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Which local anesthetic is safe for pregnant patients: Comparison in pregnant rats

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Abstract

Regional anesthesia and postoperative analgesia procedures have been widely used in obstetric interventions in recent years. These procedures have higher side effects of local anesthetic toxicity. Systemic effects of local anesthetic drugs develop, by absorption of the drug from the injected site in a dose-dependent manner or given directly to the systemic circulation. Levobupivacaine is a local anesthetic, which is an S (-) isomer of bupivacaine. Its pharmacodynamic properties are like bupivacaine, but it is less cardiotoxic. We aimed to compare the hemodynamic measurements of rats to observe cardiotoxic effects. Cardiotoxic effects of intravenous bupivacaine and levobupivacaine infusions were studied on pregnant rats. We continued to infuse local anesthetics until the rats developed cardiac arrest. Total amount of local anesthetic infused was, 3.23±1.01 mg in the bupivacaine group and 4.17±0.75 mg in the levobupivacaine group. We observed that higher amounts of levobupivacaine were infused until cardiac arrest developed in the levobupivacaine group ($p<0.05$ p:0.001). Our findings demonstrate that pregnancy alters local anesthetic effects on cardiac function. We conclude that pregnancy increases the direct cardiotoxicity of bupivacaine, and levobupivacaine.

Keywords: Local anesthetics, cardiotoxicity, pregnancy

Introduction

Acute-chronic pain and analgesia procedures have been widely used in obstetric patients in recent years. These procedures have higher side effects due to local anesthetic toxicity in obstetric patients. Systemic effects of local anesthetic drugs develop, by absorption of the drug from injected site in dose dependent manner or given directly to the systemic circulation.

In parallel with the advances in medicine, we see more often, pregnant patients with cardiovascular diseases. Also, regional anesthesia and analgesia techniques are applied more often nowadays. As a result, side effects and systemic toxicity of local anesthetics are seen more often.

Local anesthetic drugs used for regional anesthesia and analgesia techniques, are widely used either during surgical procedures or for pain management after the surgery. Systemic toxicity caused by accidental intravenous injection or overdose of local anesthetic use, is a rare complication. But, unfortunately it is a potentially mortal complication. It is seen less then in 1/1000 patients [1-6].

Local anesthetic drugs, decrease fast Na influx inside nerve cell membrane by inhibiting Na+ channels at excitable cell membranes. They also inhibit channels located at other excitable membranes, other then channels located at nerve cell membranes; and this phenomenon is responsible for their cardiotoxic effects [7-9].

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Bupivacine is a long acting local anesthetic drug. Bupivacaine inhibits both voltage dependent K+ (Kv) channels and L-type Ca+2 channels. When accidentally higher doses given to vascular system fast, atrioventricular conduction slows first. Bupivacaine shows its cardiotoxic effect primarily by slowing atrioventricular conduction and then by myocardial depression [7-10].

Levobupivacaine is a local anesthetic, which is S (-) isomer of bupivacaine. Its farmacodynamic properties are like bupivacine, but it is less cardiotoxic [7,8,11].

In this experimental study, we aimed to compare hemodynamic measurements of rats in order to observe cardiotoxic effects of intravenously applied bupivacaine and levobupivacaine.

Material and Methods

After the approval of the Experimental Animal Practice and Research Unit, 18-21-days-old age and weighing 200-300 grams, 32 pregnant Wistar rats were given for the study, were divided into control (n=5), bupivacaine (n=13) and levobupivacaine (n=14) groups. All rats were anesthetized intraperitoneally with 1g.kg-1 Ethyl carbomate (Ürethan, Sigma). Rats were fixed from their extremities in a supine position. Left carotid artery and right jugular veins were catheterized. The rats' blood pressure values and heart rates were monitored via the catheter at the carotid artery. Electrocardiography (ECG) recording was done with electrodes placed on the extremities. Systolic, diastolic and mean arterial pressures, heart rates and ECG recordings of D1-D2 derivations were recorded every 2 minutes. After initial measurements, intravenous (iv) local anesthetic infusions started. In bupivacaine group, bupivacaine HCL (Marcaine, 0.5%, Astra Zeneca) was given at 2 mg.kg.min-1 infusion rate. In levobupivacaine group, levobupivacaine (Chirocaine, 0.5%, Abbott) was also given at 2 mg.kg.min-1 infusion rate. Infusions were continued until the rats developed cardiac arrest (until asystole recorded on ECG) and total time until asystole developed and total local anesthetic amounts given during this time were recorded. PR distance and QRS width measurements were recorded from ECG recordings.

Heart rates (beat/min), mean arterial pressures (mmHg), lengths of PR distance and QRS widths (milliseconds), rats weights (gram), total local anesthetic given until asystole developed and the time until asystole developed were statistically analyzed.

Results

5 rats were only catheterized and monitored as control group. Data collected and examined from 13 rats in bupivacaine group, 14 rats in levobupivacaine group. Weights of the pregnant rats were similar between groups (p>0.05)(Table 1).

Initial heart rates, systolic, diastolic and mean arterial blood pressures, lengths of PR distance and QRS width measurements were similar. There weren't any statistical difference between groups (p>0.05). However, after the local anesthetic infusions started, hemodynamic measurements collected at 2nd, 4th, 6th, 8th and 10th minutes were statistically lower then the initial values (p<0.05). There was also, statistically difference between control group and the other groups (p<0.05).

Table 1. The data of study groups

Group	Weight (Gram)*	Total local anesthetic dose (mg)**	Total arrest time (Minute)***
Bupivacaine (n:13)	268.46±30.23	3.23±1.01	5.85±0.42
Levobupivacaine (n:14)	259.28±20.55	4.17±0.75	8.14±0.46
Control (n:5)	244.00±18.16	0	0

*P > 0.05 p:0.113
** P < 0.05 p:0.01
*** P < 0.05 p:0.0001

Heart rates were significantly lower in both bupivacaine and levobupivacaine groups when compared with the initial values (p<0.05). Heart rates slowed similarly, in both bupivacaine and levobupivacine groups (p>0.05)(Figure1).

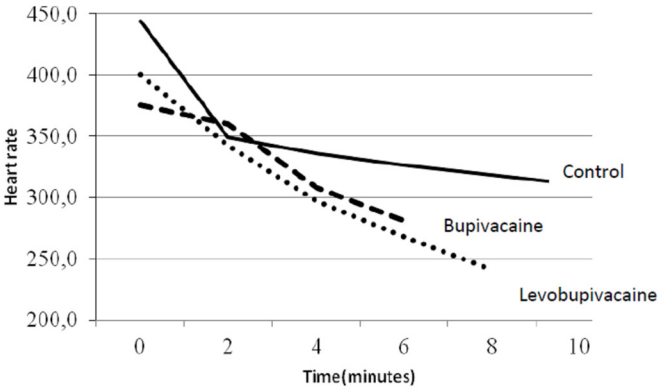

Figure 1. Heart rate values of the groups

Systolic blood pressure values were found to be lower then initial values in both bupivacaine and levobupicaine groups. These differences in systolic blood pressure values were statistically significant (p<0.05). But, systolic blood pressure values in bupivacaine group were significantly lower then the systolic blood pressure values recorded in levobupivacaine group (p<0.05) (Figure 2).

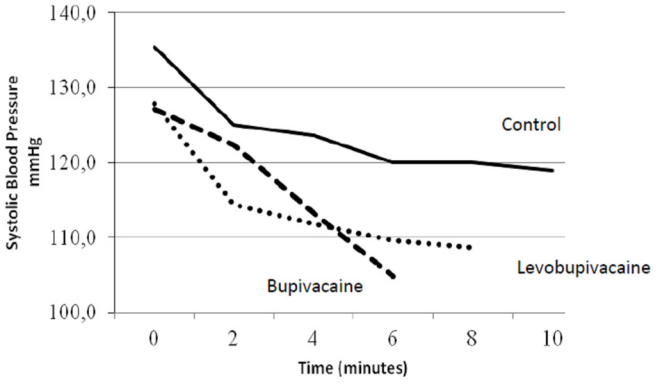

Figure 2. Systolic blood pressure values of the groups

The changes observed in diastolic and mean arterial blood pressure measurements were similar with the systolic arterial

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blood pressure measurements. The measurements were significantly lower in bupivacaine group, then levobupivacaine group ($p<0.05$) (Figure 3).

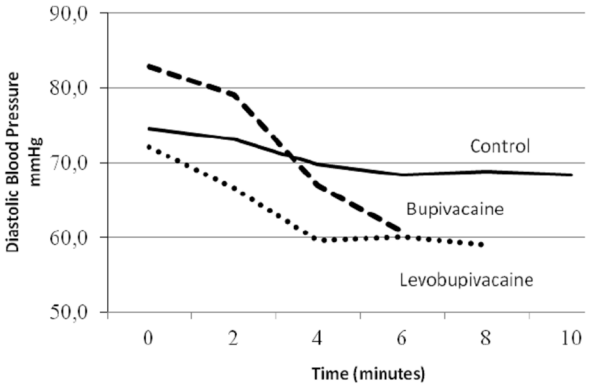

Figure 3. Diastolic blood pressure changes of groups

We observed that, the length of PR distance started to elongate at the second minute of infusion. PR distance elongation continued to increase until cardiac arrest developed in bupivacaine group and it was found statistically significant ($p<0.05$). The PR elongation was moderate in levobupivacaine group. The prolongation was significant starting from sixth minute. The measurements obtained from bupivacaine and levobupivacaine groups were significantly different ($p<0.05$)(Figure 4).

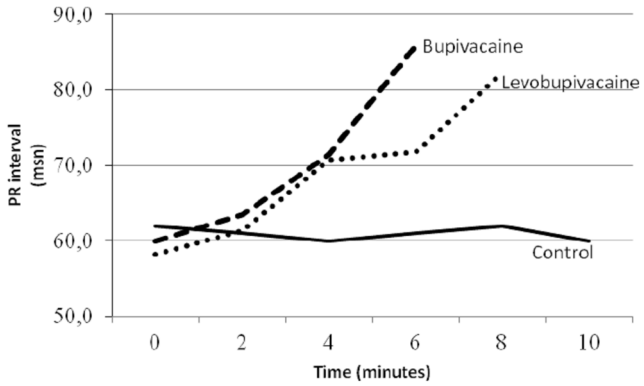

Figure 4. PR interval changes of groups

QRS widening, at D1 and D2 derivations, increased with time in both bupivacaine and levobupivacaine groups (Figure 5). QRS widening continued to increase with time in bupivacaine group. In levobupivacaine group, we found out that, QRS widening slowed at fourth and sixth minutes and then continued to increase, until cardiac arrest developed. The changes at D2 derivation were similar. The QRS measurement changes between bupivacaine and levobupivacaine groups were statistically significant ($p<0.05$) (Figure 5).

We also compared, total amount of local anesthetic doses given to the pregnant rats, until cardiac arrest developed. Total amount of doses were 3.23±1.01 mg in bupivacaine group and 4.17±0.75 mg in levobupivacaine group. Total amount of levobupivacaine dose was significantly higher then the bupivacaine dose ($p<0.05$ $p=0.01$). Pregnant rats developed cardiac arrest with higher amounts of levobupicaine doses then bupivacaine doses.

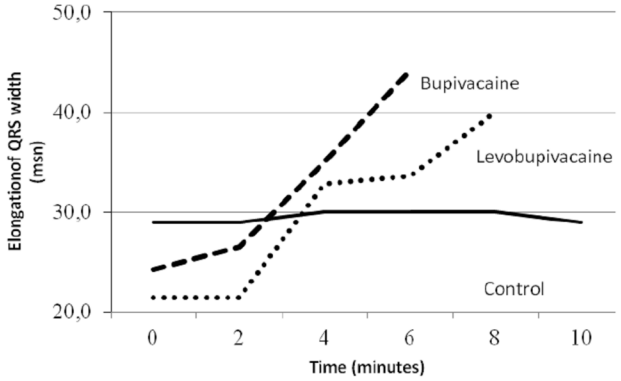

Figure 5. Elongation of QRS width

The mean elapsed time, until cardiac arrest developed, was compared between bupivacaine and levobupivacaine groups. The rats lived longer in levobupivacaine group and elapsed time until cardiac arrest developed was significantly longer. The elapsed time until cardiac arrest developed was 5.85±0.42 minutes in bupivacaine group and 8.14±0.46 minutes in levobupivacaine group. There was a significant difference between groups ($p<0.05$, $p=0.0001$) (Figure 6, Table 1).

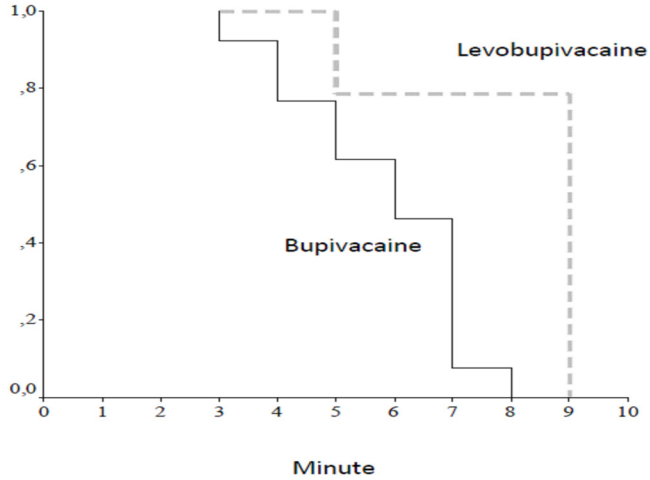

Figure 6. Comparison of Survival times of Bupivacaine and Levobupivacaine groups. Mean survival time±SE (Bupivacaine)= 5.85±0.42. Mean survival time± SE (Levobupivacaine)= 8.14±0.46. Log rank test = 14.90 (p=0.0001)

Discussion

Local anesthetic drugs cause bradycardia, elongation of length of PR distance, varying degrees of AV block, QT widening and varying degrees of ventricular arrhythmia by inhibiting transmission at sinoatrial and atrioventricular node. Local anesthetic drugs disrupt transmission function first, and then, they cause arterial hypotension by myocardial depression and smooth muscle dilatation at veins causing vasodilatation [7-9,11,12].

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Local anesthetic drugs, decrease fast Na+ influx into the cells by inhibiting opening of Na+ channels at excitable cell membranes at heart, brain and peripheral nerve tissues, in a dose dependent manner. The affinity of local anesthetics, to the Na+ channels are typically higher, when channels are open or in inactive state. Local anesthetic drugs, also extend cardiac action potential time by inhibiting voltage dependent K+ channels at myocardium. This phenomenon, contributes to the cardiotoxicity of local anesthetic drugs by increasing blockage of inactive form of Na+ channels. In addition, local anesthetic drugs cause cardiac depression by inactivation of L-type Ca+2 channels and inhibition of release of Ca+2 into the cell from the sarcoplasmic reticulum [13-18].

Systemic effects of local anesthetic drugs develop, by absorption of the drug from injected site in dose dependent manner or given directly to the systemic circulation. This means cardiotoxic effects are seen, when local anesthetic drugs are given high doses fast or given directly to the intravascular system. Systemic effects of local anesthetic drugs are on cardiovascular (CVS) and central nerve (CNS) systems. CVS is more resistant then CNS to the toxic effects. This means, CNS symptoms like seizures are seen before CVS symptoms. Long acting and highly lipid soluble local anesthetic drugs have higher risk of toxicity. The most carditoxic local anesthetic is bupivacaine [7-9,11,12].

Accidental intravascular injection of bupivacaine results cardiovascular collapse with ventricular tachycardia, fibrillation, arrhythmia, asystole and complete AV block. The cardiotoxic effect of bupivacaine is a result of inhibition of fast Na+ channels. Bupivacaine, while showing high affinity to inactive Na+ channels, also inhibits slow Ca+2 and K+ channels. Cardiotoxicty of bupivacaine is more serious, at the state of acidosis, hypoxia and hypercarbia [1,2,7-11,19].

In similar studies levobupivacaine was found to be less cardiotoxic then bupivacaine. Vanhoutte et al. showed that bupivacaine slows cardiac transmission more then levobupivacaine and causes deeper Na+ inhibition then levobupivacaine in a study, which they conducted on papillary muscle [20]. In experimental studies, which were conducted on heart tissue, it was shown that, levobupivacaine causes less arrhythmia and QRS widening. In these studies, they reported that levobupivacaine, causes less delay on AV transmission and QRS widening [1,2,7-11,19,20].

We observed QRS widening in both bupivacaine and levobupivacaine groups. As the bupivacaine infusion started, QRS began to widen and QRS widening continued to increase in dose dependent manner. In levobupivacine group, QRS also began to widen as the infusion had started but, we observed that QRS widening slowed at fourth and sixth minutes and then continued to increase until cardiac arrest developed.

In some case reports, during peripheral nerve block, levobupivacaine was given intravenously (iv) accidentally and seizure activity was reported. But not any cardiac pathology was reported. In a study which was conducted on volunteers, levobupivacaine infusion was given either at 10 mg.kg-1 rate or total 150 mg dose until CNS symptoms developed. No serious cardiac pathology was observed but only mild raise in blood pressure and heart rate. In another case report, after 125 mg iv levobupivacaine was given to a patient accidentally, arterial hypotension, bradycardia, ST-T changes and supraventricular arrhythmia had developed [21-25].

We observed that, bupivacaine caused fast and significant drops in systolic, diastolic and mean arterial blood pressures. These blood pressure drops were significantly higher then the blood pressure drops caused by levobupivacaine.

In another experimental study conducted on animals, it was reported that, when bupivacaine was given 2 mg.kg-1 iv, it caused serious bradycardia and arterial hypotension and the subjects didn't respond to the cardiorespiratory resuscitation (CPR) and all of the 12 animal subjects had died. At the same study, levobivacaine given rats, developed medium level of bradycardia and 10 of the rats survived with CPR [26].

Bupivacaine can cause ventricular tachycardia (VT), ventricular fibrillation (VF), asystolia and electromechanical dissociation at 4 µgr.ml-1 plasma levels. In animal studies, it was reported that, lethal dose of levobupivacaine was 1.3-1.6 times more then lethal dose of bupivacaine [7,8,14,15].

We continued local anesthetic drug infusions, until rats developed cardiac arrest. Total amount of given bupivacaine dose was 3.23±1.01 mg and total amount levobupivacaine dose was 4.17±0.75 mg. We observed that higher total amount of local anesthetic doses were given in levobupivacaine group until cardiac arrest developed ($p<0,05$ $p=0.001$).

Levobupivacaine is especially chosen for the patients with cardiac disease, because it has less cardiotoxic and neurotoxic side effects, despite of similar anesthetic efficiency [27].

In a study, they performed inguinal hernia operations under local anesthesia. They reported that, bupivacaine and levobupivacaine had similar clinical results with levobupivacaine having lower cardiac and neurological toxicicity, therefore it should be preferred [28]. As outpatient anesthesia practice becomes more common in the near future, levobupivacaine will be a more preferable local anesthetic, with less side effects and better clinical results [28].

In obstetric cases, bupivacaine is the most commonly used local anesthetic for epidural analgesia [29].

During caesarean section operations, after bupivacaine was given to the epidural space, it was shown with Doppler ultrasound (USG) that, vascular resistance of non-placental and placental veins increases. This phenomenon causes deterioration of umbilical blood flow, acid-base disorders and lower Apgar scores of the infants [30].

Pregnancy, also increases risk of seizure activity, caused by local anesthetic systemic toxicity (LAST). Bupivacaine has the highest risk. Accidental iv bupivacaine injection, results with seizures

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and cardiac collapse [29]. In pregnant patients, LAST is more common when bupivacaine is given for epidural anesthesia, since high volumes and concentrations of local anesthetics are required for epidural anesthesia for caesarean section operations. LAST is less observed during epidural analgesia for labor in pregnant patients since lower volumes and concentrations of local anesthetics are sufficient [29].

It was reported that, bupivacaine used for epidural analgesia and anesthesia can cause cardiotoxicity and neurotoxicity and even can lead to death in pregnant patients. For this reason lower concentrations of local anesthetics must be used for pregnant patients. S isomer of bupivacaine is known to be less cardiotoxic [31].

Accidental IV injection of bupivacaine can cause cardiovascular collapse in humans. During caesarean section operation or analgesia management for labor, cardiotoxicity can develop in pregnant patients. If bupivacaine toxicity develops, cardiovascular collapse incidence is more often observed in pregnant patients. Pregnant patients are more sensitive to toxic effects of bupivacaine and also some physiologic changes are observed during pregnancy. Affinity of drugs to the proteins in plasma changes; and uncombined, free form of bupivacaine elevates in blood. As the effective form of bupivacaine elevates in plasma, toxicity risk increases. Authors compared bupivacaine and mepivacaine in a study, and they showed that free form of bupivacaine in plasma, is increased during pregnancy [31].

In pregnant and non-pregnant but treated with progesterone rats, negative inotropic effects of cocaine on papillary heart muscles were observed. Researchers stated that, pregnancy increases cardiotoxic effects of cocaine and progesterone might be responsible of this cardiotoxic effect [32].

It is known that, during pregnancy cocaine toxicity risk elevates and side effects are observed. Krutzman et al. reported that, cardiotoxic risk of cocaine increases when estrogen and progesterone are given and estrogen might play a role as mediator. They showed that, when estrogen or estrogen and progesterone were given, cardiotoxicity develops, but when progesterone is given alone, carditoxicity does not develop. According to these results, they stated that, cardiotoxicty of cocaine can be observed in pregnant patients or in patients who takes oral contraceptives [33].

When applying regional anesthesia or analgesia, iv injections can be observed by USG. Regional techniques must be applied to pregnant patients in a room, where close cardiovascular monitorization is applied and local anesthetic systemic toxicity (LAST) treatment is accessible when needed. Checklists, according to guidelines and algorithms must be prepared and all applications to the patient must be closely recorded during the procedure [34].

In another case report, for shoulder surgery, interscalen block was applied with 100 mg bupivacaine and 300 mg mepivacaine, to a 58 years old patient who had coronary artery disease. The patient first had seizures and then VT and asystole. VT did not respond to defibrillation or medication. Then, 100 ml 20% lipid solution was given. In 20 seconds, normal cardiac rhythm was provided and blood pressure returned normal levels. The patient recovered without any neurologic complication [35].

It is advised that, as soon as cardiotoxic symptoms of LAST is observed, lipid treatment should be started. Propofol is also prepared in 10% lipid emulsion. Lower doses of propofol might be useful for treating seizures caused by LAST, but its use is contraindicated if cardiotoxic symptoms of LAST exist [19,24,35,36].

As a result, we observed that, levobupivacaine is less toxic then bupivacaine.

In recent years in spite of additional systemic diseases, life expectancy is extended. As a result, pregnancy or other surgical interventions are raised for patients with cardiovascular disease. As regional anesthesia techniques become more common, complication risks of local anesthetics can cause an elevation of risks of morbidity and mortality in practice. As outpatient surgery interventions become more common, levobupivacaine will be more preferred because of its low side-effect risk and better clinical results profile, in the near future.

We observed that, bupivacaine caused fast and significant drops in systolic, diastolic and mean arterial blood pressures. These blood pressure drops were significantly higher then the blood pressure drops caused by levobupivacaine. As a result, we observed that, levobupivacaine is less toxic then bupivacaine.

Conflict of interests

The authors declare that there is no conflict of interest in the study.

Financial Disclosure

There is no financial support.

Ethical approval

The consent form is not issued . Rats are given to studies approved by the experimental animal ethics committee. Once approved by the board, the animal is allocated.

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