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The Comparison of the Relaxant Effects of Propofol, Thiopental, Ketamine, and Etomidate on Isolated Rat Uterine Smooth Muscle

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이 논문을 의학박사 학위신청 논문으로 제출함.

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백서 자궁평활근 절편에서 Propofol, Thiopental, Ketamine, Etomidate의 이완효과 비교

은 삼 성
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배경

최면제는 임신, 분만과 출산시 사용된다. 이러한 최면제는 자궁평활근 뿐만 아니라 다른 평활근에도 여러가지 효과를 갖고 있다.그러나 자궁 평활근에 대한 etomidate에 대한 효과는 알려져 있지 않다. 이에 저자는 propofol, thiopental, ketamine, etomidate가 흰 쥐에서 추출된 자궁근에 미치는 이완효과를 관찰하였고 비교하였다.

대상 및 방법

준비된 자궁근은 비임신 암컷 Sprague-Dawley 쥐(200-250g)로부터 추출되었다. 쥐의 자궁은 10mm의 절편으로 절단하여 Krebs용액에 담그었다. 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 and glucose 11.1로 구성되어 있다. 수조내의 용액은 37°C로 유지시켰고, 95% O_2와 5% CO_2의 혼합가스가 공급되었다. 자발적인 자궁수축이 이루어진후, 다양한 농도 (10^{-7}～10^{-3} M)의 propofol (n = 25), thiopental (n = 25), ketamine (n = 25), etomidate (n = 25)을 수조에 첨가하였고, 자궁이완효과를 지속적으로 기록하였다. 자궁근의 수축장력과 빈도에 있어서 각 약물의 EC_5, EC_{25}, EC_{50}, EC_{75}, EC_{95}는 probit model을 사용하여 계산되었다.

결과

Propofol, thiopental, etomidate (10^{-7}～10^{-3} M)와 고농도의 ketamine (10^{-4}～10^{-3} M)는 용량 의존적으로 자궁수축을 억제시켰고, 저농도의 ketamine (10^{-7}～

10^{-5} M)는 자궁수축을 촉진시켰다($P < 0.05$).
Propofol, thiopental, ketamine, etomidate의 수축장력에 대한 EC_{50}은 각각 1.88×10^{-5} M, 5.90×10^{-5} M, 3.41×10^{-4} M, 2.53×10^{-5} M이었고, 수축빈도에 대한 EC_{50}은 각각 2.53×10^{-5} M, 5.36×10^{-5} M, 2.07×10^{-4} M, 2.76×10^{-5} M 이었다. 자궁 평활근에 대한 최면제의 이완효과는 propofol > etomidate > thiopental > ketamine의 순서이었다.

결론

Ketamine의 저농도(10^{-7}~10^{-5} M)를 제외한 propofol, thiopental, ketamine, etomidate의 모든 농도에서 자궁근을 이완시켰다. Propofol은 이 최면제들 중에서 가장 강력한 자궁근 이완효과를 보였다. 따라서, 저자는 자궁수축이 필요로 하는 산모에서는 ketamine을 이용하고, 자궁이완이 필요로 하는 산모에서는 propofol을 사용하는 것이 좋을 것으로 생각한다.

Introduction

Intravenous hypnotics have been used for induction of general anesthesia in cesarean section delivery. They are also used in pregnancy, labor and delivery. Therefore, hypnotics using in obstetrics should have the rapid induction of anesthesia and a wide margin of safety for mother and fetus. It is well known that uterine smooth muscle has spontaneous contractility in non pregnant rat and human. Mechanism of spontaneous uterine contractions may be suspected by intrauterine calcium concentration. As in other tissues, intracellular free Ca^{2+} is a primary regulator of uterine smooth muscle contraction.[1] It was reported that some hypnotics have variable effects on the spontaneous uterine contractions.[2-6]

Propofol (2, 6-diisopropylphenol), a non-water-soluble aqueous emulsion, is used for induction and maintenance of general anesthesia. Because of its pharmacokinetic profile, it has excellent recovery characteristics.[7] Although neonatal elimination is slower than that in the mother,[8] there was no correlation between Apgar scores and propofol concentrations in the umbilical blood.[7] Propofol has relaxant effects on vascular,[9,10] tracheal,[11] and uterine[2] smooth muscles.

Thiopental is the most frequently used intravenous hypnotics today. It was reported that thiopental has an excellent relaxation of tracheal smooth muscle in rats.[11] Thiopental can cause an initial drop in maternal blood pressure, which may cause a reduction in uteroplacental blood flow.[12] Despite a rapid placental transfer and incompletely developed hepatic metabolic capacity in neonates, Apgar scores and neurobehavioral scores after elective cesarean section at term were reported satisfactory.[13-15]

Ketamine (2-0 -chlorophenyl-2-methylamino-cyclohexanone hydrochloride) is a phencyclidine derivative.[16] It is different from most other hypnotics in that it has significant analgesic effect. It has been used in obstetric patients because of its rapid induction of anesthesia with profound analgesia.[16] It does not usually depress the cardiovascular and respiratory systems.[17] It does not inhibit laryngeal and pharyngeal reflexes. It is also a potent bronchodilator.[18,19] In parturients, ketamine has been reported to have variable effects on uterine tone and contractility.[3-6]

Etomidate is an imidazole derivative (R-(+)-pentylethyl-1H-imidazole

-5 carboxylate sulfate).[20] It has been commonly used to induce anesthesia in patients who have limited hemodynamic reserve[21,22] after its introduction into clinical practice in 1972.[23] It has properties of hemodynamic stability, minimal respiratory depression, and cerebral protection. Although a smooth muscle relaxant effect of etomidate has also been described in isolated rat trachea,[24] the effect of etomidate on uterine smooth muscle is unknown well.

The current study was designed to investigate and compare the relaxant effects of propofol, thiopental, ketamine, and etomidate on isolated rat uterine smooth muscle. Furthermore, the present study aimed to suggest the guidelines for the choice of the correct hypnotics in various clinical situations of parturients.

Materials and Methods

The study was approved by the Medical College Animal Care and Use Committee. As experimental animals, 100 Sprague-Dawley rats weighing 200-250 g were used. All rats were killed by inhalation of carbon dixoide. The abdomen was opened immediately through a midline incision and the uterus was extracted. The myometrial tissue specimens were dissected into strips of myometrium (approximately 2 ㎜ wide and 10 ㎜ 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 25 ㎖-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°C 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 appoximately 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 (FTO3®; Grass Instruments Co, MASS, USA) and the recordings of traces were made on a computer (PowerLab® data recording system; ADInstruments Pty Ltd., Castle Hill, Australia). An initial resting tension of 2.0 g was applied. The bath solution was flushed with fresh solution every 20 minutes. The uterine smooth muscle strips were allowed to equilibrate for 90 min after being mounted in the bath, and develop rhythmic spontaneous contractions. After spontaneous uterine activity had been accomplished, propofol (n = 25), ketamine (n = 25), thiopental (n = 25), and etomidate (n = 25) in various concentration (10^{-7} to 10^{-3} M) was added accumulatively every 20 minutes by increasing to 10^{-7}, 10^{-6}, 10^{-5}, 10^{-4}, and 10^{-3} M to the baths, and the change of the contraction pattern was examined. To express the quantitative changes in muscle contractility, we measured three parameters: resting tension, active tension, and frequency of contraction. The active tension was defined as an increase in tension (the tension

between peak tension and resting tension) during muscle contraction. The frequency of contraction was defined as the number of contraction during 20 minutes for the application of each concentration of an agent.

The parameters of the contraction before application of each drug were used as controls. The inhibitory effects were compared with the control, and were described as % inhibition. EC_5(effective concentration of 5% reduction), EC_{25}, EC_{50}, EC_{75}, and EC_{95} on active tension and frequency of contraction 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 ANOVA between groups. If repeated measures ANOVA showed significance, the comparisons to control were performed, with the paired two-tailed students's T-test. The probabilitiy values were then adjusted by bonferroni correction. P values less than 0.05 were considered statistically significant.

Results

Propofol, thiopental, ketamine, and etomidate (10^{-7} to 10^{-3} M) decreased resting tension in a concentration-dependent manner ($P < 0.05$) but, ketamine had significant differences with propofol on the resting tension of 10^{-5} to 10^{-3} M (Table 1).

Table 1. Effects of Propofol, Thiopental, Ketamine, and Etomidate on Resting Tension (g) in the Uterine Smooth Muscle.

Drug	Concentration (M)					
	control	10^{-7}	10^{-6}	10^{-5}	10^{-4}	10^{-3}
Propofol(n=25)	0.39±0.11	0.39±0.11	0.39±0.11*	0.37±0.11*†	0.36±0.10*†	0.32±0.09*†
Thiopental(n=25)	0.44±0.10	0.44±0.10	0.43±0.11*	0.43±0.10*	0.40±0.12*	0.37±0.09*
Ketamine(n=25)	0.46±0.06	0.46±0.06	0.45±0.06*	0.45±0.06*	0.45±0.07*	0.44±0.07*
Etomidate(n=25)	0.43±0.11	0.43±0.11	0.42±0.11*	0.41±0.11*	0.40±0.11*	0.38±0.10*

Data are expressed as mean ± SD. "n" indicates the number of experiments.
*: < 0.05, versus control.
†: < 0.05, versus ketamine.

Propofol, thiopental, and etomidate (10^{-7} to 10^{-3} M) decreased active tension and frequency of contraction in a concentration-dependent manner ($P < 0.05$) (Table 2, 3)(Fig. 1-3). Ketamine had significant differences with propofol and etomidate on the active tension of 10^{-7} to 10^{-4} M (Table 2). Ketamine had also significant differences with propofol and etomidate on the frequency of contraction of 10^{-7} to 10^{-4} M (Table 3).

Table 2. Effects of Propofol, Thiopental, Ketamine, and Etomidate on Active Tension (g) in the Uterine Smooth Muscle.

Drug	Concentration (M)					
	control	10^{-7}	10^{-6}	10^{-5}	10^{-4}	10^{-3}
Propofol(n=25)	4.16±1.06	3.97±1.06*†	3.58±1.17*†	2.47±0.65*†	0.81±0.21*†	0.37±0.10*
Thiopental(n=25)	4.24±1.04	4.01±1.07*	3.66±1.13*	3.41±0.88*	2.29±0.6*	0.42±0.11*
Ketamine(n=25)	4.06±1.11	4.11±1.10*	4.26±1.16*	4.53±1.15*	3.70±1.02*	0.49±0.06*
Etomidate(n=25)	4.21±1.10	4.07±1.07*†	3.79±1.01*†	2.78±0.78*†	1.29±0.34*†	0.43±0.12*

Data are expressed as mean ± SD. "n" indicates the number of experiments.
*: < 0.05, versus control.
†: < 0.05, versus ketamine.

Table 3. Effects of Propofol, Thiopental, Ketamine, and Etomidate on Frequency of Contraction (f/20 minutes) in the Uterine Smooth Muscle.

Drug	Concentration (M)					
	control	10^{-7}	10^{-6}	10^{-5}	10^{-4}	10^{-3}
Propofol (n=25)	21.20±5.26	21.20±5.26*†	20.04±5.27*†	14.44±5.04*†	4.72±1.20*†	0.64±0.75*
Thiopental(n=25)	22.16±5.01	21.92±5.01*	20.16±5.20*	16.28±4.43*	10.4±4.33*	1.84±1.10*
Ketamine(n=25)	21.60±5.05	21.64±4.97*	22.24±5.20*	23.32±5.10*	16.00±3.91*	1.24±1.01*
Etomidate(n=25)	21.24±4.88	21.16±4.93*†	19.80±4.49*†	14.88±3.81*†	6.28±1.92*†	0.96±1.05*

Data are expressed as mean ± SD. "n" indicates the number of experiments.
*: < 0.05, versus control.
†: < 0.05, versus ketamine.

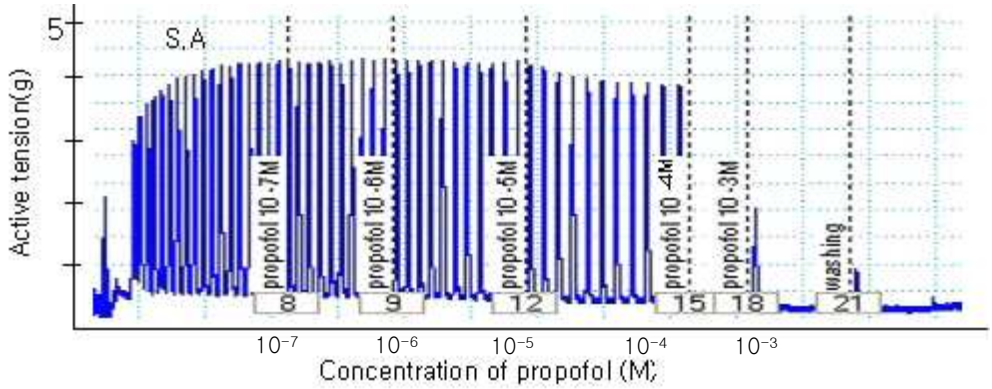

Fig. 1. The depressing effects of propofol on spontaneous activity (S.A) of rat uterine myometrium.

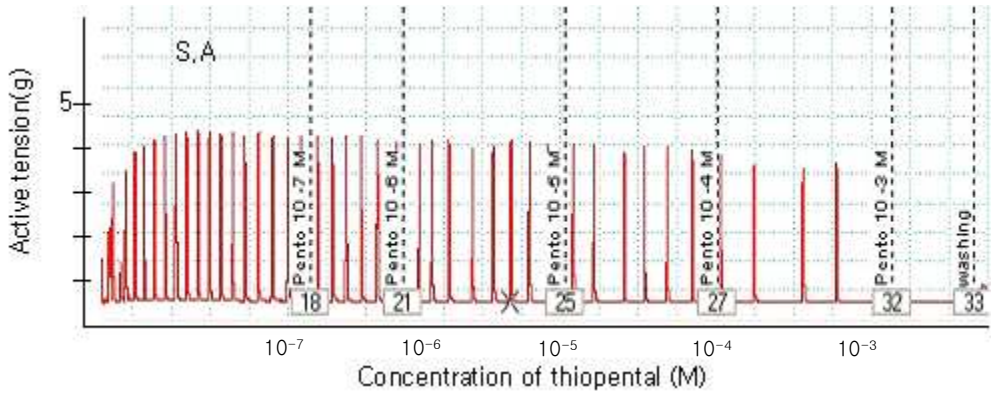

Fig. 2. The depressing effects of thiopental on spontaneous activity (S.A) of rat uterine myometrium.

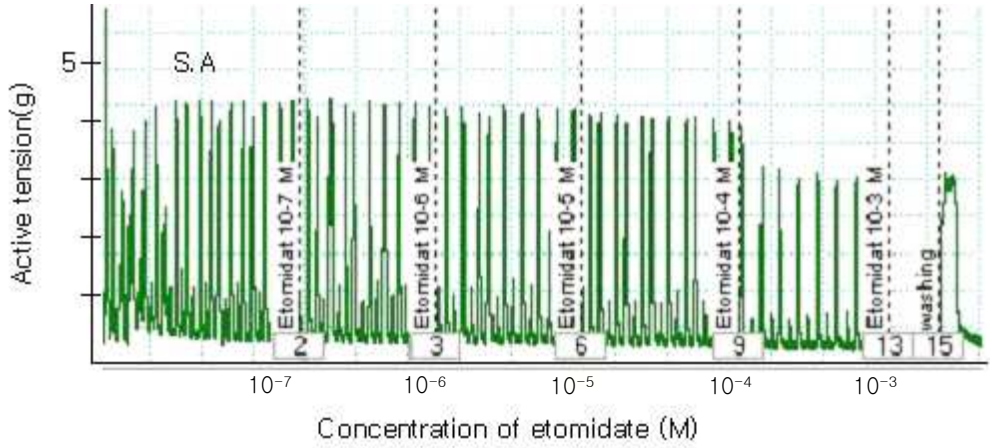

Fig. 3. The depressing effects of etomidate on spontaneous activity (S.A) of rat uterine myometrium.

Ketamine in low concentrations (10^{-7} to 10^{-5} M) increased active tension and frequency of contraction. But, ketamine in high concentrations (10^{-4} to 10^{-3} M) decreased active tension and frequency of contraction in a concentration-dependent manner ($P < 0.05$)(Table 2, 3)(Fig. 4).

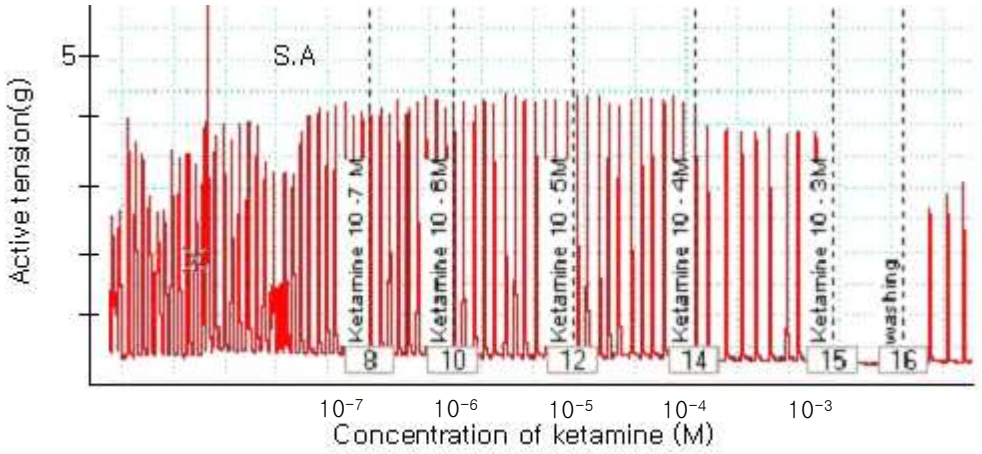

Fig. 4. The depressing effects of ketamine on spontaneous activity (S.A) of rat uterine myometrium.

The EC_{50}'s of propofol, thiopental, ketamine, and etomidate on active tension in the uterine smooth muscle were 1.56 x 10^{-5} M, 4.97 x 10^{-5} M, 3.52 x 10^{-4} M, and 2.73 x 10^{-5} M, respectively. The relaxant potency of propofol was the greatest; thiopental (1/3.2), ketamine (1/22.6), and etomidate (1/1.8)(Fig. 5)(Table 4).

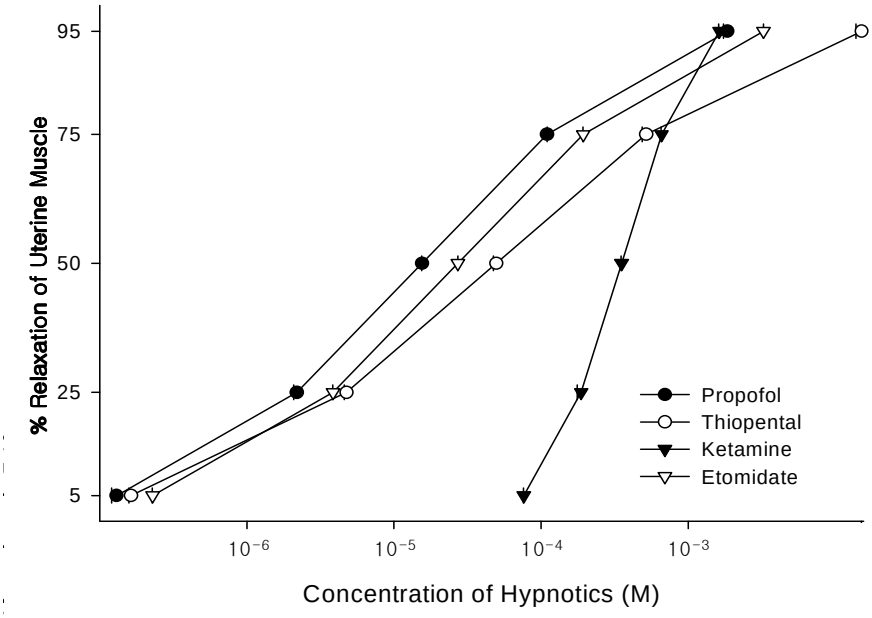

Fig. 5. Relaxant effects of propofol, thiopental, ketamine, and etomidate on active tension of rat uterine myometrium. Propofol has the greatest uterine relaxant effects and ketamine has the least uterine relaxant effects.

Table 4. Effective Concentrations (M) of Propofol, Thiopental, Ketamine, and Etomidate on Active Tension in the Uterine Smooth Muscle.

Drug	EC_5	EC_{25}	EC_{50}	EC_{75}	EC_{95}
Propofol	$1.30(1.02) \times 10^{-7}$	$2.19(1.25) \times 10^{-6}$	$1.56(0.95) \times 10^{-5}$	$1.10(0.75) \times 10^{-4}$	$1.85(1.23) \times 10^{-3}$
Thiopental	$1.64(1.45) \times 10^{-7}$	$4.77(2.04) \times 10^{-6}$	$4.97(1.48) \times 10^{-5}$	$5.18(1.06) \times 10^{-4}$	$1.51(1.25) \times 10^{-2}$
Ketamine	$7.63(0.75) \times 10^{-5}$	$1.88(1.10) \times 10^{-4}$	$3.52(2.07) \times 10^{-4}$	$6.59(1.25) \times 10^{-4}$	$1.63(1.11) \times 10^{-3}$
Etomidate	$2.30(2.03) \times 10^{-7}$	$3.85(1.25) \times 10^{-6}$	$2.73(1.54) \times 10^{-5}$	$1.93(1.13) \times 10^{-4}$	$3.24(0.89) \times 10^{-3}$

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

The EC_{50}'s of propofol, thiopental, ketamine, and etomidate on frequency of contraction were 2.34×10^{-5} M, 4.20×10^{-5} M, 1.98×10^{-4} M, and 2.82×10^{-5} M, respectively (Fig. 6)(Table 5).

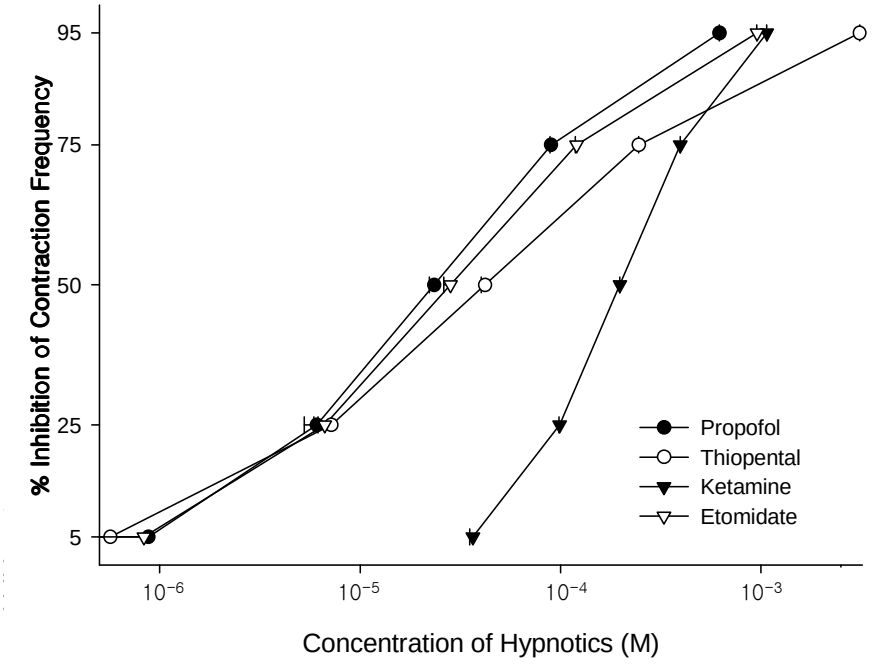

Fig. 6. Inhibitory effects of propofol, thiopental, ketamine, and etomidate on contraction frequency of rat uterine myometrium. Propofol and etomidate are the greatest and ketamine is the least in the frequency reduction of uterine contraction.

Table 5. Effective Concentrations (M) of Propofol, Thiopental, Ketamine, and Etomidate on Frequency of Contraction in the Uterine Smooth Muscle.

Drug	EC_5	EC_{25}	EC_{50}	EC_{75}	EC_{95}
Propofol	$8.78(0.52) \times 10^{-7}$	$6.08(0.82) \times 10^{-6}$	$2.34(1.24) \times 10^{-5}$	$8.97(1.08) \times 10^{-5}$	$6.21(1.23) \times 10^{-4}$
Thiopental	$5.67(0.34) \times 10^{-7}$	$7.19(1.02) \times 10^{-6}$	$4.20(1.89) \times 10^{-5}$	$2.46(0.78) \times 10^{-4}$	$3.11(1.32) \times 10^{-3}$
Ketamine	$3.65(1.24) \times 10^{-5}$	$9.90(0.78) \times 10^{-4}$	$1.98(1.06) \times 10^{-4}$	$3.96(1.54) \times 10^{-4}$	$1.07(2.01) \times 10^{-3}$
Etomidate	$8.35(0.70) \times 10^{-7}$	$6.67(0.79) \times 10^{-6}$	$2.82(2.11) \times 10^{-5}$	$1.20(1.65) \times 10^{-4}$	$9.55(1.05) \times 10^{-4}$

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

The frequency reduction of propofol was similar to that of etomidate and was greater than thiopental (1.8 times), or ketamine (8.5 times).

Discussion

Obstetric anesthesia continues to evolve through the manipulation of new drugs and the development of anesthetic techniques in order to improve patient outcome. Pregnant women have traditionally been therapeutic orphans. The use of new agents offer benefits to the parturients (e.g. propofol for emesis). Hypnotics are mainly used for induction of general anesthesia today. The commonly used hypnotics are propofol, thiopental, ketamine and etomidate. Therefore, particular consideration of these drugs is not only the influence on uterine contraction but also the safety of mother and fetus during pregnancy and labor.

Propofol is substituted derivatives of phenol with hypnotic properties resulted in the development of 2,6-diisopropofol. Since propofol was introduced clinically by Kay and Rolly for the first time in 1977,[25] it is a safe and effective anesthetic induction agent. It has excellent recovery characteristics,[7] such as rapid recovery with reliable amnestic properties and antiemetic effect. Propofol is used for induction and maintenance of anesthesia, as well as for sedation in and outside the operating room. It was reported that hypotension, caused by a direct vasodilatory effect of propofol, can cause a decrease in uteroplacental blood flow resulting in fetal distress.[9] A significant reduction in uterine smooth muscle tone has been described, but only at concentrations much higher than those that are commonly used in clinical practice.[2] Propofol has been also reported to be safe for fetus as an induction agent for cesarean section.[26] Perioperative blood loss is not increased with the use of propofol.[1,26] Transplacental passage of propofol is rapid because it is a lipid-soluble, large unionized drug with low molecular weight. When pregnant women were given a bolus induction of propofol 2.0 mg/kg for elective cesarean section, the maternal venous concentration of propofol ranged from 0.53 to 1.48 ug/ml,[7] which is 2.33 x 10^{-6} to 6.51 x 10^{-6} M. This plasma concentration is 4.66 x 10^{-8} to 1.30 x 10^{-7} M propofol in vitro, because 98 % of propofol given intravenously is bound to plasma protein.[27] Therefore propofol in concentration that is commonly used clinically would not decrease uterine contraction. It has been described that propofol has relaxant effects on vascular,[9,10] and tracheal,[11] and uterine[2] smooth muscles. In this study, as the concentration of propofol was increased during spontaneous uterine

contractions, resting tension, active tension, and frequency of contraction were reduced in a concentration-dependent manner. It has been suggested that the relaxant effects of propofol may be caused by decreasing the concentration of intracellular free Ca^{2+}($[Ca^{2+}]_i$) without affecting agonist-receptor binding.[28] The inhibitory effect of propofol on $[Ca^{2+}]_i$ might be mediated both by a decrease in intracellular inositol 1, 4, 5-triphosphate ($[IP_3]_i$) and by inhibition of voltage-dependent Ca^{2+} channel activity.

Thiopental is a barbituric-acid derivative with hypnotic and anticonvulsive properties. It has been used the most freqently for induction of general anesthesia for cesarean section because of its rapid, smooth and predictable action. However, it can also cause a decrease in maternal arterial blood pressure, and this, together with the rapid placental transfer, may induce some depression of the fetus. But, Valtonen et al[29] investigated the comparison of propofol and thiopentone for induction of anesthesia for elective caesarean section, and discovered that there was no significant neonatal depression as assessed by Apgar score and blood analyses. Despite a rapid placental transfer and incompletely developed hepatic metabolic capacity in neonates, Apgar scores and neurobehavioral scores after elective cesarean section at term were reported satisfactory.[13-15] Thiopental caused relaxation of tracheal smooth muscle in the guinea pig[30], dog and cats,[31] and rats.[11] In addition, it antagonized the ability of acetylcholine to cause contraction of the tracheal smooth muscle and produced dose-related reductions in total lung resistance induced by vagal stimulation. On the other hand, thiopental caused a dose-dependent constriction of guinea pig trachea.[40] This effect is mediated by constrictor prostaglandins and thromboxane. But it was known that thiopental has an relaxant effect of tracheal smooth muscle recently.[5,41] Yamakage et al[33] reported that thiopental inhibit the influx of Ca^{2+} through voltage-dependent Ca^{2+} channels in porcine tracheal amooth muscle cells. Although a smooth muscle relaxant effect of thiopental has also been observed in isolated tracheal smooth muscle,[11,20,31,38] the effect of thiopental on uterine smooth muscle is unknown. In this study, as the concentration of thiopental was increased during spontaneous contration, resting tension, active tension and frequency of contraction were reduced in a concentration-dependent manner. When thiopental is given intravenously to the mother (4-5 ㎎/㎏), there is no significant clinical effect on the outcome

of the newborn and mother. When thiopental 4.53(SD 0.65) ㎎/㎏ was given intravenously to induce sleep, the maternal venous plasma level was 4.67 ㎎/L,[34] which is 2.62×10^{-5} M. This plasma concentration is comparable to 5.24×10^{-6} M in vitro, because 80% of thiopental given intravenously is bound to plasma protein. This concentration had mild relaxant effect on the uterine contraction in this study. The degradation of thiopental involves hepatic oxidation into inactive water-soluble metabolites. Therefore, thiopental in concentration that is commonly used clinically would not decrease uterine contraction.

Ketamine is a phencyclidine derivative. It consists of two stereoisomers: S-ketamine and R-ketamine. The S-(+)-isomer is more potent and is associated with fewer side effects. S-ketamine is now available for clinical use. Ketamine is more lipid soluble (5 to 10 times) and less protein bound (6 times) than thiopental.[35] The drug is metabolized by hepatic microsomal enzymes, and some of the metabolites (norketamine) have anesthetic actions.[36] Ketamine has been used in obstetric patients because of its rapid induction of anesthesia with profound analgesia.[16] It does not usually depress the cardiovascular and respiratory system.[17] Ketamine elicits an increase in maternal blood flow and heart rate, due to central stimulation of the sympathetic nervous system.[12] Therefore, it is contraindicated in obstetric patients who have hypertension. This makes it especially suitable for patients with asthma or hypotension, such as in cesarean section with major blood loss before surgery (e.g. placental abruption). Ketamine is also a potent bronchodilator.[18,19] It inhibits smooth muscle contraction of the airway. This bronchodilating effect of ketamine may be achieved directly by relaxing smooth muscle cells of the airway and indirectly by blocking airway reflexes.[37] For example, ketamine has been shown both to inhibit the excitability of the vagus nerve and to relax airway smooth muscle.[37] Ketamine may be suitable for patients with asthma. It has been reported that keamine may be related to increase both uterine tone as well as the frequency of uterine contractions.[3,4] These results agreed with my results of low concentrations (10^{-7} to 10^{-5} M). The stimulation effect of ketamine on the uterine contraction is unknown. But, as ketamine increases catecholamines by stimulating sympathetic nervous system,[12] uterine contraction may be mediated by the stimulation of alpha-receptor. However, Kim[3] also reported

that "ketamine exerted a stimulatory action on the uterus under the influence of pregesterone. This progesterone-dependent uterine stimulatory action of ketamine not concerned with agrenergic and cholinergic mechanisms but appears to be a direct action on the uterine muscle." It was also reported that ketamine inhibits the uterine contration in a concentration-dependent manner.[5,6] These results agreed with my results of high concentrations (10^{-4} to 10^{-3} M). The direct relaxant effect of ketamine could be related to the blockade of calcium translocation processes (intracellular Ca^{2+} influx).[5,6] Yamakage et al[33] reported that ketamine inhibits the influx of Ca^{2+} through voltage-dependent Ca^{2+} channels in porcine tracheal smooth muscle cells. In this study, Ketamine showed dual effects (contraction in low concentrations and relaxation in high concentrations) in the rat uterine muscle. Placental transfer of ketamine is rapid because it is lipid soluble and less protein bound. But, at high doses, low Apgar scores and neonatal muscular hypertonicity have been described.[38] Little et al[39] also reported that newborn infant is not unduly depressed if the dose is kept below a priming dose of 1.5 mg/kg and the plasma concentration of ketamine is 4.2 x 10^{-6} to 6.7 x 10^{-6} M following single injection of ketamine (2.2 mg/kg). Twelve % of ketamine given intravenously is bound to plasma protein. So, this plasma concentration is comparable to 3.7 x 10^{-6} to 5.9 x 10^{-6} M ketamine in vitro. Plasma concentration at this level increased the uterine contraction in this study. Galloon[40] reported that the intravenous injection of ketamine (2.2 mg/kg) produces a significant increase in uterine tonus and activity, with the intensity of the contractions increasing more than the frequency. Therefore, ketamine in concentration that is commonly used clinically stimulates the uterine contraction.[39]

Etomidate is an imidazole derivative that is widely used as an anesthetic induction agent for hemodynamically unstable patients because it produces few cardiopulmonary side effects and has a very stable profile[21,22]. However, it is associated with several disturbing side effects,[41-44] such as pain on injection, postoperative nausea and vomiting, electroencephalic activation, adrenal suppression, and myoclonus. Etomidate is not commonly used in obstetric anesthesia, because it causes adrenocortical suppression[41,42] which has also been shown to occur in the neonate after elective cesarean section.[45] But, etomidate is a good IV induction drug in the obstetric patients with

unstable cardiac disease. Hypotension during anesthetic induction with IV hypnotics is often attributed, at least in part, to myocardial deppression. During clinical use, etomidate is believed to be free of negative inotropic actions on the myocardium.[46] Brussel et al.[47] showed that the hemodynamic effects of a standard induction dose of etomidate, 0.3 mg/kg, were negligible. The onset of anesthesia after a routine induction dose of 0.3 mg/kg etomidate is rapid and equivalent to that obtained with an induction dose of thiopental.[23] The plasma level of etomidate is 300 to 500 ng/ml, which is the concentration necessary for hypnosis.[48] Etomidate caused relaxation of the tracheal smooth muscle in rat,[24] the porcine coronary artery,[49] and rat thoracic aorta.[50] This effect is mediated via inhibition of the calcium influx through the voltage-operated calcium channel.[24,49] In addition, it is related with cyclooxygenase inhibition and guanylate cyclase activation.[50] But, the effect of etomidate on uterine smooth muscle is unknown. In this study, as the concenteration of etomidate was increased during spontaneous contraction, resting tension, active tension, and frequency of contraction were reduced in a concentration-dependent manner. When the standard induction dose of etomidate (0.3 mg/kg) is given intravenously to induce sleep, the plasma level of etomidate is 300 to 500 ng/ml,[48] which is 1.2×10^{-6} to 2.0×10^{-6} M. Etomidate is metabolized in the liver primarily by ester hydrolysis and 75% of etomidate given intravenously is bound to plasma protein.[51] So, the etomidate concentration of 1.2×10^{-6} to 2.0×10^{-6} M in vivo would be comparable to 3.0×10^{-7} to 5.0×10^{-7} M etomidate in vitro. Plasma concentration at this level affected slightly uterine contraction (less than 5% relaxation) in this study. Therefore, etomidate in concentration that is commonly used clinically would slightly decrease uterine contraction.

In conclusion, propofol, thiopental, and etomidate at concentrations ranging from 10^{-7} to 10^{-3} M reduces the contraction of uterine smooth muscle obtained from non-pregnant rats in a concentration-dependent manner. But ketamine at concentrations ranging from 10^{-7} to 10^{-5} M increased the spontaneous uterine contraction but ketamine at concentrations of 10^{-4} to 10^{-3} M reduced the contraction of uterine smooth muscle. Propofol had the greatest relaxant effects and ketamine had the least effect on isolated rat uterine smooth muscle among these hypnotics. Propofol, thiopental, and etomidate have no significant effect on uterine smooth muscle contraction in

dose that is commonly used clinically. Extrapolation of our results to the clinical situation must be viewed with caution because of possible species differences, in vivo/vitro differences. Nonetheless I suggest that ketamine may be a suitable obstetric hypnotic agent for hypovolemic parturients (eg. placenta previa) and propofol may be a useful hypnotic agent for uterine relaxation during pregnancy.6 Further study on the pregnant rats remains.

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