British Journal of Pharmaceutical Research

16(4): 1-7, 2017; Article no.BJPR.32591
ISSN: 2231-2919, NLM ID: 101631759

Comparison of the Effects of Ropivacaine and Bupivacaine on Human Umblical Artery Vasoreactivity

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Authors' contributions

This work was carried out in collaboration between all authors. Authors KB, KN and BZ designed the study, wrote the protocol, managed the literature searches and wrote the first draft of the manuscript. Authors DS and TA managed the analyses of the study, performed the statistical analysis and wrote the first draft of the manuscript. All authors read and approved the final manuscript.

Article Information

DOI: 10.9734/BJPR/2017/32591
Editor(s):
(1) R. Deveswaran, M.S. Ramaiah College of Pharmacy, Bangalore, India.
Reviewers:
(1) Jan Jakobsson, Danderyds University Hospital, Sweden.
(2) Yao Yao, Ningxia Medical University, P.R. China.
(3) Ipek Duman, Necmettin Erbakan University, Turkey.
Complete Peer review History: http://www.sciencedomain.org/review-history/18969

Original Research Article

Received 3rd March 2017
Accepted 15th April 2017
Published 8th May 2017

ABSTRACT

The primary aim of the current study was to examine the effect of ropivacaine and bupivacaine on human umblical artery reactivity and on clinical outcomes. Neither bupivacaine nor ropivacaine produce a significant effect on the maternal systolic blood pressure and heart rate during operation. However, ropivacaine and bupivacaine were used by addition of increasing concentrations of agonist (0.2-8 microg/ml) to the baths in a cumulative manner and the isometric tension devoloped by the tissue. In organ bath studies, bupivacaine caused a significant relaxation response in human umblical artery rings precontracted with either KCl or 5-hydroxytriptamine. Conversely, ropivacaine did not induce a relaxation response in umblical vessels which have been previously induced to contract by an activator. In conclusion, the results of this study have shown that bupivacaine, but not ropivacaine, may cause a significant effect on human umblical vessel tonus.

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Keywords: Bupivacaine; ropivacaine; human umblical artery.

1. INTRODUCTION

The choice of anesthetic and analgesic methods and drugs may alter the uterine contractility. The frequency and force of uterine contractions can be increased by oxytocin or decreased by opioids and local anesthetics [1,2,3].

Local anesthetics are known to have vasoactive properties on a variety of vascular tissues and umblical resistance, and therefore, blood flow may be affected by using of these agents. Since the oxygenation of the foetus is not depend only on the maternal systemic and uterine circulation but also on the umblical circulation of the foetus [4], recent researchs have been focused on the direct effect of local anesthetic agents on the uterine vessels at birth, which is an essential component in the regulation of the umblical-placental circulation.

Bupivacaine is a local anesthetic commonly used in obstetrical pratice while ropivacaine is a new amide local anesthetic structurally similar to bupivacaine [5]. Previous studies reported that ropivacaine has a similar clinical effect as bupivacaine with regard to sensory anesthesia and slightly less motor blockade than bupivacaine [6]. Also, ropivacaine appears to be less cardiotoxic and arrhythmogenic than bupivacaine [7,8]. However, the vasoactive effect of ropivacaine and bupivacaine on human umblical artery has not been investigated enough. Thus, in this in vitro study, we evaluated the vasoactive effects of two local anesthetics commonly used in obstetric anaesthesia, ropivacaine and bupivacaine, on the human umblical artery preparations using an organ bath system.

2. MATERIALS AND METHODS

Patients of 46 ASA physical status I and II, healty, full-term parturients undergoing elective lower-segment cesarean delivery were eligible for the study. Parturients older than 18 yr who were between 37 and 40 weeks gestation. Patients who had obstetric complications, multiple gestation or suspected fetal abnormality were excluded. The patients received oral information about the nature of study. A small segment of umblical cord was taken from the maternal side of umblical cord (discharged cord).

All patients had general anesthesia. The patients were fasted overnight and received no medication preoperatively. After introduction of an intravenous cannula (18G) an infusion of 0.9% saline solution 15 $mg.kg^{-1}$ was administered. Standard monitoring (pulse oximetry, non-invsive blood pressure and five-lead electrocardiograms) was instituted before anesthesia. Baseline maternal heart rate and non-invasive blood pressure were recorded before induction, 1., 3., 5., 10. minutes after induction, during delivery and the end of the operation during discharge from recovery room. Hypotension, defined by a decrease in systolic blood pressure to less than 100 mmHg or <80% of baseline, was treated with IV ephedrine 5-10 mg and additional colloid solutions. Bradycardia, defined as heart rate <60 $beats.min^{-1}$ was treated with IV atropine 0.5 mg.

General anesthesia was induced with 4-5 $mg.kg^{-1}$ IV thiopental and 1-2 $mg.kg^{-1}$ succinylcholine (Lysthenon, Fako). After delivery, general anesthesia was maintained with 0.1 $mg.kg^{-1}$ IV vecuronium bromide (Norcurone, Organon), IV 0.1 mg fentanyl (Fentanyl citrate, Abbott), % 1,5 sevoflurane (Sevorane, Abbott) and 50% nitrous oxide with oxygene. During the surgery, all patients received an intravenous infusion 0.9% isotonic sline at a rate of 5-7 $mg.kg^{-1}.h^{-1}$. Apgar scores were assesssed at 1 and 5 min by the attending paediatrician.

In order to perform the functional studies, a small segment of umblical cord was taken from the cord between the placenta and discharged cord. The specimen was placed in cold physiological salt solution and immediately transferred to the laboratory. A total 46 umblical cords from normal and healty pregnancies were utilized for this study. Approximately 20 cm segments were cut from the cords, clamped and placed immediately in cold Krebs solution. The full length of umblical artery was removed and cleaned of the connective tissue. The umblical arteries were carefully dissected out of the cords and cut into 2-3 mm width rings. Then, the rings were carefully suspended by two stainless steel clips passed through the vessel lumen in 20 ml organ baths filled with physiological salt solution (PSS) (mM: NaCl 118, KCl 5, $NaHCO_3$ 25, KH_2PO_4 1.0, $MgSO_4$ 1.2, $CaCl_2$ 2.5, and glucose 11.2) maintened at 37℃ gassed with 95% O_2 and 5% CO_2 to obtain a pH of 7.4. The rings were suspended under 2 g of tension, and the preperation was allowed the equilibrate for 120 min. Isometric tension was continuously

measured with an isometric force transducer (FDT10-A, Commat Ltd., Ankara, Turkey), connected to a computer based data acquisition system (TDA 97, Commat Ltd., Ankara, Turkey).

After the equilibration time, cumulative consentration-response curves for ropivacaine and bupivacaine (0.2-8 microg/ml) were constructed on baseline resting tension. The tissue response was allowed to reach a stable plateau before each successive concentration of the agent was added. In a seperate set of experiments, tissues were precontracted with either 40 mM KCl (10^{-8}-10^{-5} M) or 5-hydroxytriptamine (5-HT, 10^{-6} M) and then, ropivacaine and bupivacaine were used by addition of increasing concentrations of agonist (0.2-8 microg/ml) to the baths in a cumulative manner and the isometric tension devoloped by the tissue recorded.

5-hydroxytriptamine, and the salts for the PSS were purchased from Sigma Chemical (St. Louis, MO). Marcaine 0.5% (Astra Zeneca, Turkey) and Naropin 10 mg/ml (Astra Zeneca, Turkey) were used as bupivacaine and ropivacaine, respectively. All drugs were prepared fresh daily during experiments, and were dissolved in distilled water before use.

2.1 Analysis of Results

Statistical analysis were performed using SPSS. All values were expressed as mean ± SD. For some of the relevant variables (heart rate, blood pressure) was performed analysis of variance test. Responses to ropivacaine and bupivacaine were expressed as percentages of the reversal of the tension developed in response to contracting agents. Changes in basal tension in response to anaesthetic agents were normalized to the maximal response induced by 80 mM KCl. Statistical analysis of the results were performed by ANOVA or Independent Samples Test. A *p* value lower than 0.05 was considered significant.

3. RESULTS

Forty-six parturients completed the protocol. Patient features are shown in Table 1. No adverse events were reported during the anesthesia period. The maternal systolic blood pressure and heart rate were not affected during operation. (Tables 2 and 3). No patients requiring rescue medication for hypotension and bradycardia.

3.1 Effects of Bupivacaine or Ropivacaine Incubation on Human Umblical Artery Vasoreactivity

Bupivacaine induced sustained increases in basal tension at concentrations ranged from 1 µg/ml to a maximum of 8 µg/ml, while ropivacaine had no significant affect on basal tonus until the 8 µg/ml concentrations (Fig. 1). When cumulative concentrations of bupivacaine were administered on human umblical artery rings precontracted with either KCl or 5-hydroxytriptamine, bupivacaine caused a significant relaxation response (Figs. 2 and 3). Conversely, ropivacaine did not induce relaxation of umblical vessels which have been previously induced to contract by an activator, such as KCl or 5-hydroxytriptamine (Figs. 2 and 3).

Table 1. Demographics and baseline characteristics of the study patients

Group	Age (year)	Bodyweight (kg)	Height (cm)
Bupivacaine	29.40 ± 3.78	79.13 ± 9.00	165.27 ± 6.04
Ropivacaine	26.83 ± 4.41	77.04 ± 7.69	165.17 ± 4.92
P-values	0.45	0.20	0.55

**Data are given as mean ± Std. deviation*

Table 2. Systolic blood pressure (SBP) differences between bupivacaine and ropivacaine groups

Variable	Bupivacaine	Ropivacaine	P-values
SBP - baseline	139.82 ± 1.58	139.75 ± 1.22	0.26
SBP - 1.min	130.23 ± 1.35	139.96 ± 1.26	0.48
SBP - 3.min	119.23 ± 1.56	118.62 ± 1.15	0.12
SBP - 5.min	111.32 ± 8.48	114.54 ± 9.69	0.31
SBP - 10.min	121.09 ± 9.50	116.96 ± 1.05	0.41
SBP - delivery	127.00 ± 6.22	123.33 ± 8.15	0.15
SBP - end of surgery	112.77 ± 7.45	109.70 ± 8.38	0.55

Data are given as mean ± SD

Table 3. Heart rate (HR) differences between bupivacaine and ropivacaine groups

Variable	Bupivacaine	Ropivacaine	P-values
HR - baseline	80.68 ± 5.22	82.54 ± 6.80	0.14
HR - 1.min	92.50 ± 8.45	94.62 ± 6.78	0.30
HR - 3.min	78.09 ± 5.12	70.91 ± 8.27	0.80
HR - 5.min	59.68 ± 5.82	62.08 ± 6.53	0.70
HR - 10.min	59.77 ± 3.90	61.70 ± 4.88	0.57
HR - delivery	71.40 ± 4.64	72.91 ± 6.49	0.49
HR - end of surgery	62.63 ± 3.10	63.25 ± 5.08	0.17

Data are given as mean ± SD

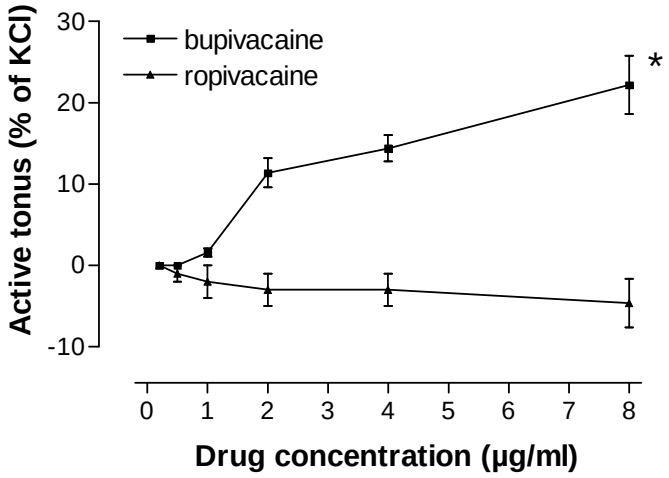

Fig. 1. Effect of bupivacaine or ropivacaine incubation on human umblical artery basal tonus

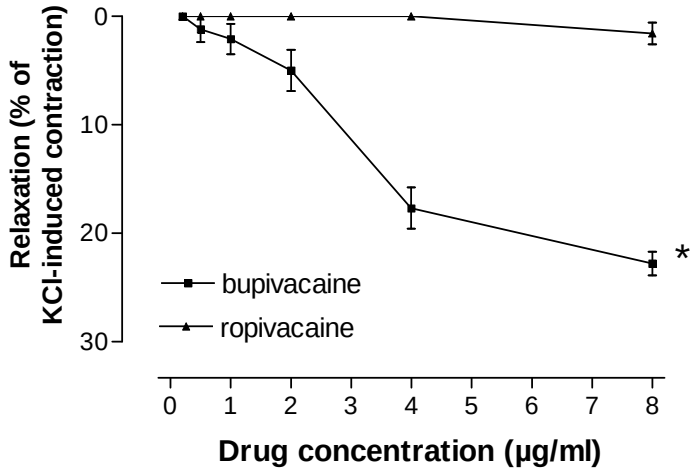

Fig. 2. Effect of bupivacaine or ropivacaine incubation on 40 mM KCL-induced contraction of human umblical artery

4. DISCUSSION

Local anesthetics are widely used for analgesia in labour and anesthesia in caserean section [9]. The safety of administration of local anesthetic (lidocaine, prilocaine, bupivacaine) has been investigated previously [10,11]). However, in vitro effects of local anesthetic drugs on

uteroplacental and fetal circulations are not well documented, and little information about direct effects of ropivacaine and bupivacaine on human umblical arteries was found. Thus, the primary aim of the current study was to examine the effect of ropivacaine and bupivacaine on human umblical artery reactivity.

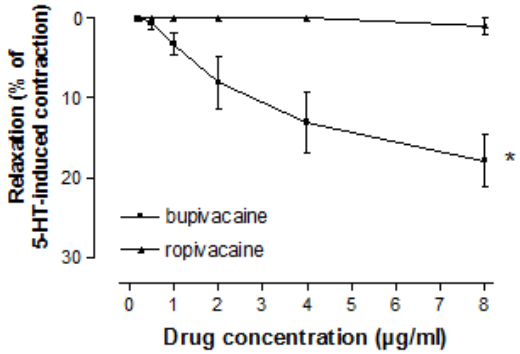

Fig. 3. Effect of bupivacaine or ropivacaine incubation on 5-hydroxytriptamine (10-6M) induced contraction of human umblical artery

Different choices of anesthetic and analgesic techniques or drugs may alter the vasoreactivity of different arteries. Bupivacaine is the most commonly used local anesthetic in obstetric analgesic practice [9,12,13]. Scull et al. demonstrated that, epidural analgesia with %0.25 bupivacaine in early labor blocks the stres response but uterine contractions remain unchanged [14]. Also, Nielsen et al found no significant differences in the number of the contractions before and after epidural analgesia using 0.025% bupivacaine in spontaneous active labour. The clinical studies suggested that bupivacaine had no effect on uterus contractility [15]. Noren et al. have been reported that bupivacaine caused contractions in the human uterine arteries, which were blocked by calcium channel antagonists and by increasing intracellular calcium concentrations [16]. Many studies demonstrated that bupivacaine decreased contractile activity in the muscles [16-21]. In these studies, some local anesthetic agents have been shown to cause relaxation of isolated arterial smotth muscle [17,18]. The effects of bupivacaine on myocardial contraction were examined in isolated dog papillary muscle. The authors reported that bupivacaine produced dose-dependent depression of contraction [19]. The effect of bupivacaine on bladder smooth muscle has also been studied. These results show that bupivacaine have inhibitory effects on contraction of bladder smooth muscle [20]. Wali et al suggested that local anesthetic drugs may have an anti-spasmatic effect on tracheal smooth muscle and inhibited the contractions [21].

Ropivacaine is a long-acting amide local anesthetic that is structurally closely related to bupivacaine. The two drugs are similar not only structurally, but also in their clinical effects. However, ropivacaine has less central nervous system and cardiovascular toxicity than bupivacaine [22,23]. Lefrant et al. examined the cardiac electr-physiologic effect of ropivacaine and bupivacaine. They found that 6 mg/kg ropivacaine dose induced similar hemodynamic alterations as 4mg/kg bupivacaine [22]. The hemodynamic effects of ropivacaine are well documanted. However, no studies on the effects of ropivacaine on uterine contractility have been reported.

It has been demonstrated that ropivacaine and bupivacaine cause different effects in the peripheral vasculature at the injection site. After intradermal injection, 0.75% bupivacaine causes an increase in cutaneous blood flow, whereas the same concentration of ropivacaine decreases it, compared with the effect of saline [24]. In a similar study, the epidural injection of 0.5% bupivacaine caused an increase in epidural blood flow, in contrast to the effect of 0.5% ropivacaine [25].

In the line with these explanations, it has been suggested that local anesthetic drugs may affect human umblical artery reactivity and umblical-placental circulation . The results of the present study clearly show that bupivacaine, but not ropivacaine may have an important effect on umblical artery vasoreactivity. Our results are in accordance with another study in animals which has suggested that ropivacaine is slightly less potent than bupivacaine [26]. These differences between two anesthetics cannot entirely be explained by the differences in drug concentrations, because, ropivacaine and bupivacaine were used in the same concentrations and doses in the current study. The mechanism for the differences in the response of the human umblical artery to two anaesthetics may also not explain the differing liposolubility and chemical characteristics, because the chemical properties of ropivacaine are similar to those of bupivacaine, although lipid solubility of ropivacaine is lower [27]. Bariskaner et al demonstrated that bupivacaine produced relaxation and ropivacaine produced contractions in human umblical artery [28]. The local

anesthetics produced contractions in some isolated artery and vein studies. Local anesthetics reversibiliy inhibit the depolarisation of excitable cells in smooth and skeletal muscles.Many studies have shown that these effects are related to the local anesthetic-induced reduction of Na Exchange in cell membranes [28,29,30]. In order to clarify the different responses to bupivacaine or ropivacaine, detailed functional studies are needed.

5. CONCLUSION

In summary, our results suggest that bupivacaine but not ropivacaine may have clinically significant adverse effects based on its ability to affect umblical vessel tonus, in concentrations which are considered to be nearly similar to maternal plasma concentrations measured following administration of local anaesthetics for Caesarean section. In the line with our results, ropivacaine administration may prove to be useful in obstetric practice for cesarean section in healthy parturient women.

CONSENT

All authors declare that 'written informed consent was obtained from the patient (or other approved parties) for publication of this paper and accompanying images.

ETHICAL APPROVAL

All authors hereby declare that all experiments have been examined and approved by the appropriate ethics committee and have therefore been performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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Peer-review history:
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