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The Comparison of the Relaxant Effects of Lidocaine, Bupivacaine, and Ropivacaine on Isolated Rat Uterine Smooth Muscle

조선대학교 대학원

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이 논문을 의학박사 학위신청 논문으로 제출함.

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배경

국소마취제는 산과영역에서 부위마취를 위해 사용된다. 이러한 국소마취제는 자궁평활근 뿐만 아니라 다른 평활근에도 여러 가지 효과를 갖고 있다. 이에 저자는 lidocaine, bupivacaine, ropivacaine이 흰 쥐에서 추출된 자궁근에 미치는 효과를 관찰하였고 비교하였다.

대상 및 방법

준비된 자궁근은 비임신 암쥐로부터 추출되었다. 쥐의 자궁근은 10 mm의 절편으로 절단하여 Krebs용액에 담았다. Krebs용액은 NaCl 118.3, KCl 4.7, $CaCl_2$ 2.5, $NaHCO_3$ 25, KH_2PO_4 1.2, $MgCl_2$ 1.2 그리고 glucose 11.1(mM)로 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 = 20), bupivacaine (n = 20), ropivacaine (n = 20)을 수조에 누적 첨가하였고, 자궁이완효과를 지속적으로 기록하였다. 자궁근의 수축장력에 대한 각 약물의 EC_5, EC_{25}, EC_{50}, EC_{75}는 probit model을 사용하여 계산되었다.

결과

Lidocaine, bupivacaine, ropivacaine은 농도 증가에 따라 자궁수축의 억제를 증가시켰다. 자궁근의 수축 빈도에서는 lidocaine은 저농도(10^{-7}～10^{-5} M)에서 수축 횟수가 감소했으나 고농도(10^{-4}～10^{-3} M)에서는 수축횟수가 증가하였다. Bupivacaine과 ropivacaine은 고농도(10^{-4}～10^{-3} M)에서 수축횟수가 감소하였다.

Lidocaine, bupivacaine, ropivacaine의 수축장력에 대한 EC_{50}은 각각 8.56 x 10^{-3} M, 9.03 x 10^{-4} M, 6.10 x 10^{-3} M 이었다. 자궁 평활근에 대한 국소마취제의 이완효과는 bupivacaine > ropivacaine > lidocaine의 순이었다.

결론

Lidocaine, bupivacaine, ropivacaine은 농도가 증가함에 따라 자궁수축의 억제를 증가시켰다. Bupivacaine이 이들 국소마취제 중에서 자궁근 이완효과가 가장 컸다. Lidocaine은 저농도(10^{-7}~10^{-5} M)에서 수축 횟수를 감소시켰으나, 고농도(10^{-4}~10^{-3} M)에서는 모두가 수축횟수를 증가시켰다.

Introduction

Local anesthetics (lidocaine, bupivacaine, and ropivacaine) are frequently used for regional anesthesia in pregnancy, labor and delivery. Therefore, local anesthetics using in obstetric practice have the rapid onset and favorable toxicity profile. It was reported that some local anesthetics change the contractility of uterine smooth muscle during regional anesthesia.[1)]

Lidocaine, the first amino-amide type local anesthetic, is the most commonly used local anesthetic drug for regional anesthesia in obstetric practice. Neonates are able to metabolize lidocaine,[2)] and the use of lidocaine is regarded as safe for cesarean section in normal-term pregnancy.[3)] Bupivacaine is a longer acting amide type local anesthetic in contrast to lidocaine. It is also widely used for regional anesthesia and analgesia in obstetric procedure. Passive diffusion is probably the mechanism of placental transfer of bupivacaine. Marishima et al.[4)] reported that a considerable amount of bupivacaine is taken up by both sides of the placenta, as well as by the amnion and myometrium. Ropivacaine is a long-acting, amino-amide type local anesthetic similar to bupivacaine, but it has less cardiotoxic potential than bupivacaine.[5,6)] Ropivacaine may gain ascendancy over bupivacaine because of its greater safety profile and its lower propensity for motor block. Lumbar epidural administration of 20 ~ 30 ml ropivacaine 0.5% provided anesthesia of a similar quality to that achieved with bupivacaine 0.5% in women undergoing cesarean section, but the duration of motor blockade is shorter with ropivacaine.[7)]

It was reported that lidocaine reduces the excitability of uterine muscle in the rat myocyte.[8)] Bupivacaine has relaxant effects on myocardial, tracheal, and bladder smooth muscle.[5,9)] Some investigators reported that bupivacaine unchanged the uterine contraction.[10-13)] Others reported that bupivacaine had relaxant effects on uterine contraction.[11,14)] Ropivacaine also causes a dose-dependent inhibition of uterine contraction.[6)]

It was also reported that the frequency of uterine contraction changed in variable pattern.[1)] Lidocaine produced a slight decrease in the frequency of myometrial contractions at the lower concentration, whereas it produced variable responses at the higher concentration.[1)] Bupivacaine did not affect the frequency of myometrial contraction but elevated the frequency of contraction

in high concentration.[6,15] Ropivacaine also did not affect the frequency of myometrial contraction.[6]

There has been still controversy about the effects of local anesthetics on the uterine contraction. The aim of the present study was to investigate and compare the effects of lidocaine, bupivacaine, and ropivacaine on active tension and frequency of contraction in the isolated rat uterine smooth muscle.

Materials and Methods

The study was approved by the Medical College Animal Care and Use Committee. As experimental animals, Sprague-Dawley rats wighing 200-250 g were used. All rats were killed by inhalation of carbon dioxide. The abdomen was opened immediately and the uterus was extracted. The myometrial tissue specimens were dissected into strip of myometrium (approximately 2 mm wide and 10 mm long) in a petri dish filled with Krebs solution; the muscle fibers of these strips were oriented parallel to the longest dimension. These 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 (FTO3® ; Grass Instruments co., MASS, USA). 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 pH is approximately 7.4. The Krebs solution was composed of 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.

The isometric tension of the myometrial strips was measured using a force displacement transducer and the recordings of traces were made on a computer (PowerLab® data recording system; AD Instruments Pty Ltd., Castle Hill, Australia). An initial resting tension of 2.0 g was applied. The bath solution was flushed with fresh solution every 15 minutes. When the contractions became regular, lidocaine (n = 20), bupivacaine (n = 20), and ropivacaine (n = 20) was added cumulatively every 15 minutes by increasing to 10^{-7}, 10^{-6}, 10^{-5}, 10^{-4}, and 10^{-3} M to the baths with a micropipette, and the change of the contraction pattern was examined. To express the quantitative changes in muscle contraction, I measured active tension and frequency of contraction. The active tension was defined as the difference between peak tension and resting tension during muscle contraction. The frequency of contraction was defined 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 relaxant effects were compared with the control, and were described as % inhibition. EC_5 (5% of maximal effective concentration), EC_{25}, EC_{50}, EC_{75} and EC_{95} on active tension were calculated using a probit model.

All obtained results are expressed as mean ± standard deviation, and the statistical significance was analyzed by repeated measures ANOVA within group, and one way ANOVA with post hoc between groups. If repeated measures ANOVA showed significance, the comparisons to control were performed with the paired two-tailed students's T-test. The probability values were then adjusted with bonferroni correction. P values less than 0.05 were considered statistically significant.

Results

Lidocane, bupivacaine and ropivacaine decreased active tension in a dose-dependent pattern ($P < 0.05$) (Table 1) (Fig. 1-3).

Table 1. Effects of Lidocaine, Bupivacaine, and Ropivacaine on Active Tension in the Uterine Smooth Muscle

Drug	Concentration (M)					
	control	10^{-7}	10^{-6}	10^{-5}	10^{-4}	10^{-3}
Lidocaine (%) (n=20)	100	98.2 ± 1.5*†‡	96.6 ± 2.2*†‡	94.1 ± 3.0*†‡	80.4 ± 1.6*†‡	72.2 ± 4.8*†‡
Bupivacaine (%) (n=20)	100	98.8 ± 1.1*	94.8 ± 1.6*	89.6 ± 4.0*	70.2 ± 1.1*	49.9 ± 1.1*
Ropivacaine (%) (n=20)	100	99.1 ± 0.6*†	98.0 ± 2.2*†	95.9 ± 5.7*†	84.7 ± 1.9*†	77.8 ± 4.7*†

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

Bupivacaine and ropivacaine in doses of 10^{-4} to 10^{-3} M increased the frequency of contraction as a dose-dependent pattern ($P < 0.05$). 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 ($P < 0.05$) (Table 2) (Fig. 4-6).

Table 2. Effects of Lidocaine, Bupivacaine and Ropivacaine on Frequency of Contraction in the Uterine Smooth Muscle

Drug	Concentration (M)					
	control	10^{-7}	10^{-6}	10^{-5}	10^{-4}	10^{-3}
Lidocaine (%) (n=20)	100	90.7 ± 11.0*†‡	78.0 ± 16.9*†‡	74.8 ± 18.1*†‡	115.3 ± 30.9*†‡	126.60 ± 38.9*†‡
Bupivacaine (%) (n=20)	100	97.6 ± 12.7*	97.0 ± 13.5*	99.5 ± 15.4*	134.2 ± 15.6*	142.6 ± 17.3*
Ropivacaine (%) (n=20)	100	97.6 ± 6.4*†	99.8 ± 10.0*†	98.7 ± 7.0*†	118.9 ± 9.1*†	126.7 ± 13.0*†

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

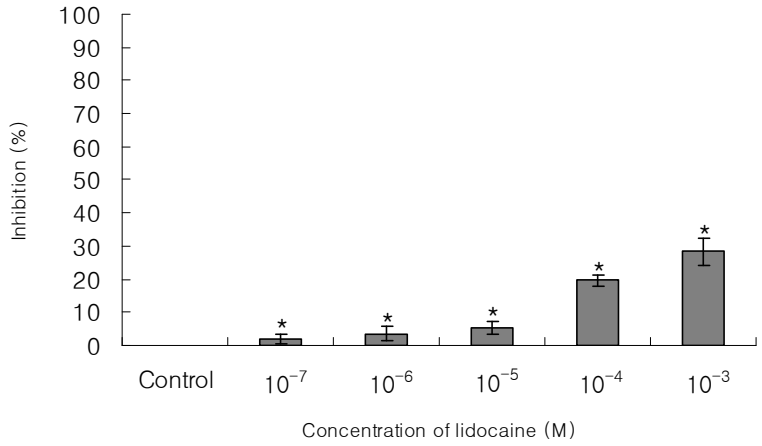

Fig. 1. The effects of lidocaine on active tension of rat uterine myometrium. Lidocaine inhibited uterine contraction in a dose-dependent pattern. * : $P < 0.05$ compared with control.

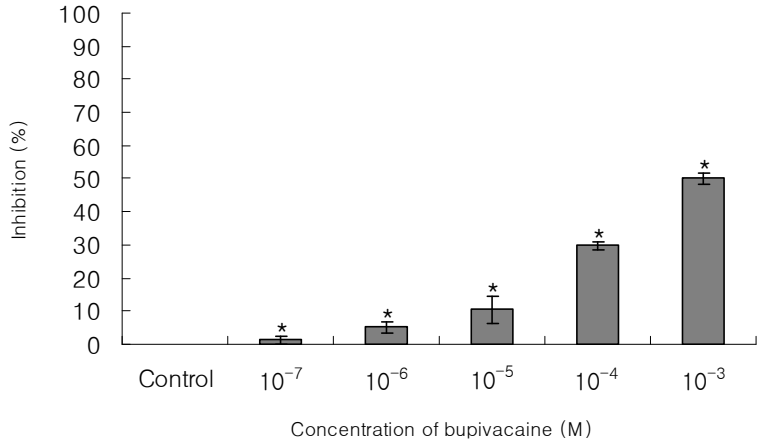

Fig. 2. The effects of bupivacaine on active tension of rat uterine myometrium. Bupivacaine inhibited uterine contraction in a dose-dependent pattern. * : $P < 0.05$ compared with control

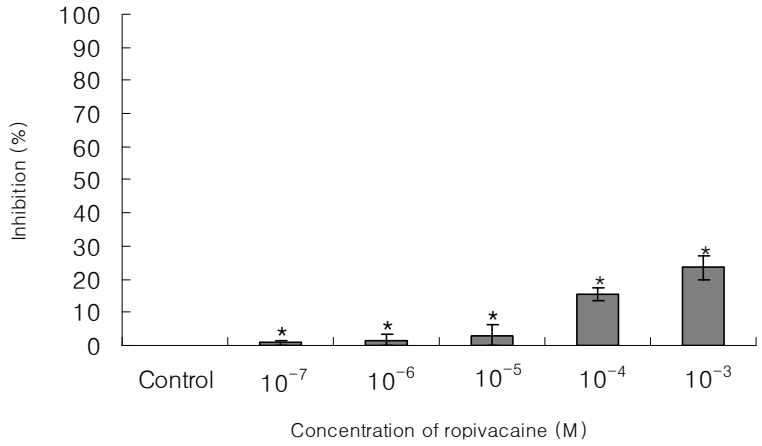

Fig. 3. The effects of roivacaine on active tension of rat uterine myometrium. Ropivacaine inhibited uterine contraction in a dose-dependent pattern. * : $P < 0.05$ compared with control.

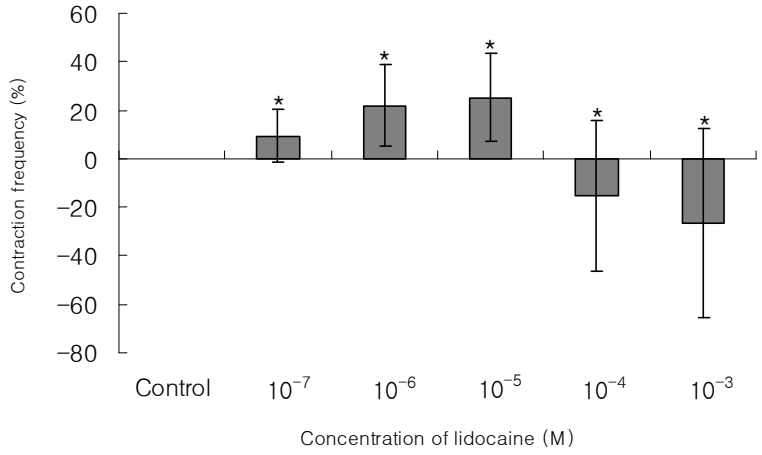

Fig. 4. The effects of lidocaine on frequency of contraction of rat uterine myometrium. Lidocaine in doses of 10^{-7} to 10^{-5} M reduced the frequency of contraction but, lidocaine in doses of 10^{-4} to 10^{-3} M increased the frequency of contraction. * : $P < 0.05$ compared with control.

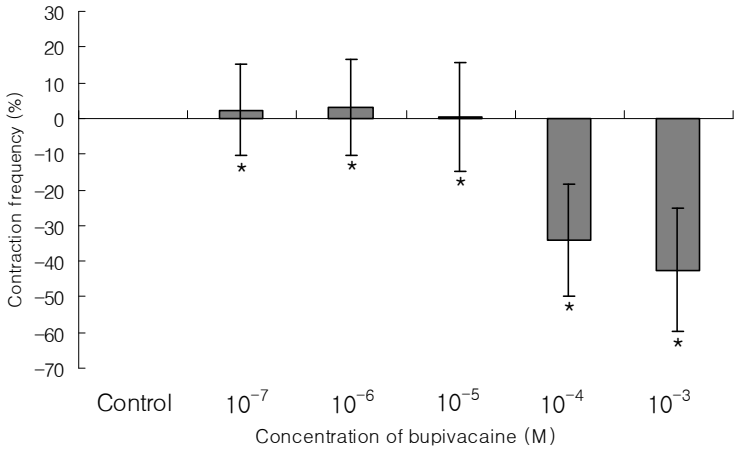

Fig. 5. The effects of bupivacaine on frequency of contraction of rat uterine myometrium. Bupivacaine increased the frequency of contraction in doses of 10^{-4} to 10^{-3} M. * : $P < 0.05$ compared with control.

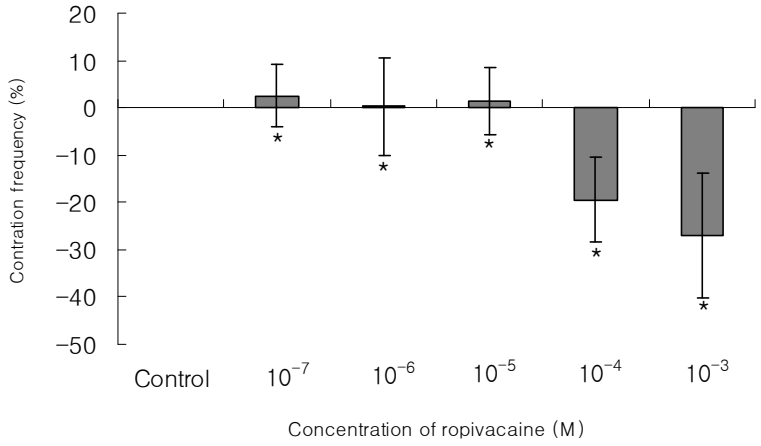

Fig. 6. The effects of ropivacaine on frequency of contraction of rat uterine myometrium. Ropivacaine increased the frequency of contraction in doses of 10^{-4} to 10^{-3} M. * : $P < 0.05$ compared with control.

The EC_{50}'s of lidocaine, bupivacaine, and ropivacaine on active tension in the uterine smooth muscle was 8.56 x 10^{-3} M, 9.03 x 10^{-4} M, and 6.10 x 10^{-3} M respectively. The order of relaxant potency was bupivacaine > ropivacaine >

lidocaine (Table 3). The relaxant potency of bupivacaine was the greatest (Fig. 7).

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

	EC_5	EC_{25}	EC_{50}	EC_{75}	EC_{95}
Lidocaine	$1.02(0.05) \times 10^{-5}$	$4.77(0.08) \times 10^{-4}$	$8.56(0.20) \times 10^{-3}$	$1.74(0.06) \times 10^{-1}$	$1.52(0.08) \times 10$
Bupivacaine	$2.10(0.04) \times 10^{-6}$	$7.23(0.05) \times 10^{-5}$	$9.03(0.05) \times 10^{-4}$	$1.29(0.01) \times 10^{-2}$	10.5(0.00)
Ropivacaine	$2.82(0.06) \times 10^{-5}$	$6.51(0.11) \times 10^{-4}$	$6.10(0.14) \times 10^{-3}$	$5.97(0.19) \times 10^{-2}$	1.71(0.08)

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

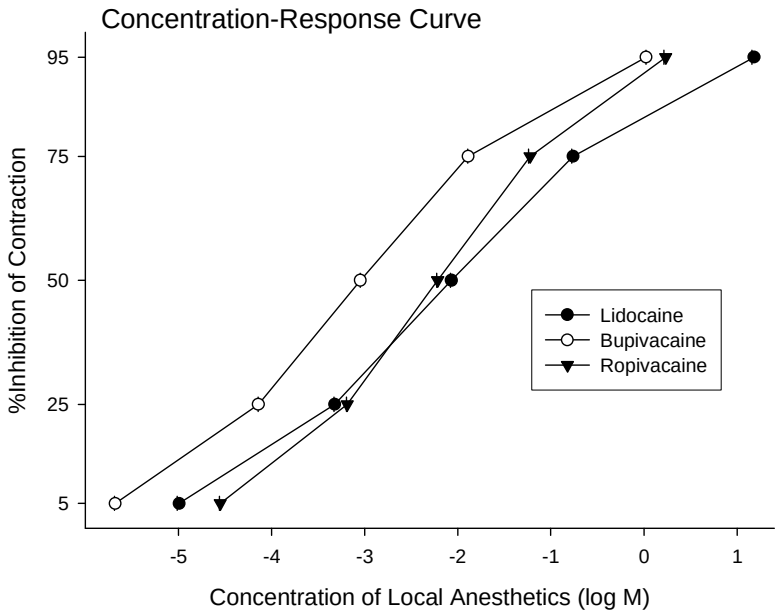

Fig. 7. Cumulative concentration-response curves of local anesthetics. The effects on the myometrial contraction are calculated as % inhibition of control. All contractile responses were spontaneous. All three local anesthetics inhibited uterine contraction in a dose-dependent pattern. Bupivacaine had the greatest uterine relaxant effects.

Discussion

Regional anesthesia is popular in obstetric practice because it provides excellent analgesia. The risks of serious complications (e.g. failed intubations, aspiration of gastric contents) are less in regional anesthesia than general anesthesia. Regional anesthesia may also lead to hypotension due to sympathetic blockade. During episodes of hypotension in the parturient, fetal acidosis may be caused and placental transfer of local anesthetics can be altered. Therefore, particular considerations of local anesthetics are not only the influence on uterine contraction but also fetal safety (placental transfer of components) during pregnancy and labor. The commonly used local anesthetics for regional anesthesia are lidocaine, bupivacaine, and ropivacaine.

Lidocaine still has a place as a local anesthetic for regional anesthesia in obstetric practice because of its rapid onset and favorable toxicity profile. Lidocaine is a weak base, with a pKa of 7.8. The ionic form of lidocaine does not cross the placenta in significant amounts, in contrast to the non-ioninc form, which is highly diffusible. The placental transfer of lidocaine is increased by fetal acidemia. Ion trapping occurs during episodes of fetal acidosis.[16] Lidocaine also has an relaxing effect on umbilical artery at concentratin of 30 μg/ml and does not interfere with the umbilical circulation and oxygenantion of the fetus.[17] The neonatal effects of epidural administration of lidocaine are mild because lidocaine is 56% protein bound. Lidocaine did not prolong the second stage of labor when administrated as continuous epidural infusion.[18] It was known that minimal local analgesic concentration of epidural lidocaine is 0.37% in the first stage of labor.[19] When pregnant women received perineal analgesia with 20 ml of 2% lidocaine (400 mg) during the expulsive period of labor, the maximum maternal venous concentration of lidocaine was 3.22 μg/ml,[20] which is equal to 1.1 x 10^{-5} M. This plasma concentration is comparable to 4.84 x 10^{-6} M in vitro, because 56% of lidocaine given intravenously is bound to plasma protein. In my study, 5 x 10^{-6} M lidocaine reduced uterine contraction by about 3% of control. It was reported that lidocaine may cause a significant reduction in uterine smooth muscle tone at concentrations much higher than those that are commonly used in clinical practice.[18] Therefore, I should take the efforts to minimize the dose of lidocaine in clinical situations. In my study, as the

concentration of lidocaine was cumulatively increased after spontaneous uterine contractions started, active tensions of uterine contraction were reduced in a concentration-dependent manner and the frequency of contractions showed variable responses. This effect is mediated via blocking the fast voltage-gated sodium channels in the uterine myocyte.[8)]

Bupivacaine is a long acting amide-type local anesthetic. This agent is effective in reducing labor pain for regional anesthesia and analgesia.[10,21)] It has a pKa of 8.1, and has greater protein binding (95%) than lidocaine. Placental transfer of bupivacaine appears to be influenced by maternal and fetal plasma protein binding, fetal pH and placental uptake.[22)] As with lidocaine, placental transfer is enhanced by fetal acidosis. Protein binding capacity and lipid solubility of bupivacaine affect the systemic absorption from tissue compartment. During epidural anesthesia with bupivacaine, no abnormalities in fetal heart rate were noted and normal pH in the umbilical cord were observed.[19)] It has been described that cumulative concentration of bupivacaine inhibited the contraction amplitude of myometrial strips.[15)] Bupivacaine also caused dose-dependent depression of contraction in the isolated dog papillary muscle,[23)] in bladder smooth muscle,[24,25)] and in tracheal smooth muscle.[26)] Bupivacaine had a greater inhibitory effect on contractility than ropivacaine.[6)] When term parturients received 0.5% bupivacaine (30 ml) epidurally in divided doses over a 10 minutes period for cesarean section, the maternal peak plasma concentration of bupivacaine was 1.1 ± 0.0 μg/ml,[27)] which is equal to 3.2×10^{-6} M. This plasma concentration is comparable to 1.6×10^{-7} M in vitro, because 95% of bupivacaine is bound to plasma protein. In my study, 2×10^{-7} M bupivacaine reduced uterine contraction by about 6% of control. Motor block from the epidural local anesthetic may reduce maternal effort in the second stage, and may also predispose to inadequate rotation of the fetal presenting part secondary to relaxation of pelvic floor muscles. Therefore, bupivacaine in concentratiion that is commonly used clinically may be decreased uterine contraction and caused prolonged labor but, it would not cause the fetal distress. So, I should not overdose bupivacaine in obstetrc practice. In addition the neonatal free plasma concentration (from umbilical vein) of bupivacine was also 0.041 ± 0.002 μg/ml. The ratio of umbilical vein to maternal vein in free concentration of bupivacaine was 0.69. In by study, as the concentration of bupivacaine was

cumulatively increased after spontaneous uterine contractions started, active tensions of uterine contraction were reduced in a concentration-dependent manner and the frequency of contractions was increased. It has been suggested that the relaxant effects of bupivacaine may be caused by inhibiting Ca^{2+} release or Ca^{2+} sequestration on sarcoplasmic reticulum[28-30] as well as by blocking on sarcolemmal Na^{+} and Ca^{2+} channels.[31-34]

Ropivacaine was released for clinical use in 1996. It is a long-acting, enantiomerically pure (S-enantionmer), amide-type local anesthetic with a high pKa[35] and low lipid solubility. Sensory nerve fibers are blocked to a greater degree than those that motor nerve fibers. Ropivacaine has a similar clinical effect as bupivacaine with regard to sensory anesthesia and slightly less motor blockade than bupivacaine.[36] Ropivacaine has less cardiotoxicity and central nervous system toxicity than bupivacaine.[37-39] The reputed equipotency of ropivacaine as compared with bupivacaine has recently been questioned, and warrants further investigation.[40-42] No local neurologic complication has been reported with ropivacaine so far. Clinically, during epidural anesthesia in nonpregnant human, ropivacaine and bupivacaine in equipotent doses showed similar onset time, duration of sensory blockade, and overall clinical efficacy. But, the intensity of motor block is less with ropivacaine compared to bupivacaine.[43] During epidural anesthesia, ropivacaine showed no abnormalities in fetal heart rate, normal neonatal Apgar scores and neurobehavior, and normal pH values in the umbilical cord blood.[27] Ropivacaine has lesser degree of protein binding capacity and lipid solubility compared to bupivacaine.[27] It has been described that ropivacaine caused a dose-dependent depression of uterine contractility.[6] When pregnant women received 0.5% ropivacaine (30 ml) epidurally in appropriate fractionated doses over 10 minutes for cesarean section, the maternal peak plasma concentration of ropivacaine was 1.3 ± 0.09 μg/ml,[27] which is equal to 4.79×10^{-6} M. This plasma concentration is comparable to 3.83×10^{-7} M in vitro, because 92% of ropivacaine is bound to plasma protein.[44] In my study, 10^{-6} M ropivacaine reduced uterine contraction by about 2% of control. Therefore, I should take the caution to minimize the dose of ropivacaine in obstetrc practice. In addition, the neonatal free plasma concentration (from umbilical vein) of ropivacaine was also 0.072 ± 0.008 μg/ml.[27] The ratio of umbilical venin to maternal vein free concentration of ropivacaine was 0.72. Therefore,

ropivacaine in concentration that is commonly used clinically would not cause the fetal distress. In my study, as the concentration of ropivacaine was cumulatively increased after spontaneous uterine contractions started, active tensions of uterine contraction were reduced in a concentration-dependent manner and the frequency of contractions was increased. This effect is mediated via inhibition of the sodium ion influx through the voltage-operated Na^+ channel and blocking on sarcolemmal Na^+ channels.[45)]

In colclusion, lidocaine, bupivacaine, and ropivacaine relaxed the uterine smooth muscle obtained from non-pregnant rats in a dose-dependent pattern. Bupivacaine had the greatest relaxant effects on isolated rat uterine smooth muscle among three local anesthetics. All three local anesthetics have little significant effect on uterine smooth muscle contraction in clinical dose. Extrapolation of our results to the clinical situation must be viewed with caution because of possible species differences, in vivo/vitro differences. Futher study on the pregnant rats remains.

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저작물 이용 허락서

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논문제목	한글 : **백서 자궁평활근 절편에서 Lidocaine, Bupivacaine, Ropivacaine의 이완효과 비교** 영문 :*The Comparison of the Relaxant Effects of Lidocaine, Bupivacaine, and Ropivacaine on Isolated Rat Uterine Smooth Muscle*				

본인이 저작한 위의 저작물에 대하여 다음과 같은 조건아래 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 편집·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 또는 출판을 허락을 하였을 경우에는 1개월 이내에 대학에 이를 통보함.
6. 조선대학교는 저작물의 이용허락 이후 해당 저작물로 인하여 발생하는 타인에 의한 권리 침해에 대하여 일체의 법적 책임을 지지 않음
7. 소속대학의 협정기관에 저작물의 제공 및 인터넷 등 정보통신망을 이용한 저작물의 전송·출력을 허락함.

동의여부 : 동의(0) 조건부 동의( ) 반대( )

2008 년 6 월 30 일

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