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ORIGINAL ARTICLE

Landiolol attenuates cardiovascular response at induction of general anesthesia for cesarean delivery

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Abstract
Purpose General anesthesia for cesarean delivery is frequently associated with hypertension and tachycardia caused by tracheal intubation, which may lead to cardiac ischemia in susceptible patients or may cause harm due to increased intracranial pressure. To prevent these adverse events, we investigated the efficacy and safety of single-dose intravenous administration of landiolol, a short-acting selective β_1 receptor blocker, just prior to intubation.
Methods Patients scheduled for cesarean delivery under general anesthesia were randomized into two groups: landiolol (group L, $n = 32$); and nontreated (group N, $n = 32$) patients. After patients entered the operating room, blood pressure (BP), heart rate (HR), and fetal heart beats were monitored to ensure no problems were present, then thiopental 5 mg/kg and rocuronium 0.9 mg/kg were given. In addition, group L received a single dose of landiolol 0.2 mg/kg. After tracheal intubation, anesthesia was maintained in both groups using sevoflurane. From before starting anesthesia to the time of delivery, BP, HR, need for additional treatment with uterotonic or vasopressor agents, and neonatal Apgar scores were recorded. Data were compared between groups.
Results Group L showed significantly lower percentage changes in BP and HR than group N ($p < 0.05$ each). Intraoperative blood loss, frequency of decreased uterine contraction, and fetal Apgar scores did not differ significantly between groups.
Conclusions In our study, landiolol reduced BP and HR changes during anesthesia induction, whereas no adverse effects on uterine contraction or the fetus were seen. These findings suggest landiolol provides adequate hemodynamic regulation during general anesthesia induction in patients undergoing cesarean delivery.

Keywords Landiolol · Intubation · Cesarean delivery · General anesthesia

Introduction

Regional anesthesia is recommended for cesarean delivery [1], but general anesthesia must sometimes be used in patients in whom regional anesthesia is contraindicated or in emergency procedures. However, general anesthesia may cause fetal sedation, as reported in a recent meta-analysis [2]. Endocrine stress responses are better controlled with regional anesthesia than with general anesthesia [3], and during abdominal surgery under general anesthesia, opioids are administered to inhibit stress-hormone release [4]. However, general anesthesia in cesarean delivery differs from general anesthesia in nonpregnant patients in terms of potential adverse effects on fetal circulation and respiration. Opioids are not usually administered until after delivery of the neonate in order to minimize neonatal respiratory depression [1]. As a result, hypertension and tachycardia may occur during anesthesia induction, and even intracerebral hemorrhage has been reported [5]. To prevent such adverse events, we investigated the efficacy and safety of single-dose intravenous administration of landiolol, a rapid-acting selective β_1 receptor blocker, just prior to tracheal intubation.

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Patients and methods

This study was approved by the institutional review board at our hospital, and written consent was obtained from all participants. The patients scheduled for cesarean delivery under general anesthesia in from October 2007 to September 2009 were included in the study. Patients who did not have enough time to make their decisions before anesthesia for emergency cases were not included. Exclusion criteria were American Society of Anesthesiologists (ASA) physical status ≥III; hepatic, renal, or cardiac dysfunction; severe obesity [body mass index (BMI) ≥35]; or expected fetal congenital abnormality. A total of 93 patients were screened for the study. Twelve patients did not give their informed consent, and 17 were excluded according to exclusion criteria. According to a computer-generated sequence of numbers, patients were randomly assigned into two groups: a landiolol group (group L, $n = 32$) and a nontreated group (group N, $n = 32$). In all patients, preoperative medication was not given. Monitoring during general anesthesia included standard electrocardiography, pulse oximetry, noninvasive blood pressure (BP), and end-tidal carbon dioxide (CO_2) concentration. Vital signs, including BP and heart rate (HR), were monitored every 1 min starting from when the patient entered the operating room. The patient was placed in a supine position and preoxygenated using a mask (100% oxygen, 3 min) before anesthesia induction. In addition, starting before anesthesia induction, fetal HR (FHR) was monitored by ultrasonography.

Anesthesia was induced with thiopental 5 mg/kg and rocuronium 0.9 mg/kg. At 75 s after administration of the induction agents, tracheal intubation was performed using a laryngoscope. At the same time as induction agent administration, landiolol 0.2 mg/kg (group L) and saline (group N) were also given intravenously. Landiolol was drawn up with 10 ml saline (prepared by blinded anesthesiologists). Clinical anesthesiologists were blinded to the agent given. Anesthesia was maintained with air, oxygen, and sevoflurane (oxygen concentration 50%, sevoflurane concentration 1.7%). After delivery and umbilical cord clamping, fentanyl was started. Thereafter, fentanyl and rocuronium were given as needed. When hypotension (systolic BP <80 mmHg) or bradycardia (HR <50 bpm) occurred, ephedrine 5 mg was administered. We did not apply left uterine displacement in any patient. Immediately after delivery of the baby, 20 U of oxytocin with 100 ml saline were given by intravenous infusion over 15 min. Uterine contractions were assessed by obstetricians. If uterine contractions were poor, another 20 U of oxytocin was administered. Apgar scores at 1 and 5 min after birth were evaluated by a neonatologist.

Statistical analysis

Changes in BP and HR during anesthesia induction were measured as hemodynamic parameters. HR, SBP, and DBP when the patient entered the operating room were baseline values, and maximum percentage changes in HR and BP were calculated until delivery. Percentage changes in hemodynamic variables were defined as follows:

$$\text{Percent change in HR} = [(\text{maximum HR} - \text{baseline HR})/\text{baseline HR}] \times 100\%$$

$$\text{Percent change in SBP} = [(\text{maximum SBP} - \text{baseline SBP})/\text{baseline SBP}] \times 100\%$$

$$\text{Percent change in DBP} = [(\text{maximum DBP} - \text{baseline DBP})/\text{baseline DBP}] \times 100\%$$

Data in groups L and N were compared for significant differences using Student's t test and the Welch test. Values of $p < 0.05$ were considered statistically significant.

Results

Table 1 shows baseline (preoperative) characteristics of the 64 patients. Age, height, weight, ASA physical status, and

Table 1 Preoperative patient data

Variable	Group N ($n = 32$)	Group L ($n = 32$)	P value
Age (years)	31.7 ± 4.25	30.3 ± 4.07	0.201
Height (cm)	157 ± 5.79	158 ± 4.48	0.665
Weight (kg)	58.5 ± 6.29	56.3 ± 4.78	0.117
ASA class (I/II)	27/5	29/3	0.450
Preoperative hemodynamic data			
Heart rate (bpm)	79.4 ± 10.3	81.0 ± 7.55	0.493
Systolic BP (mmHg)	127 ± 18.2	134 ± 16.0	0.100
Diastolic BP (mmHg)	80.7 ± 14.0	85.6 ± 18.2	0.232
Indication for general anesthesia			
Refusal of regional anesthesia	3 (9.3%)	6 (18.8%)	0.221
Thrombocytopenia	27 (84.4%)	26 (81.2%)	
Previous spinal surgery	2 (6.3%)	0 (0%)	
Indication for cesarean delivery			
Previous cesarean delivery	18 (56.3%)	21 (65.4%)	0.742
Multiple pregnancy	4 (12.5%)	3 (9.3%)	
Breech presentation	10 (31.2%)	8 (25%)	

Data are expressed mean ± standard deviation (SD)

ASA American Society of Anesthesiologists, *BP* blood pressure

noninvasive BP/HR on entry into the operating room did not differ significantly between groups.

Figure 1 depicts the percent change in hemodynamic parameters. Percentage change in HR was 15.1 ± 22.3% in group L and 48.5 ± 35.9% in group N. Percentage change in SBP was 16.2 ± 7.57% in group L and 41.0 ± 15.9% in group N. Percentage change in DBP was 29.2 ± 19.0% in group L and 41.7 ± 23.8% in group N. Percentage changes in each hemodynamic parameter were significantly lower in group L than in group N ($p < 0.05$ each).

Table 2 shows perioperative data. Duration of surgery, anesthesia time, infusion volume, and blood loss did not differ significantly between groups. In addition, no significant differences were seen between groups for induction–delivery (I–D) time, additional doses of uterotonic agents after delivery, and additional doses of vasopressor agents.

Table 3 lists Apgar scores (1 and 5 min) and umbilical-cord blood-gas analysis data; results did not differ significantly between groups.

Discussion

Sympathetic nervous system responses to laryngeal exposure, tracheal intubation, and surgical stimuli may lead to serious complications, including myocardial ischemia and increased intracranial pressure [6]. Opioids can control these responses [7] and reduce postoperative pain [8]. However, during general anesthesia in a cesarean delivery, administration of opioids to the mother before delivery can cause complications, including neonatal respiratory depression [9]. Therefore, opioids are not usually administered until after delivery to minimize neonatal respiratory depression [1]. This may result in hypertension and tachycardia in the mother during anesthesia induction. Various studies have investigated the prevention of such adverse events [10–13]. El-Hakim et al. [10, 11] reported that tenoxicam during anesthesia induction reduces hemodynamic fluctuations and postoperative pain, but bleeding time is prolonged. A study by El-Tahan et al. [12] reported beneficial effects with ketorolac, and Draisci et al. [1] and Ngan Kee et al. [13] likewise reported the effectiveness of remifentanil.

In this study, we investigated the efficacy and safety of single-dose intravenous administration of landiolol, a short-acting selective β_1 receptor blocker, just prior to tracheal intubation. The use and effectiveness of β receptor blockers, including esmolol, [14–22] labetalol, [23, 24] and landiolol, [6, 25] to reduce hemodynamic changes during general anesthesia induction have previously been reported. However, landiolol has not previously been evaluated for prevention of hemodynamic changes during general anesthesia induction in cesarean delivery. Landiolol is a short-acting selective β_1 receptor blocker with an elimination half-life of 4 min and a clearance of 2.52 l/h/kg [26], whereas esmolol has a peak effect at 6 min, a distribution half-life of 2 min, an elimination half-life of 9 min, and a clearance 17.1 l/h/kg [27]. We found that a single dose of landiolol significantly inhibited changes in BP and HR (Fig. 1). Furthermore, no hypotension or bradycardia requiring treatment occurred.

When administering drugs to pregnant women, the effects on the mother, fetal transfer, and breast-milk

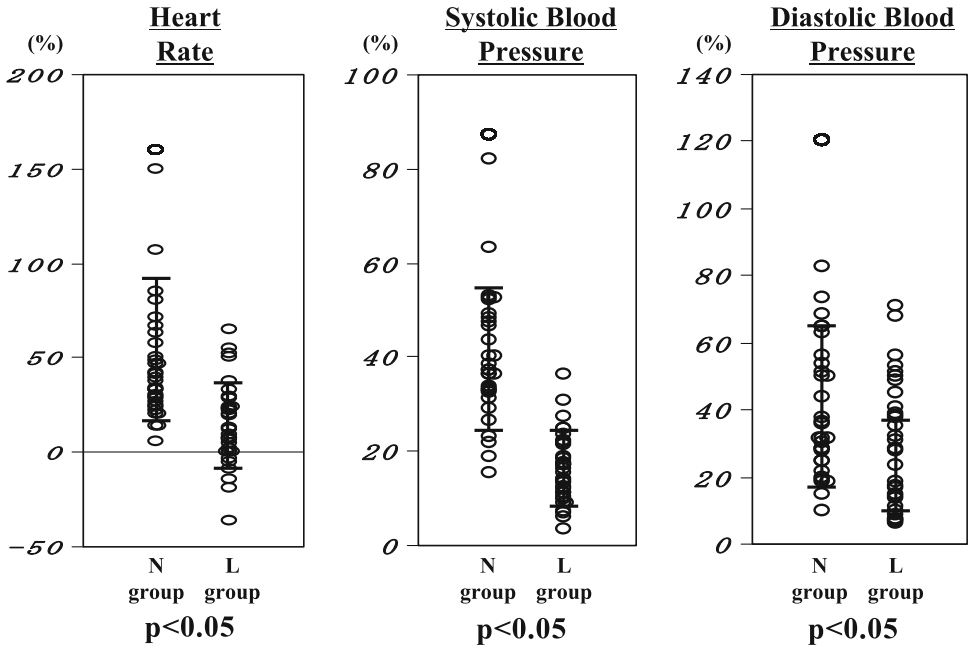

Fig. 1 Hemodynamic change in both groups. Percentage changes in each hemodynamic parameter were significantly lower in group L than in group N ($p < 0.05$ each)

Table 2 Patient perioperative data

Variable	Group N ($n = 32$)	Group L ($n = 32$)	*P* value
Operation time (min)	82.1 ± 33.4	74.6 ± 24.2	0.308
Anesthetic time (min)	56.2 ± 30.4	45.1 ± 20.1	0.090
Infusion volume (min)	2140 ± 531	1950 ± 392	0.363
Blood loss (ml)	1310 ± 878	1220 ± 888	0.690
I–D time (min)	4.97 ± 1.73	5.03 ± 5.57	0.910
FHR (bpm)	140 ± 7.88	142 ± 7.53	0.705
Additional administration			
Uterotonic agents (cases)	8 (25%)	10 (31%)	0.578
Vasoactive drugs (cases)	0 (0%)	0 (0%)	1.0

Data are expressed mean ± standard deviation (SD)

I–D time induction-to-delivery time, *FHR* fetus heart rate

Table 3 Apgar scores and umbilical-cord blood-gas analysis

Variable	Group N ($n = 32$)	Group L ($n = 32$)	*P* value
Apgar scores at 1 min (cases)			
10	2 (6.3%)	1 (3.1%)	0.958
9	17 (53%)	19 (59%)	
8	3 (9.4%)	2 (6.3%)	
7	2 (6.3%)	3 (9.4%)	
6	4 (13%)	3 (9.4%)	
5	3 (9.4%)	2 (6.3%)	
<5	1 (3.1%)	2 (6.3%)	
Apgar scores at 5 min (cases)			
10	21 (66%)	22 (69%)	0.887
9	3 (9.4%)	2 (6.3%)	
8	2 (6.3%)	3 (9.4%)	
7	2 (6.3%)	2 (6.3%)	
6	4 (13%)	2 (6.3%)	
5	0 (0%)	1 (3.1%)	
<5	0 (0%)	0 (0%)	
Umbilical artery			
pH	7.26 ± 0.06	7.27 ± 0.05	0.603
BE (mEq/l)	−1.94 ± 1.50	−1.68 ± 1.62	0.526

Data are expressed mean ± standard deviation (SD)

BE base excess

transfer during breast feeding must all be considered. In our study, landiolol, a short-acting β_1 receptor blocker with a serum half-life of about 4 min, was effective in maintaining hemodynamic parameters. Placental transfer data of landiolol is unknown, and its safety for the fetus when it is given to the mother has not been fully established. However, it was reported that landiolol, if the total amount administered was not large, caused few developmental problems in offspring [28, 29], and landiolol was safety used for a pregnant patient during cesarean section [26, 30]. Taking into consideration the potential fetal effects, we administered a single dose of landiolol in this study rather than continuous administration. Comparison between group L and group N showed no adverse effects on Apgar scores or umbilical-cord blood-gas results (Table 3). Our findings demonstrate fetal safety. Also, comparison between groups L and N showed no significant increase in additional required doses of uterotonic agents or blood loss due to poor uterine contractions (Table 2). Landiolol is a highly β_1-selective drug with a β_1/β_2 ratio of 251 [31]. Uterine contractions are mainly due to β_2 receptor blockade, so postpartum uterine contractions are unaffected. Also, when given together with uterotonics, excessive uterine contractions and uterine rupture are less likely. In our study, landiolol given during anesthesia induction did not affect uterine contractions.

Esmolol could be an alternative drug to landiolol to attenuate cardiovascular response at induction of general anesthesia for cesarean delivery. However, esmolol appears insufficient to achieve these objectives, as they still have hypotensive effects [32–34]. In this regard, it has been reported that landiolol could prevent increase in HR after tracheal intubation without affecting BP [35]. With the point of the effect on fetal transfer, it has been reported that esmolol had a negative chronotropic effect on a fetus despite its short duration of action [36]. Esmolol has an elimination half-life of 9 min and might have a more potent negative chronotropic effect on a fetus than landiolol. Regarding uterine contractions, landiolol might be superior to esmolol. The ratio of β_1/β_2-blocking potency of esmolol is 32 [31]. Therefore, esmolol could affect uterine muscle tone. Ducey et al. [37] reported ill effects of esmolol on the fetus. They reported that an esmolol bolus and infusion administered in an attempt to treat supraventricular tachycardia in a pregnant woman at term was associated with profound fetal bradycardia, requiring emergency cesarean delivery.

As the limitation of this study, we did not administer nitrous oxide for maintenance. Sevoflurane 1.7% only may seem inadequate to suppress sympathetic response, but it has less effect for uterine contraction and neonatal respiratory depression. And we did not use nitrous oxide to decrease postoperative nausea and vomiting. Another limitation of this study is that we did not monitored FHR after administration of landiolol. Apgar score was not significantly different between groups N and L. However, further studies are needed to examine placental transfer data of landiolol and its negative chronotropic effect on the fetus.

Conclusions

We evaluated the effectiveness of landiolol during general anesthesia induction in cesarean delivery. Landiolol

reduced BP and HR changes during anesthesia induction, and no adverse effects on uterine contraction or the fetus were seen. These findings suggest landiolol provides adequate hemodynamic regulation during general anesthesia induction in patients undergoing cesarean delivery.

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