 0.05 compared with pre-anaesthesia; #means p < 0.05 compared with pre- Hemabate; $ means p < 0.05 compared with Group C

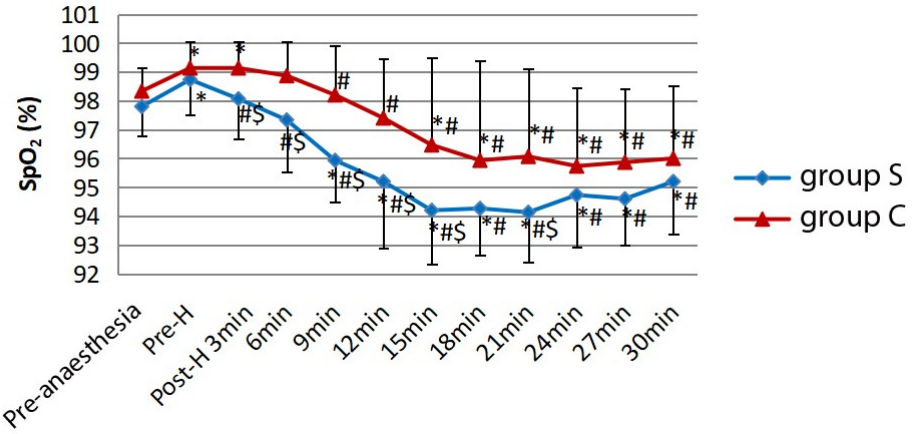

Figure 5. The SpO2 tread over time between the two groups. Generally, the SpO2 of the patients in two groups was decreased over time after Hemabate injection. The SpO2 of Group S was lower than that of Group C at post-H 3-15minute and 21minute point; Post-H — post-Carboprost administration; Pre-H — Pre-Carboprost administration; *means p < 0.05

compared with pre-anaesthesia; #means $p < 0.05$ compared with pre- Hemabate; $ means $p < 0.05$ compared with Group C