Effects of Ketamine, Propofol and Midazolam on Spontaneous Contractions of Isolated Pregnant Rat Myometrium

GEBE RAT MYOMETRİYUMUNDAKİ SPONTAN KONTRAKSİYONLAR ÜZERİNE KETAMİN, PROPOFOL VE MİDAZOLAM'IN ETKİLERİ

Bilge KARSLI*, Tijen KAYA**, Yusuf SARIOĞLU*

* Dept. of Anesthesiology and Reanimation, Medical School of Akdeniz University, Antalya,
** Dept. of Pharmacology, Medical School of Cumhuriyet University, Sivas, TURKEY

Summary

Emergent or elective surgical procedures under general anesthesia may be required during pregnancy for some patients. For this reason, effects of anesthetics on uterine contractions are important. General anesthesia is not limited to administration of inhalation agents, since induction and maintenance of anesthesia usually involve intravenous administration of different anesthetic agents. The effects of these agents on uterine contractions and bloodflow are vety important. The unexpected relaxation or contraction of myometrium can be harmful to fetus and continuing pregnancy. Our aim in this study is to investigate the effects of intravenous anesthetic agents on uterine contractions.

In this study, we examined the effects of ketamine, propofol and midazolam on isolated pregnant rat myometrium contractions. We observed that propofol, ketamine and midazolam 10-5- 10-4 M concentrations decreased spontaneous contractile activity in myometrial strips isolated from pregnant rats. There was statistically significant difference between the control group and all concentrations of propofol, ketamine and midazolam groups.

Key Words: Ketamine, Propofol, Midazolam, Myometrium

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Özet

Bazı hastalarda gebelik süreci içerisinde acil veya planlanmış cerrahi müdahale için genel anestezi gerekebilir. Bu nedenle anestezik ilaçların uterus kontraksiyönleri üzerine etkileri önemlidir. Genel anestezi ise inhalasyon anestezikleri ile sınırlı değildir, anestezi indüksiyonu ve idamesinde genellikle intravenöz olarak verilen ajanlar kullanılır. Bu ilaçların da uterus kontraksiyonları ve kan akımı üzerine etkileri önemlidir. Myometriumdaki beklenmedik kasılma ve gevşemeler gebeliğin devamı ve fetus için zararlı olabilir. Bu çalışmamızın amacı, intravenöz anestezik ajanların uterus kontraksiyonları üzerine etkilerini araştırmaktır.

Bizim çalışmamızda, ketamin, propofol ve midazolamın izole gebe rai myometriyumundaki kontraksiyonlar üzerine etkileri araştırıldı. Propofol, ketamin ve midazolamın gebe rat myometriyumundaki spontan kontraksiyonları 10-5-10-4 M konsantrasyonlarda azalttığını gözledik.

Anahtar Kelimeler: Ketamine, Propofol, Midazolam, Miyometriyum

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Ketamine, a phencyclidine derivative, is a short-acting intravenous anesthetic, which has been shown to produce a marked increase in arterial blood pressure, heart rate and cardiac output in man and several animal species. Ketamine can reduce the contractile response of the muscle by an effect on the central nervous system (1,2). Propofol (2,6 diisopropylphenol) is a rapidly acting intravenous anesthetic. Induction of anesthesia with intravenous propofol is often accompained by hypotension, which has been ascribed to a decrease in either systemic vascular resistance (1) or cardiac output (2) or both (3,4). Midazolam is a water-soluble benzodiazepine. It has been used for induction of anesthe-

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Correspondence: Bilge KARSLI
Yıldız Mah. 233.sok.
Ferda Kahraman Apt. D:5
Antalya, TURKEY

sia, but the main use of midazolam has been to produce sedation during local and regional anesthesia.

We have investigated, in vitro, the effect of clinically used doses of three intravenous anesthetics (ketamin, propofol and midazolam) on the electrically stimulated contractile activity of isolated smooth muscle from pregnant rats.

Materials and Methods

Tissue preperations. The pregnant Albino rats; 15 to 21 days (200 to 250 gm body weight, n=8) were cared according to the guideline of the Animal Care Center. Animals were killed by cervical subluxation. The uterine horns were rapidly excised and carefully cleaned of surrounding connective tissue and opened longitudinally along the mesenteric border. Fetuses of the late-stage pregnant rats were removed and non-uterine tissues were dissected away and discarded. We obtained four full-thickness myometrial muscle strips (approximately 4x10 mm length) from each animal. Longitudinal strips were incubated and mounted vertically in a 10 ml organ bath containing modified Krebs solution (composition in millimoles per liter: sodium chloride 125 mEq, potassium chloride 2.4 mEq, calcium chloride 1.8 mEq, magnesium chloride 0.5 mEq, sodium bicarbonate 23.9 mEq and glucose 11g/dl) in jacketed tissue baths aerated continuously with 95% oxygen and 5% carbon dioxide at 37 °C.

Measurement of contractile activity. Myometrial strips were mounted in an organ bath and connected to an isometric tension recording system. The myometrial strips were allowed to equilibrate at lg tension for 30 minutes before the addition of the experimental drug. The myometrial tension was recorded isometrically with a Grass FT03 force- displacement transducerand registered on a Grass79E polygraph (Grass, Quincy, Mass, USA). The recorder was calibrated to a scale that 1 g tension was represented as 1cm vertical displacement. The recorder paper speed was set at 5 mm/minute. Isometric forces were recorded continuously.

Three sets of experimental studies were performed. While performing each set of 3 experimental studies, we used four muscle strips obtained from each rat uterus. In the first set of studies, we evaluated the effects of ketamine at cumulative concentrations (10^{-5}-$3x10^{-4}$M) on spontaneous contractions in myometrium isolated from pregnant rats (n=8). In the second set of studies, we evaluated the effects of propofol at cumulative concentration (10^{-5}-10^{-4}M) on spontaneous contractions in myometrium isolated from pregnant rats (n=8). In the third set of studies, we evaluated the effects of midazolam at cumulative concentrations (3x10"^{5} M-10*^{4} M) on spontaneous contractions iri myometrium isolated from pregnant rats (n=8).

Drugs. Ketamine (Ketalar; Parke-Davis), Propofol (Diprivan; Zeneca) and midazolam (Dormicum; Roche) were used in the study. Drug containing solutions were dissolved in 0,9% NaCl and added to the bath in volumes of 50 ml at once. The solutions were prepared immediately before the experiment.

Data analysis. The characteristics of the contractions analyzed over 1000 second intervals immediately before and after the addition of drugs included frequency (number Per 1000 seconds), mean duration (second), and amplitude (grams) of each contraction, and integrated area under the contraction curve (representing contractile force over 1000 seconds) measured with a digitalized plotter. Data were presented as mean ± SE and were analyzed by analysis of variance and the Newman-Keuls test with $p<0,05$ considered statistically significant.

Results

Effect of ketamine on spontaneous contractions of isolated pregnant rat myometrium. Exposure to ketamine at cumulative concentrations (10"^{5}-$3x10^{-4}$M) decreased spontaneous contractile activity in myometrial strips isolated from pregnant rat (n=8 rats) (Figure 1). The greatest effect was detected on the amplitude and integrated area of contractions, there was statistically significant difference between control and all concentrations of ketamine (3x10"^{5}-3x10-^{4}M) (Figure 2). The frequency and duration of contractions changed with increasing concentrations of $1O^{-4}$ and $3x10^{-4}$ M (Figure 2).

Effect of propofol on spontaneous contractions of isolated pregnant rat myometrium. Exposure to propofol at cumulative concentrations (10^{-5} -10^{-4}M) decreased spontaneous contractile activity in myometrial strips isolated from pregnant rat (n=8) (Figure 3), with significant effect on the amplitude and integrated area of contractions.

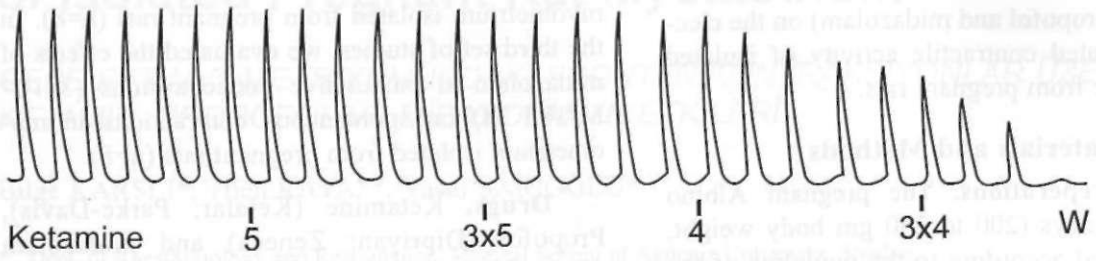

Figure 1. Ketamine decreased contractile activity in myometrial strips.

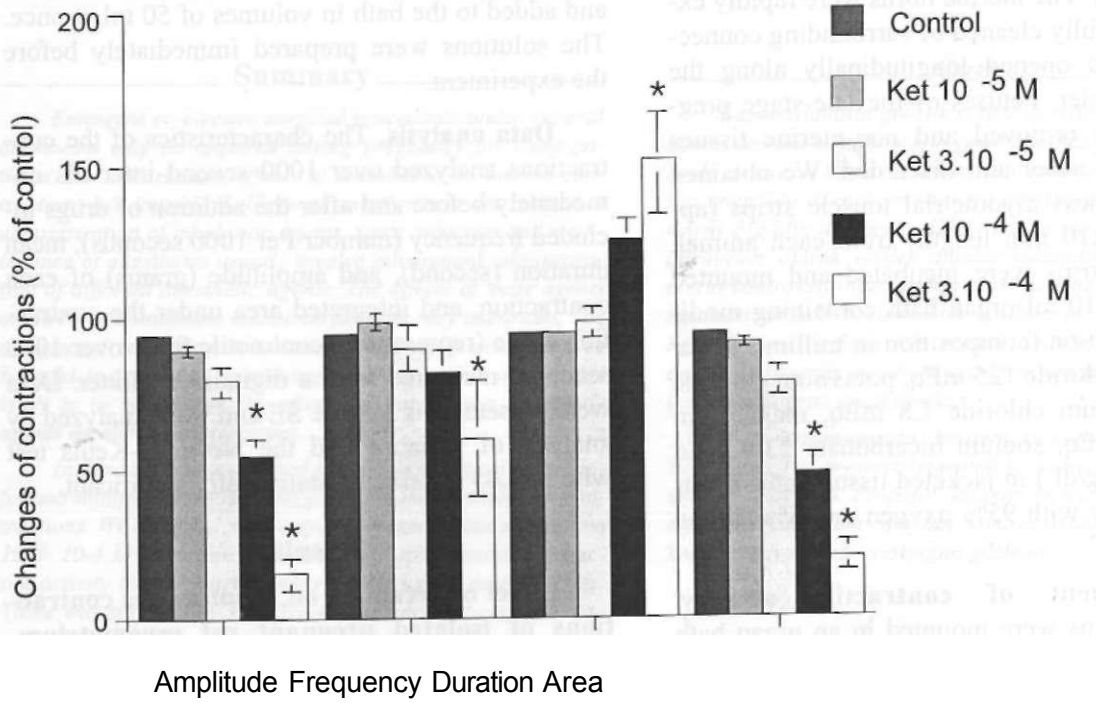

Figure 2. Effects of control and different concentrations of ketamine.

There was statistically significant difference between control and concentrations of propofol (10^{-5}-10^{-4}M) in the amplitude and integrated area of contractions (Figure 4). The frequency and duration of contractions changed with increasing concentrations of propofol, reaching statistical significance at a concentration of 10^{-4} M.

Effect of midazolam on spontaneous contractions of isolated pregnant rat myometrium. Midazolam at cumulative concentrations ($3x10^{-5}$ - 10^{-4} M) decreased spontaneous contractile activity in myometrial strips isolated from pregnant rat (Figure 5). The greatest effect was detected on the frequency and duration of contractions changed with increasing concentrations of midazolam, reaching statistical significance at a concentration of 10^{-4} M (Figure 6).

Discussion

The contractile response of smooth muscles to spasmogens can be divided into two components according to modification of the extracellular Ca^{2+} concentrations. The phasic component depends on the mobilization of Ca^{2+} from intracellular stores

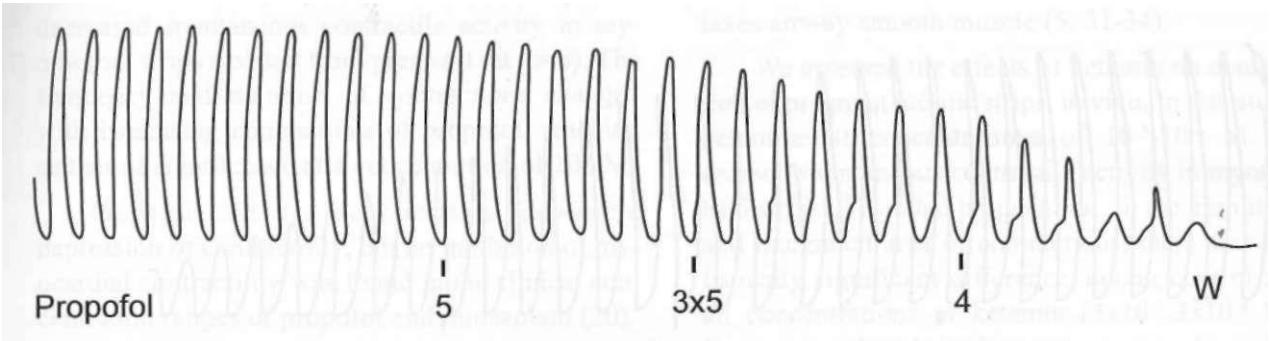

Figure 3. Propofol decreased contractile activity in myometrial strips.

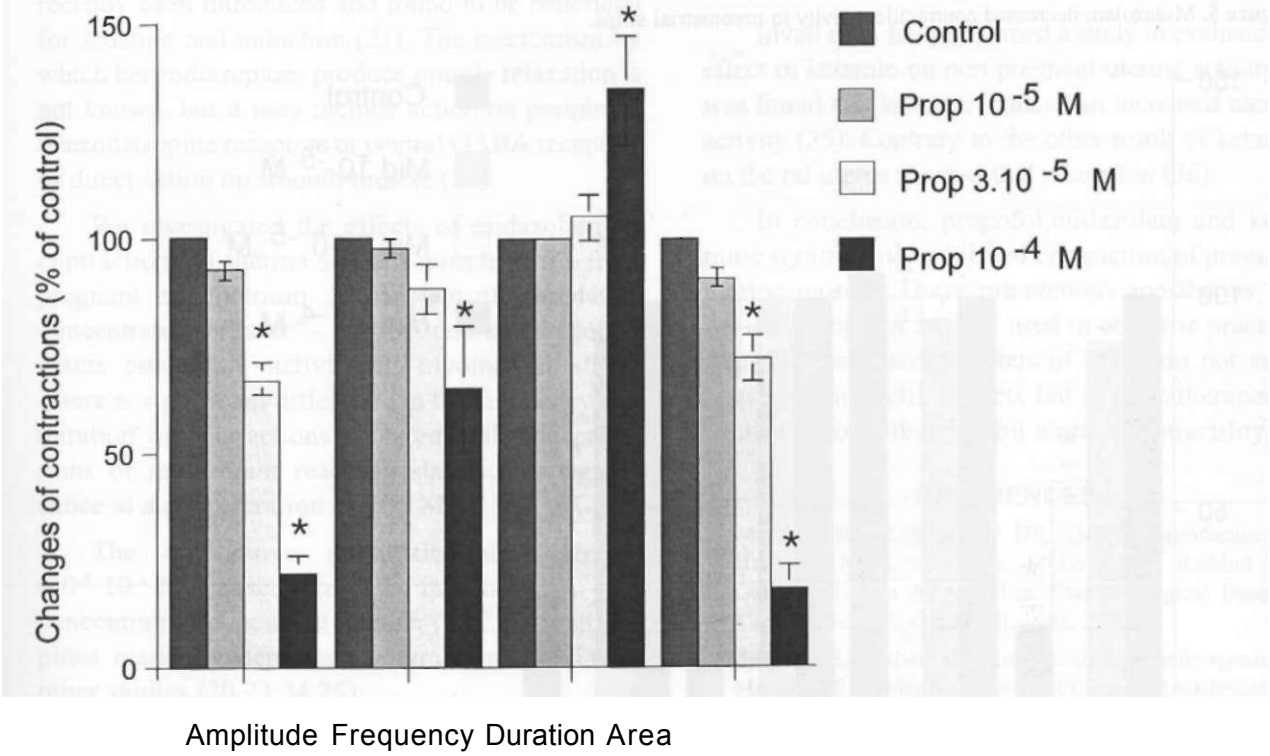

Figure 4. Effects of control and different concentrations of propofol.

where as the tonic component depends, to a large extent, on the influx of extracellular Ca^{2+} (5). The intracellular concentration of Ca^{2+} is thought to play an essential role in regulation of the contraction-relaxation cycle in uterine smooth muscle cells (6-8).

We have investigated the effect of intravenous anesthetic agents on contraction of myometrial strips isolated from pregnant rats.

Propofol, a relatively new agent, is being used increasingly for obstetric and non-obstetric surgical procedures (9-11). However, its effects on uterine blood flow and contractions are not well documented. Propofol is an alternative to thiopental as an intravenous induction agent for cesarean section (12). It has relaxant effects on vascular and other smooth muscle, the authors determined propofol in various types of smooth muscle in an isolated preperation (2,13-15).

Propofol is known to produce a decrease in blood pressure in man and animals, and it has been suggested that the hypotension may result from a direct vasodilator action on the veins and arterioles (1). Propofol caused concentration-dependent relaxation of vessel ring in vivo and in vitro (13,15).

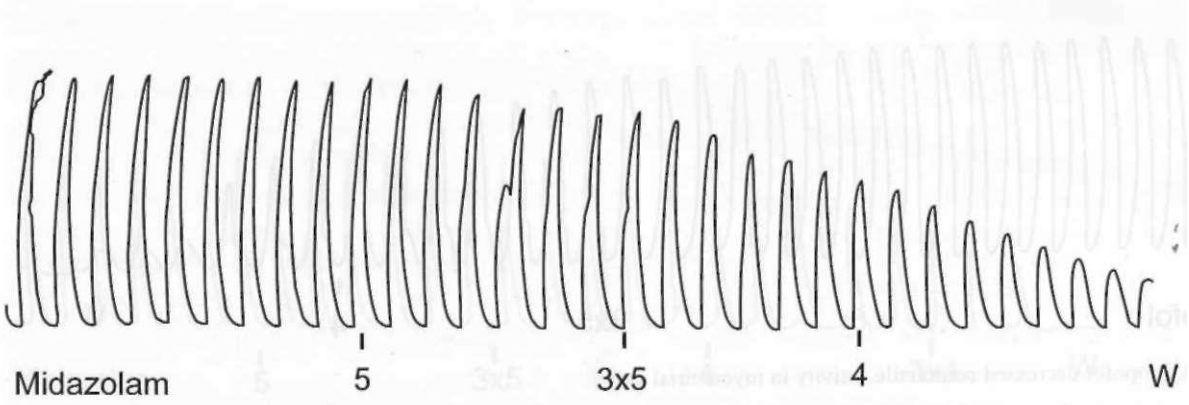

Figure 5. Midazolam decreased contractile activity in myometrial strips.

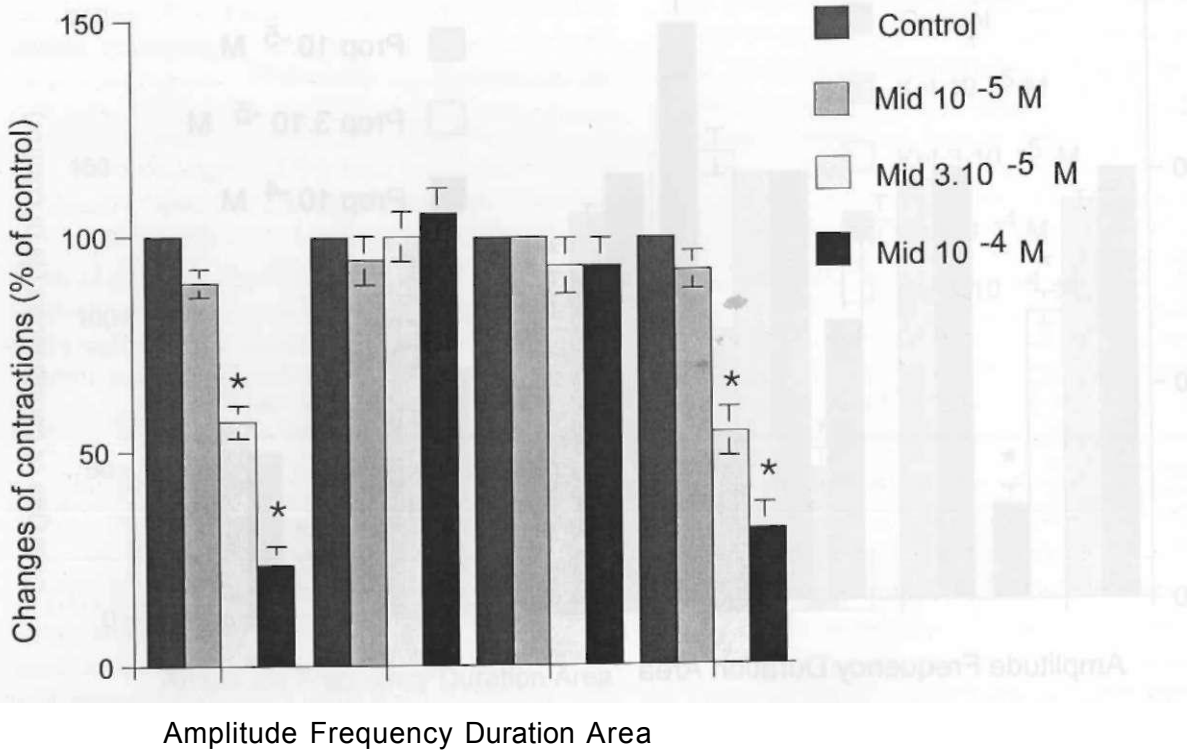

Figure 6. Effects of control and different concentrations of midazolam.

A study by Kaminati et al has showed that propofol has a more potent vasodilator effect on veins then arteries. (16). Propofol produced venodilatation in a concentration-dependent manner (10"M0^{-4}M) (16,17). However, Mimaroglu et al. demonstrated that clinically relevant concentrations of propofol (10-6M or less) has no direct vasodilator effect (18).

In this study, we examinated the effect of propofol on spontaneous contractions of isolated pregnant rat myometrium. In the present study, propofol concentrations of 10^{-5}-10^{-4} M decreased spontaneous contractile activity in myometrial strips isolated from pregnant rat. Similar to our results, Skin et al. have demonstrated that the propofol concentrations of 5.5x10~^{5} M reduced the active tension of pregnant human uterin smooth muscle (12). Contrary to the findings of these authors, Shibuya et al. reported that, low concentrations of propofol 10^{-5} M had no effect on contractile responses, but high doses above 10^{-4} M of propofol decreased contractions (19).

In our results, propofol (1OMCr^{4} M) exposure decreased spontaneous contractile activity in myometrial strips isolated from pregnant rat (n=8). The frequency and duration of contractions changed with increasing contractions of propofol, reaching statistical significance at a concentration of 1(H M.

Propofol caused a concentration -dependent depression of contractility, but no inhibition of myocardial contractility was found in the clinical concentration ranges of propofol and midazolam (20).

Midazolam, a water-soluble benzodiazepine has recently been introduced and found to be beneficial for sedation and induction (21). The mechanism by which benzodiazepines produce muscle relaxation is not known, but it may include action on peripheral benzodiazepine receptors or central GABA receptors or direct action on smooth muscle (22).

Wc investigated the effects of midazolam on contractions in uterine smooth muscle strips from pregnant myometrium. Midazolam at cumulative concentrations (3x10"^{5} - 10^{-4} M) decreased spontaneous contractile activity in myometrial strips. There is significant difference in the frequency and duration of contractions changed with concentrations of midazolam reaching statistically significance at a concentration of 10"^{4} M.

The cumulative application of midazolam (10~^{7}-10-^{4} M) caused decreases in contraction in a concentration-dependent manner (23). Benzodiazepines markedly depressed contractions similar to other studies (20,22,24,25).

Ketamine is a dissociative anesthetic (26,27). It has direct relaxant effect on isolated smooth muscle (28). Ketamine inhibits the contractions of smooth muscles by interfering with the influx of extracellular Ca^{2+} (5).

Ketamine was found to inhibit the contractile responses of ileum in a concentration-dependent manner. Ketamine was effective at concentrations between 10^{-4}- 10^{-3} M and depressed the contractions of ileum (26, 29, 30).

The effect of ketamine on isolated veins and arteries were studied. Ketamine acts directly on vascular smooth muscle causing relaxation. Ketamine in concentrations above 5x10^{-6} M or 2x10"^{5} M caused significant relaxation in a dose-dependent manner (27-29).

Ketamine is a potent bronchodilator which relaxes airway smooth muscle (5, 31-34).

We assessed the effects of ketamin on contraction of pregnant uterine strips, in vivo. In this study, ketamine at concentrations of 1O-MO^{4} M decreased spontaneous contractile activity in myometrial strips of isolated pregnant rat. In the amplitude and integrated area of contractions, there was statistically significant difference among control and all concentrations of ketamin (3x10~^{5}-3x10-^{4} M). Ketamin produced similar concentration-dependent relaxations in the pregnant myometrium (5).

Idvall et al. has performed a study to evaluate the effect of ketamin on non-pregnant uterine activity. It was found that ketamin induced an increased uterine activity (35). Contrary to the other result of ketamin on the rat uterus showed that relaxation (36).

In conclusion; propofol,midazolam and ketamine significantly inhibited contraction of pregnant uterine muscle. These intravenous anesthetics, especially propofol are still used in obstetric practice. That clinical concentrations of drugs do not exert negative contractile effects but at supratherapeutic concentrations, they inhibit uterine contractility.

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