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Comparison of the effects of lidocaine, mepivacaine, and levobupivacaine on the isolated rat uterine smooth muscles

조선대학교 대학원

의 학 과

정 기 태

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백서 자궁평활근 절편에서 Lidocaine, Mepivacaine, Levobupivacaine의 효과 비교

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CONTENTS

Legends for Tables

Legends for Figures

Abstract

Comparison of the effects of lidocaine, mepivacaine, and levobupivacaine on the isolated rat uterine smooth muscles

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The purpose of this study is to evaluate the effects of lidocaine, mepivacaine, and levobupivacaine on the isolated rat uterine smooth muscles. Uterine smooth muscle tissues were obtained from non-pregnant female rats (n = 54). The uterine segments were dissected and cut into 2 × 10 × 8 mm strips. The muscle strips were mounted in tissue baths filled with Krebs solution saturated by 95% O_2 and 5% CO_2. After spontaneous uterine contractile activity had been accomplished, lidocaine (n = 18), mepivacaine (n = 18), and levobupivacaine (n = 18) in various concentrations (10^{-7} to 10^{-3} M) were added cumulatively to the baths and the active tension and frequency of contraction were continuously registered. EC_5, EC_{25}, EC_{50}, EC_{75} and EC_{95} of each drug on active tension were calculated using a probit model. Lidocaine inhibited uterine contraction in concentrations of 10^{-5} to 10^{-3} M. Mepivacaine increased uterine contraction in concentrations of 10^{-5} to 10^{-3} M. Levobupivacaine increased uterine contraction in concentrations of 10^{-5} to 10^{-4} M but, decreased uterine contraction in a concentration of 10^{-3} M. Lidocaine in concentrations of 10^{-7} to 10^{-5} M reduced the frequency of contraction but, lidocaine in concentrations of 10^{-4} to 10^{-3} M increased the frequency of contraction. Mepivacaine had no significant effects on the frequency of contraction. Levobupivacaine reduced the frequency of contraction in concentrations of 10^{-5} to 10^{-3} M. The EC_{50} of lidocaine, mepivacaine, and levobupivacaine on active tension was 4.82×10^{-4} M, 9.78×10^{-1} M, and 1.52×10^{-2} M, respectively. Lidocaine had the greatest relaxant effects on isolated rat uterine smooth muscle among these local anesthetics.

Key Words: lidocaine, levobupivacaine, mepivacaine, rat, uterine contractility

Introduction

In obstetric practice, local anesthetic agents are widely used for obstetric anesthesia and analgesia. Such local anesthetics can alter the spontaneous uterine contractility (1), and it may have negative impacts on the success of labor and delivery.

Lidocaine is the most frequently used local anesthetics. It has no adverse effects on mother, fetus, neonate or the progress of labor during epidural anesthesia in the normal parturient (2). It was known that lidocaine inhibits uterine activity (3).

Mepivacaine, a local anesthetic of amino-amide type, has similar physiochemical properties as lidocaine (4). It has no adverse effects on mother and the newborn when used for epidural anesthesia for cesarean section (5, 6). It was reported mepivacaine increases the uterine contractility (7).

Levobupivacaine, S(-)-enantiomer of racemic bupivacaine, is a new long-acting amide local anesthetic. It has equal local anaesthetic potency with reduced potential for cardiac and CNS toxicity (8, 9) and longer duration of action (9) compared to bupivacaine. It was reported that levobupivacaine has no difference in the onset, spread, and duration of analgesia in laboring women compared to bupivacaine (10). It was also reported that levobupivacaine caused a concentration dependent inhibition on contractility of myometrial strips from rats (11).

There have been many studies about the effects of local anesthetics on the uterine contraction. But, there has been a lot of controversy over the results. The purpose of this study was to evaluate and compare the effects of lidocaine, mepivacaine, and levobupivacaine on the isolated rat uterine smooth muscles.

Materials and Methods

Animal prepareation

The study was approved by the Medical College Animal Care and Use Committee. Sprague-Dawley rats weighing 200-250 g were killed by inhalation of carbon dioxide. The abdomen was opened immediately and the uterus was extracted. The myometrial tissue were rapidly cleaned of connective tissue and specimens were dissected into strip of myometrium (approximately 2 × 10 × 8 mm) in a petri dish filled with Krebs solution (118.3 mM NaCl. 4.7 mM KCl, 2.5 mM $CaCl_2$, 25 mM $NaHCO_3$, 1.2 mM KH_2PO_4, 1.2 mM $MgCl_2$, and 11.1 mM glucose).

Experimenta procedures

Dissected myometrial strips were mounted in 20 ml tissue baths containing Krebs solution. One end of the longest dimension of a muscle strip was connected to a hook that was fixed to the base of the bath. The other end of the strip was connected to another hook fixed to an extension of the lever arm of a force displacement transducer. The bath solution was maintained at 37℃ by circulating the heated water in the space between the double walls, and continuously aerated with a gas mixture of 95% oxygen and 5% carbon dioxide. The myometrial strips were allowed to equilibrate at 2.0 g tension for 90 minutes with flushing fresh solution every 15 minutes. After muscle preparations developed spontaneous regular contractions, strips were exposed to various concentrations of lidocaine (n = 18), mepivacaine (n = 18), and levobupivacaine (n = 18). At that time, cumulative concentrations of each drug were added to the baths with a micropipette every 15 minutes by increasing to 10^{-7}, 10^{-6}, 10^{-5}, 10^{-4}, and 10^{-3} M. The change of the contraction pattern was examined.

The isometric tension of the myometrial strips was measured using a force displacement transducer (FTO3® ; Grass Instruments co., MASS, USA) and the recordings of traces were made on a computer (PowerLab® data recording system; AD Instruments Pty Ltd., Castle Hill, Australia). Active tension and frequency of contraction was used to express the quantitative changes in muscle contraction. We defined the active tension as the tension between peak tension and resting tension and the frequency of contraction as the number of contraction during 15 minutes for the application of each concentration of an agent. The active tension and frequency of contraction measured before application of each drug were used as controls. The effects of each local anesthetics were compared with the control.

EC_5, EC_{25}, EC_{50}, EC_{75}, and EC_{95} on active tension were calculated using a probit model.

Statistical analysis

All results are expressed as mean ± standard deviation. The differences within group and between groups were analyzed by repeated measures ANOVA and one-way ANOVA with post hoc test with Turkey's HSD test. P values less than 0.05 was considered to be statistically significant.

Results

Lidocaine decreased active tension in a dose-dependent manner in higher concentrations (10^{-5} to 10^{-3} M) ($P < 0.05$) (Table 1) (Fig. 1). Mepivacaine increased active tension in a dose-dependent pattern in higher concentrations (10^{-5} to 10^{-3} M) ($P < 0.05$) (Table 1) (Fig. 2). Levobupivacaine increased active tension in concentrations of 10^{-5} to 10^{-4} M but decreased active tension at a concentration of 10^{-3} M ($P < 0.05$) (Table 1) (Fig. 3).

Table 1. Effects of Lidocaine, Mepivacaine, and Levobupivacaine on Active Tension in the Uterine Smooth Muscles

Drug	Concentration (M)					
	control	10^{-7}	10^{-6}	10^{-5}	10^{-4}	10^{-3}
Lidocaine (%) (n=18)	100	99.65 ± 25	98.75 ± 25	94.90 ± 24*	81.46 ± 26*	70.44 ± 25*
Mepivacaine (%) (n=18)	100	99.84 ± 52	105.55 ± 52	116.08 ± 55*†	123.33 ± 55*†	130.96 ± 55*†
Levobupivacaine (%) (n=18)	100	100.36 ± 33‡	104.47 ± 33‡	112.19 ± 31*‡	115.28 ± 34*‡	81.03 ± 38*‡

Data are expressed as mean ± SD. "n" indicates the number of experiments.
* : compared with control, † : compared with lidocaine, ‡ : compared with mepivacaine

Lidocaine in concentrations of 10^{-7} to 10^{-5} M reduced the frequency of contraction but lidocaine in concentrations of 10^{-4} to 10^{-3} M increased the frequency of contraction ($P < 0.05$) (Table 2) (Fig. 4). Mepivacaine had no significant effect on the frequency of contraction (Table 1) (Fig. 5). Levobupivacaine reduced the frequency of contraction in a dose-dependent pattern in higher concentrations (10^{-5} to 10^{-3} M) ($P < 0.05$) (Table 2) (Fig. 6).

Table 2. Effects of Lidocaine, Mepivacaine, and Levobupivacaine on Frequency of Contraction in the Uterine Smooth Muscles

Drug	Concentration (M)					
	control	10^{-7}	10^{-6}	10^{-5}	10^{-4}	10^{-3}
Lidocaine (%) (n=18)	100	89.33 ± 41*	85.33 ± 43*	81.33 ± 43*	110.67 ± 29*	120.67 ± 27*
Mepivacaine (%) (n=18)	100	100 ± 25	98.81 ± 21	97.02 ± 27†	96.43 ± 21	98.21 ± 20
Levobupivacaine (%) (n=18)	100	99.46 ± 30†	92.43 ± 31†	81.08 ± 28*	78.38 ± 34*	76.76 ± 41*

Data are expressed as mean ± SD. "n" indicates the number of experiments.
* : compared with control, † : compared with lidocaine

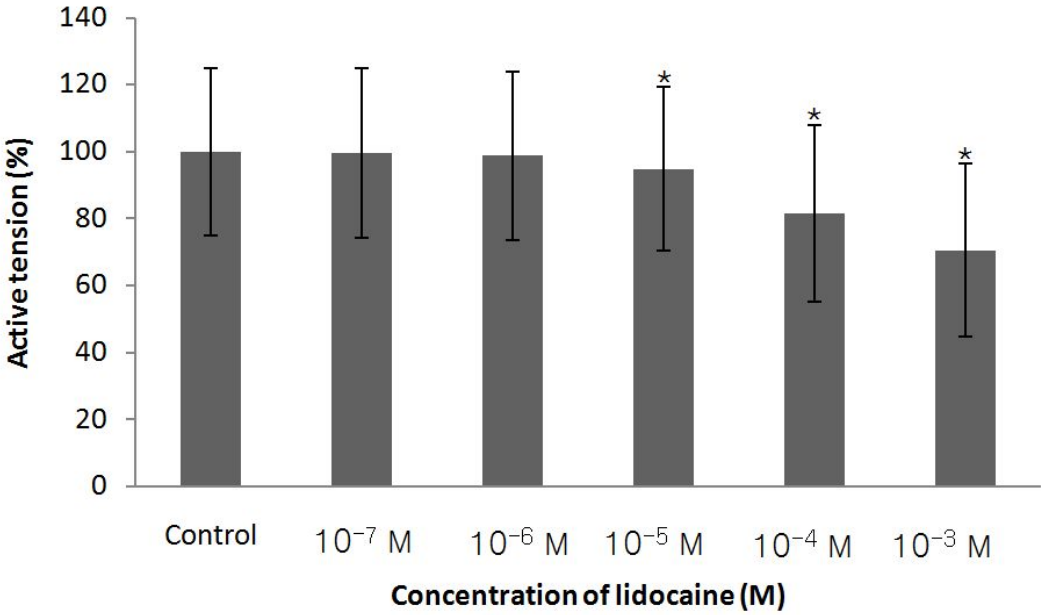

Fig. 1. Effects of lidocaine on active tension of rat uterine myometrium.
* : P < 0.05 compared with control. Lidocaine inhibited uterine contraction in a dose-dependent pattern in higher concentrations (10^{-5} to 10^{-3} M).

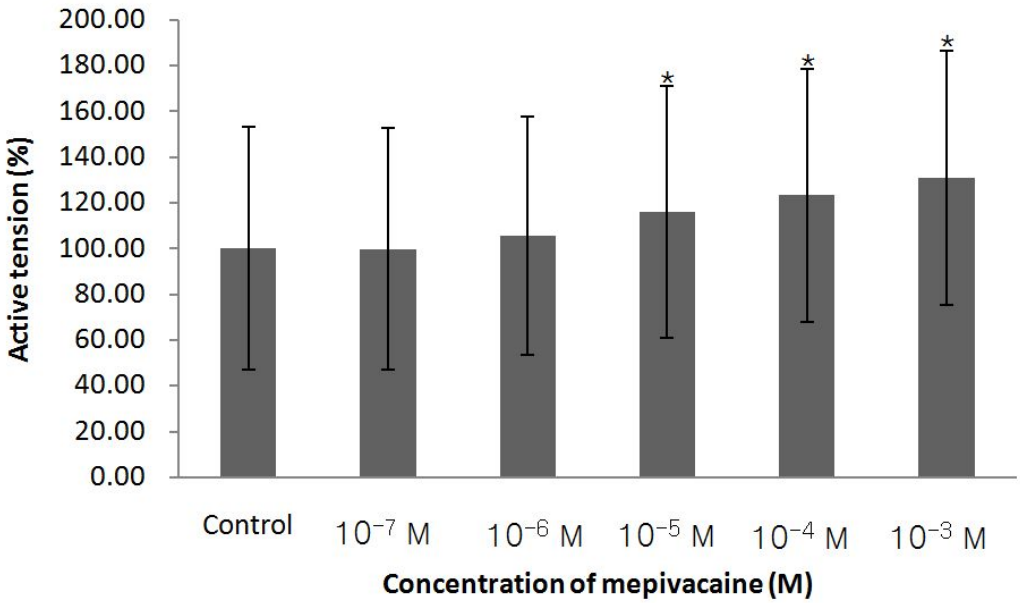

Fig. 2. Effects of mepivacaine on active tension of rat uterine myometrium.
* : P < 0.05 compared with control. Mepivacaine increased active tension in a dose-dependent pattern in higher concentrations (10^{-5} to 10^{-3} M).

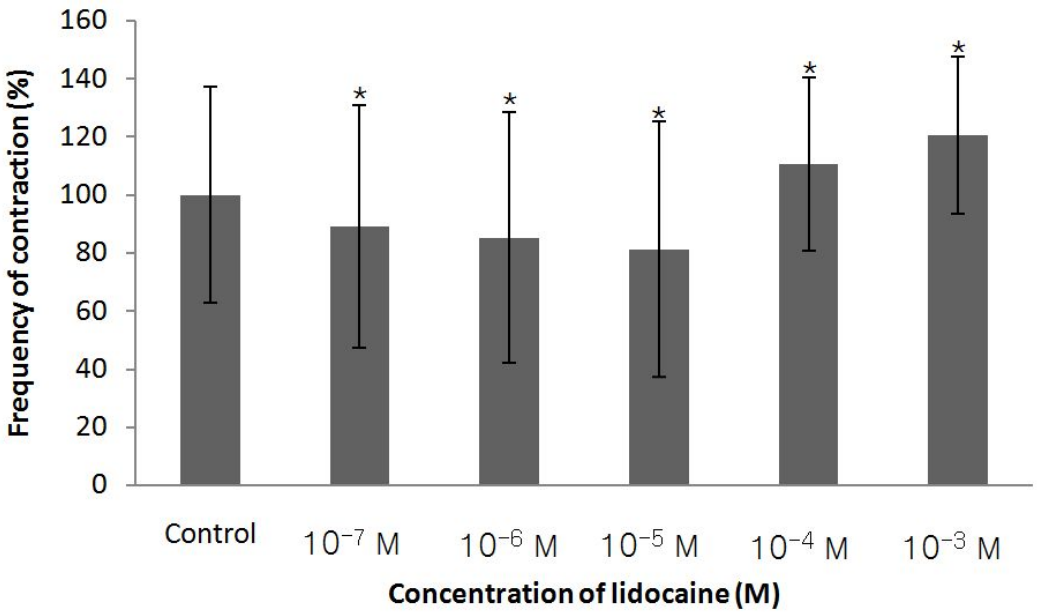

Fig. 3. Effects of levobupivacaine on active tension of rat uterine myometrium.
* : P < 0.05 compared with control. Levobupivacaine increased active tension in concentrations of 10^{-5} to 10^{-4} M but decreased active tension in a concentration of 10^{-3} M.

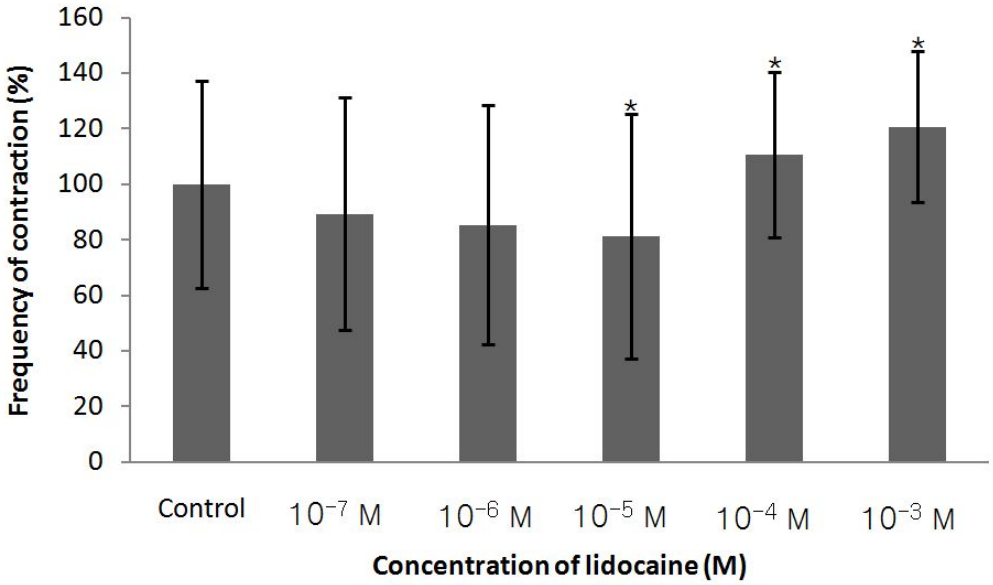

Fig. 4. Effects of lidocaine on frequency of contraction of rat uterine myometrium. * : $P < 0.05$ compared with control. Lidocaine in doses of 10^{-7} to 10^{-5} M reduced the frequency of contraction but, lidocaine in doses of 10^{-4} to 10^{-3} M increased the frequency of contraction.

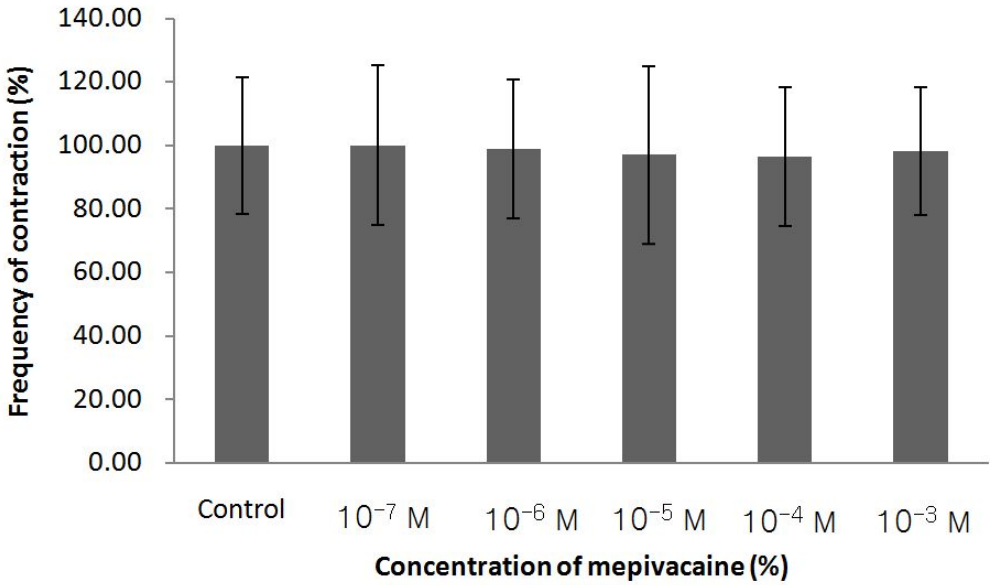

Fig. 5. Effects of mepivacaine on frequency of contraction of rat uterine

myometrium. Mepivacaine had no significant effect on the frequency of contraction.

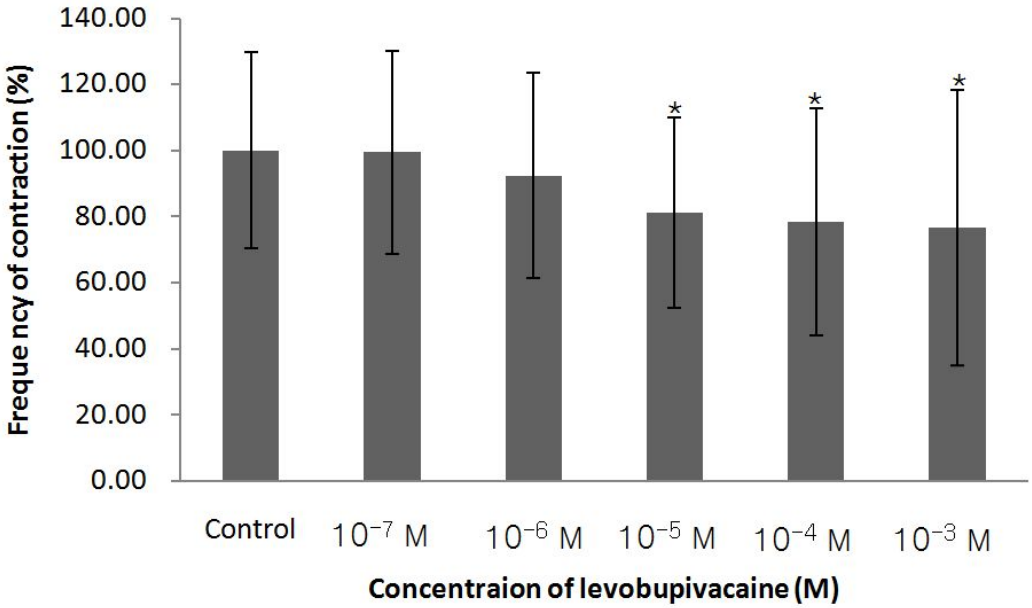

Fig. 6. Effects of levobupivacaine on frequency of contraction of rat uterine myometrium. * : $P < 0.05$ compared with control. Levobupivacaine reduced the frequency of contraction in a dose-dependent pattern in high concentrations (10^{-5} to 10^{-3} M).

The EC_{50}'s of lidocaine, mepivacaine, and levobupivacaine on active tension in the uterine smooth muscle was 4.82 x 10^{-4} M, 9.78 x 10^{-1} M, and 1.52 x 10^{-2} M respectively (Table 3).

Table 3. Effective Concentrations (M) of Lidocaine, Mepivacaine, and Levobupivacaine on Active Tension in the Uterine Smooth Muscle

Drug	Concentration (M)				
	EC_5	EC_{25}	EC_{50}	EC_{75}	EC_{95}
Lidocaine	3.26(2.97) x 10^{-6}	5.42(3.02) x 10^{-5}	4.82(2.87) x 10^{-4}	5.15(4.43) x 10^{-3}	1.89(2.15) x 10^{-1}
Mepivacaine	9.86(0.76) x 10^{-1}	9.80(1.15) x 10^{-1}	9.78(1.39) x 10^{-1}	9.77(1.6) x 10^{-1}	9.76(1.87) x 10^{-1}
Levobupivacaine	1.33(2.97) x 10^{-5}	7.75(3.02) x 10^{-4}	1.52(0.93) x 10^{-2}	3.51(3.31) x 10^{-1}	4.38(5.81) x 10

Data are expressed as mean(SD). EC : effective concentration.

The order of relaxant potency was lidocaine > levobupivacaine > mepivacaine. In addition , lidocaine had the greatest relxant effects and mepivacaine had the least relaxant effects amont these local anesthetics (Fig. 7).

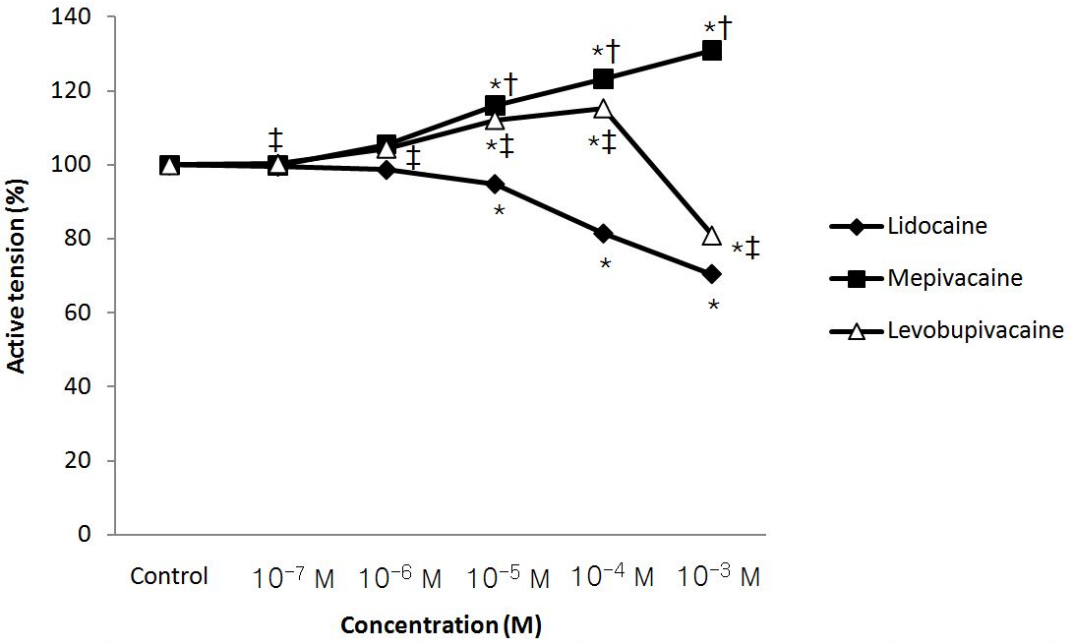

Fig. 7. Comparison of the effects of lidocaine, mepivacaine, and levobupivacaine on active tension. * : $P < 0.05$ compared with control, † : compared with lidocaine, ‡ : compared with mepivacaine. Lidocaine had relaxant effects on uterine smooth muscle. Mepivacaine increased active tension in a dose-dependent pattern (10^{-5} to 10^{-3} M). Levobupivacaine increased active tension in concentrations of 10^{-5} to 10^{-4} M but, decreased active tension in a concentration of 10^{-3} M.

Discussion

Regional anesthesia has come into widespread use for obstetric anesthesia and analgesia because it provides outstanding analgesia during labor, delivery, and operation. Obstetric anesthesia should give adequate analgesia and be free from risks to mother and fetus. Regional anesthesia with local anesthetics reduces pain effectively during and after labor, and has lessen the risks of serious complications than general anesthesia such as failed intubation or pulmonary aspiration of gastric contents. Many local anesthetics are used for regional anesthesia during pregnancy. In this study, we investigated the effects of lidocaine, mepivacaine, and levobupivacaine on the isolated rat uterine smooth muscles.

Lidocaine is still popular for regional anesthesia in obstetrics because of its rapid onset and intermediate duration. It was known that lidocaine may cause a significant reduction in uterine smooth muscle tone, but only at concentrations much higher than those that are commonly used in clinical practice (12). This is agreed with my results. In this study, as the concentration of lidocaine was increased during spontaneous uterine contraction, active tension was reduced in a concentration-dependent manner at higher concentrations (10^{-5} to 10^{-3} M) and the frequency of contractions showed variable responses. When 5 ml of 2% lidocaine administered for the epidural anesthesia in pregnant women, the maximum maternal venous concentration of lidocaine was 6.4 μg/ml (13), which is 2.3 x 10^{-5} M. This plasma concentration is comparable to 8.4 x 10^{-6} M in vitro, because 63.6% of lidocaine given intravenously is bound to plasma protein (13). In this study, there was no significant effect on the uterine contraction at this concentration. Therefore, lidocaine in concentration that is commonly used clinically would not decrease uterine contraction. It was known that the neonatal free plasma concentration of lidocaine was 1.23 ± 0.26 μg/ml. Fetal/maternal concentration ratio of lidocaine was 0.67 (2). In this concentration, lidocaine caused no significant change in the fetal heart rate and Apgar socre (2), and would not decrease uterine contraction. Although it is true, we should pay attention to the dosage, when using of lidocaine in pregnant women. It was also known that minimal local analgesic concentration of epidural lidocaine is 0.37% in the first stage of labor (15). It was reported that the relaxant effects of lidocaine are mediated via blocking the fast sodium channels. It was known that lidocaine selectively blocks myometrial sodium channels and reduces excitability (14).

Mepivacaine is an amide local anesthetic that has rapid onset and moderate

duration of action. It has a pKa of 7.7 and 40% protein binding property (16). Characteristics of mepivacaine is similar to lidocaine but, mepivacaine has less transient neurologic symptoms after spinal anesthesia than lidocaine (17). Mepivacaine also provides satisfactory anesthesia for cesarean section and had no adverse effects on the newborn (6). It has been described that mepivacaine increases uterine contractility (7). The result is in accordance with my results. In this study, as the concentration of mepivacaine was increased during spontaneous contraction, active tension was increased in concentrations of 10^{-5} to 10^{-3} M as a concentration-dependent manner. But, frequency of contraction showed no significant change. When pregnant women received 2% mepivacaine (359 mg) epidurally, the maternal peak plasma concentration of mepivacaine was 6.7 ± 2.02 μg /ml (6), which is 2.72 x 10^{-7} M. This plasma concentration is comparable to 1.63 x 10^{-7} M in vitro, because 40% of mepivacaine is bound to plasma protein (18). Mepivacaine had no significant effects on the uterine contraction at this concentration in this study. The neonatal free plasma concentration of mepivacaine was also 3.5 ± 1.05 μg/ml (6). Fetal/maternal concentration ratio of mepivacaine was 0.57 ± 0.17. Therefore, mepivacaine would not alter the uterine contractility and cause the fetal distress in concentration that is commonly used clinically. Some investigators reported that mepivacaine has vasoconstrictive effects when administered during intravenous regional anesthesia (19). But others reported that mepivacaine causes vasodilation through an alpha-adrenergic receptor antagonism and interferes with the transmembrane influx of calcium in vascular smooth muscle at higher concentrations (20). However, the effects of mepivacaine on the smooth muscles and vasculature are not fully understood and needs futher investigation.

Levobupivacaine is a long acting local anesthetic with clinical profile that is silmilar to bupivacaine. It has a pKa of 8.1 and 95% protein binding property which is almost same as bupivacaine (21). Levobupivacaine is less arrhythmogenic and has less inhibitory effect on cardiac sodium channels than bupivacaine (16). Levobupivacaine and bupivacaine have same quality of anesthesia in epidural anesthesia for cesarean section (22). It has been described that cumulative concentration of levobupivacaine significantly decreased the contractile activity and freqeuncy of myometrial contraction (11). These results are agreed with my results. In this study, levobupivacaine slightly increased active tension at concentrations of 10^{-5} to 10^{-4} M as the concentration of levobupivacaine was increased during spontaneous contraction. But after all, levobupivacaine decreased active tension at a concentration of 10^{-3} M. The frequency of contractions

decreased in a dose-dependent manner in higher concentrations (10^{-5} to 10^{-3} M). When term parturients received 0.5 % levobupivacaine (30 ml) epidurally for cesarean section, the maternal peak plasma concentration of levobupivacaine was 1.017 μg/ml (22), which is 9.25 x 10^{-7} M. This plasma concentration is comparable to 4.63 x 10^{-8} M in vitro, because 95% of levobupivacaine is bound to plasma protein.() Therefore, levobupivacaine in concentration that is commonly used clinically would not change the uterine contractility. The neonatal free plasma concentration of levobupivacine was 0.191 μg/ml. Fetal/maternal concentration ratio of levobupivacaine was 0.303 (22). It was reported that minimal local analgesic concentration of epidural lidocaine is 0.083 % (10). Placental transfer and fetal effects of levobupivacaine is similar to bupivacaine and ropivacaine. There were no adverse effects on fetal heart rats, blood pressure, acid-base status, or uterine blood flow in pregnant sheep when levobupivacaine is administered intravenously (23). Although levobupivacaine is very similar to bupivacaine, it may be less toxic and have wider margin of safety because it is a levorotatory isomer of bupivacaine (24). It has been suggested that the cardiovascular inhibitory effects of local anesthetics such as levobupivacaine, bupivacaine, and ropivacaine may be caused by inhibiting sarcolemmal adenosine triphosphate-sensitive potassium channels as well as by blocking sodium channels (25).

In conclusion, lidocaine had relaxant effect on the isolated rat uterine smooth muscle strips, but on the contrary, mepivacaine increased the active tension in a dose-dependent pattern at concentrations ranging from 10^{-5} to 10^{-3} M. Lidocaine had the greatest relaxant effects and levobupivacaine had relaxant effect at a higher concentration (10^{-3} M) among these local anesthetics. In clinical dosage, all the three local anesthetics have no significant effects on the uterine smooth muscle contractions. But more investigations on pregnant rats or in vivo studies are required to evaluate these effects.

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<국문 초록>

백서 자궁평활근 절편에서 Lidocaine, Mepivacaine, Levobupivacaine의 효과 비교

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산과영역에서 부위마취의 비중이 커짐에 따라 국소마취제의 사용 역시 증가되고 있다. 이에 저자는 lidocaine, mepivacaine, levobupivacaine이 흰 쥐에서 추출된 자궁근에 미치는 효과를 관찰하였고 비교하였다. 비임신 암쥐로부터 자궁 평활근 조직을 추출하여 10 mm 크기로 절단한 후, 절편을 Krebs용액에 담았다. Krebs용액(mM)은 NaCl 118.3, KCl 4.7, $CaCl_2$ 2.5, $NaHCO_3$ 25, KH_2PO_4 1.2, $MgCl_2$ 1.2 그리고 glucose 11.1로 구성되어 있다. 수조내의 용액은 37°C로 유지시켰고, 95% O_2와 5% CO_2의 혼합가스가 공급되었다. 자발적인 자궁수축이 이루어진 후, 다양한 농도 (10^{-7}~10^{-3} M)의 lidocaine (n = 18), mepivacaine (n = 18), levobupivacaine (n = 18)을 수조에 첨가하였고, 지속적으로 자궁근의 수축장력과 횟수를 기록하였다. 자궁근의 수축장력에 대한 각 약물의 EC_5, EC_{25}, EC_{50}, EC_{75}, EC_{95}는 probit model을 사용하여 계산되었다. Lidocaine은 10^{-5} ~ 10^{-3} M의 농도에서 자궁수축을 억제하였다. 이와는 반대로 mepivcaine은 10^{-5} ~ 10^{-3} M의 농도에서 자궁수축을 증가시켰다. levobupivacaine은 10^{-5} ~ 10^{-4} M의 농도에서 자궁수축을 증가시켰으나 10^{-3} M의 농도에서는 자궁수축을 억제하였다. 자궁근의 수축빈도에서는 lidocaine은 저농도 (10^{-7} ~ 10^{-5} M)에서 수축 횟수가 감소했으나 고농도 (10^{-4}~10^{-3} M)에서는 수축횟수가 증가하였다. 이에 반해 mepivacaine은 수축횟수에 유의한 변화가 없었다. Levobupivacaine은 10^{-5} ~ 10^{-3} M의 농도에서 수축횟수를 감소시켰다. Lidocaine, mepivacaine, levubupivacaine의 수축장력의 변화에 대한 EC_{50}은 각각 4.82 x 10^{-4} M, 9.78 x 10^{-1} M, 1.52 x 10^{-2} M 이었다. 이러한 국소마취제 중에서 lidocaine이 가장 큰 자궁근 이완효과를 보였다.

저작물 이용 허락서

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	(영문) Comparison of the effects of the lidocaine, mepivacaine and levobupivacaine on the isolated rat uterine smooth muscles				

본인이 저작한 위의 저작물에 대하여 다음과 같은 조건 아래 조선대학교가 저작물을 이용할 수 있도록 허락하고 동의합니다.

- 다 음 -

1. 저작물의 DB구축 및 인터넷을 포함한 정보통신망에의 공개를 위한 저작물의 복제, 기억장치에의 저장, 전송 등을 허락함.
2. 위의 목적을 위하여 필요한 범위 내에서의 편집과 형식상의 변경을 허락함. 다만, 저작물의 내용변경은 금지함.
3. 배포·전송된 저작물의 영리적 목적을 위한 복제, 저장, 전송 등은 금지함.
4. 저작물에 대한 이용기간은 5년으로 하고, 기간종료 3개월 이내에 별도의 의사 표시가 없을 경우에는 저작물의 이용기간을 계속 연장함.
5. 해당 저작물의 저작권을 타인에게 양도하거나 출판을 허락을 하였을 경우에는 1개월 이내에 대학에 이를 통보함.
6. 조선대학교는 저작물 이용의 허락 이후 해당 저작물로 인하여 발생하는 타인에 의한 권리 침해에 대하여 일체의 법적 책임을 지지 않음.
7. 소속 대학의 협정기관에 저작물의 제공 및 인터넷 등 정보통신망을 이용한 저작물의 전송·출력을 허락함.

동의여부 : 동의(○) 반대( )

2010년 2월

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