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Research Article

The Effect of Rocuronium and Sugammadex on Progesterone Levels in Pregnant Rabbits Under General Anesthesia [1] [2]

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Abstract

The purpose of this study was to investigate the effect of rocuronium and sugammadex on progesterone (P4) levels in pregnant rabbits under general anesthesia. Twenty-one pregnant New Zealand rabbits were used in the study. After the rabbits were divided into three groups of three (Control, Group I and Group II), each animal was given 0.5 mg/kg midazolam and 6 mg/kg propofol and then put under general anesthesia with sevoflurane on the 21st day of pregnancy. No procedure was performed on the control group apart from anesthesia. Rocuronium was administered to GI at the onset of anesthesia, and in GII, sugammadex was administered 60 min after general anesthesia + rocuronium. All of the rabbits were monitored during the anesthesia procedure. A sample of venous blood was taken and biochemically analyzed to test P4 levels. The administration of rocuronium was determined to have caused an increase in the serum progesterone level in all recorded min. Sugammadex was found to cause a quantitative decrease in the level of progesterone. In conclusion, it was found out that rocuronium and sugammadex administration did not have a negative effect on progesterone levels in pregnant rabbits receiving general anesthesia.

Keywords: *Pregnant, Progesterone level, Rabbit, Sugammadex, Rocuronium*

Genel Anestezi Altındaki Gebe Tavşanlarda Rocuronium ve Sugammadex'in Progesteron Düzeyine Etkisi

Öz

Sunulan çalışmada, genel anestezi uygulanan gebe tavşanlarda, rocuronium ve sugammadex uygulamasının progesteron düzeyine etkisinin saptanması amaçlandı. Çalışmada, 21 adet gebe Yeni Zelanda tavşanı kullanıldı. Her grupta 7 tavşan olacak şekilde üç gruba ayrıldı (Kontrol, Grup I, Grup II). Gebeliğin 21. gününde bulunan tüm tavşanlara 0.5 mg/kg midazolam ve 6 mg/kg propofol verildi. Daha sonra Sevofluran ile genel anesteziye alındı. Kontrol (C; n=7) grubundaki tavşanlar ise yalnızca genel anesteziye alındı. Grup I'deki tavşanlara genel anestezi başladığında roküronyum verildi. Grup II'de yer alan tavşanlara ise, genel anestezi ve rocuronium uygulamasından 60 dk sonra sugammadex verildi. Tüm tavşanlar genel anestezi süresince monitorize edildi. Tüm tavşanlardan venöz kan örneği alındı ve biyokimyasal olarak progesteron düzeyi analiz edildi. Rocuronium uygulamasının serum progesteron düzeyini tüm kaydedilen dakikalarda artışa neden olduğu belirlendi. Sugammadex uygulamasının ise, progesteron düzeyinde sayısal bir azalmaya neden olduğu belirlendi. Sonuç olarak, genel anesteziye alınan gebe tavşanlarda, rocuronium ve sugammadex uygulamasının progesteron düzeyi üzerine olumsuz bir etkisinin olmadığı saptandı.

Anahtar sözcükler: *Gebe, Progesteron düzeyi, Tavşan, Sugammadex, Rocuronium*

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INTRODUCTION

In addition to events that occur in pregnancy like appendicitis, ovarian diseases and trauma [1], surgical operations are performed in intensive care units [2] for various indications. These surgical operations are usually performed under general anesthesia.

Rocuronium is a one of the steroid-type non-depolarizing neuromuscular blocker muscle relaxants with a short duration of action [3]. Sugammadex, on the other hand, is a new generation reversal agent used to terminate the effect of neuromuscular blockers (vercuronium and rocuronium). The mechanism of action is that it creates a complex with the circulating muscle relaxant at the nerve juncture to terminate its effect [4]. The sugammadex-rocuronium interaction reduces the amount of free rocuronium in plasma, thus altering rocuronium in plasma by significantly reducing the levels of rocuronium at the neuromuscular juncture. This ensures that muscle activity resumes because it quickly releases the acetylcholine receptors [5]. However, there have not been enough studies conducted on rocuronium and/or sugammadex's effect on pregnancy [6].

Progesterone prevents the endometrium from breaking down in pregnancy and suppresses the stimulating effect of estrogen on uterine contractions to ensure that pregnancy continues [7]. The decline in P4 levels causes the relaxing effect on the uterus to disappear, thus terminating pregnancy [8,9].

The aim of this study was to demonstrate how the use of rocuronium, an effective neuromuscular blocker, and its antagonist sugammadex in pregnant rabbits given general anesthesia affects P4 levels at different times in pregnancy.

MATERIAL and METHODS

Ethics Approval

This study was conducted after obtaining approval from the Kafkas University Local Experimental Animals Ethics Committee (Approval no: KAÜ-HADYEK: 2016-096).

Animals

This study used twenty-one pregnant New Zealand rabbits with an average weight of 2.7-3.3 kg obtained from the Fırat University Experimental Research Center. The veterinarian was delivered with a referral report. The rabbits were transported in a single cage and vented for 10 min per hour by transit minibus. Rabbits that were bred on the same day were included in the study, and the day of mating was considered day 0. Rabbits were housed in individual cages where they received 12 h of sunlight and 12 h of darkness. Rabbits were fed *ad-libitum* with a daily average of 250 g of pellet feed and 100 mL of water.

Ultrasonography Examination

Pregnancy was confirmed with an ultrasound examination immediately before anesthesia was administered 21 days after mating. A maximum of four at least one fetus was detected in the ultrasound examination of rabbits The rabbits were shaved up to their rib cage and a trans-abdominal examination was performed on the abdominal region of the rabbits as they were held on their back. The ultrasound device used for the ultrasonography procedure was a B Mode real-time device with a 7.5 mHz linear probe (DRAMINSKI iScan, Poland).

Anesthesia Procedure

All of the rabbits were sedated with 0.5 mg/kg midazolam (Zolamid®, 5 mg/5 mL, Defarma Pharmaceutical Industry and Trade Company., Turkey). Propofol İntravenous (IV) (Propofol-Lipuro 10 mg/mL 20 mL, Braun Pharmaceuticals, Germany) was administered slowly at a dose of 6 mg/kg. Anesthesia maintenance was started in the first five min with a mixture of sevoflurane (AbbVie Pharmaceutical Industry and Trade Company, Turkey) 3-4% + oxygen 4 L/min. Because the surgical procedure would not be performed five min later, inhalation anesthesia was reduced and continued with a mixture of sevoflurane 2% + oxygen 4 L/min. All the rabbits were provided with respiration support via ventilation mask. Spontaneous breathing was blocked in the group, which had been given rocuronium, due to the medication. Breathing was administered in head extension via mask ventilation. No respiratory arrest or a complication occurred in any of the groups.

Sevoflurane was cut off sixty min later. All of the rabbits were monitored prior to anesthesia 0 and at 5, 30, 60 and 90 min after the onset of anesthesia to measure physiological parameters. Furthermore, venous blood was collected from the marginal ear vein at each of these time intervals.

Experimental Groups

The anesthesia procedures were performed on pregnant rabbits 21 day after mating.

Control Group: The rabbits in the control (C: n=7) group were only given general anesthesia.

Group I: The rabbits in group 1 (GI: n=7) were given rocuronium (Esmeron®, 50 mg/5 mL, Merck Sharpoo Dohme (MSD) Pharmaceuticals Ltd., Germany) at a intravenous dose of 0.6 mg/kg.

Group II: Unlike the rabbits in Group I, the rabbits in this group were given sugammadex (Bridion® 200 mg/2 mL, Merck Sharpoo Dohme (MSD) Pharmaceuticals Ltd., The Netherlands) at the 60th min mark via IV.

Measurements

Pulse (P), systolic (SAP), diastolic (DAP) and median artery pressure (MAP), oxygen saturation (SPO_2), respiration (R)

and body temperature (T) were monitored using a multi-parametric monitor (Veteriner Monitör, MMED6000DP S6-V). This parameters were recorded for all rabbits at 0, 5, 30, 60 and 90 min.

In Group I and Group II, the Train of Four (TOF) values for the rabbits (TOF time to zero and TOF time to return to 100) were recorded. Firstly the hair on the foreleg of the rabbit was shaved. Since the weight of the rabbit was equal to a baby's, two pediatric electrodes were placed on the ulnar nerve trace of the foreleg. TOF device was switched to pediatric mode and the device's connection clips were mounted on the electrodes. Heat probe was placed on the first phalanges of the extremity with electrodes. Then, transducer was assembled on the phalanges with heat probe. Induction agents were injected as the device was turned on. Finally, electrical stimulation was applied at 10 sec intervals on pediatric mode and TOF values on the device were monitored and recorded.

At the same time that the vital signs were checked, blood was collected from the marginal ear vein with a yellow intravenous catheter and stored in an eppedorf tube. These samples were centrifuged at 1200 rpm for 10 min and stored at -20°C until the tests were performed. The P4 levels were determined using the Rabbit Progesterone ELISA (ABIN365369, Antibodyonline, USA) kit.

Statistical Analysis

Statistical analyses were performed using the SPSS® (SPSS 20, IL, USA) software program. The data was analyzed with the Shapiro Wilk normality test. Paired comparisons were examined with the Mann Whitney U test. The internal differences on day 21 of pregnancy were established with Friedman's test. The results were analyzed as mean ±S.D. A P value of <0.05 was considered statistically significant.

RESULTS

Signs of sedation were observed in all of the individuals given midazolam, and the animals were then given propofol for induction, followed by problem-free general anesthesia for 60 min with sevoflurane.

On day 21 after mating, there was no statistically significant difference among the groups in terms of (P/min, SAP/mmHg, DAP/mmHg, MAP/mmHg) and (sPO_2/%) values (P>0.05).

On day 21 of pregnancy, respiratory values of control group at the 5th, 30th and 60th min were found out to be significantly lower than those of Group II (P<0.05). Respiratory values of both the Control Group and Group II were also significantly lower at the 90th min than they were at the 5th, 30th and 60th min (P<0.05) *(Table 1)*.

There was a statistically significantly difference in body temperature between the control group and Group I on day 21 of pregnancy (P<0.05). There was a statistically significant difference within the control group between min 5 and 60 (P<0.05). There was a statistically significant difference within Group I between baseline and 60 min and 0 and 5 min (P<0.05) *(Table 1)*.

In Group I, it was observed that TOF went down to zero approximately 45.4 sec after administering rocuronium. In Group II, TOF went down to zero 43.2 sec after the same process and it took TOF an average of 73.6 sec following sugammadex administration to reach 100%.

P4 levels (ng/mL) at 60 and 90 min in Group I were significantly higher than in Group II (P<0.05). Although there was a statistically significant difference in Group I between 0 and 5 min with 30 and 60 min (P<0.05), in Group II, P4 levels at 30 min were significantly higher than at 60 and 90 min (P<0.05) *(Table 2)*. None of the groups in the study experienced abortus, early birth or still birth. The births took place when due. Each rabbit delivered 4 to 6 babies.

DISCUSSION

It is a known fact that the rate of non-obstetrical operations in pregnancy is quite high [10]. Anaesthesia means, loss of sensation in the entire body or any part of the body [11]. Modern anesthesia methods are used in many of the stated operations. One of the most important aspects of modern anesthesia methods is the use of neuromuscular blocker agents. These agents create better intubation conditions by preventing voluntary and/or reflexive muscle movements. As a result, muscle relaxation sufficient for the operation is achieved using fewer less anesthetic. If the neuromuscular junction does not adequately recover after anesthesia, post-operative pulmonary complications may develop, and mortality rates can rise [10]. Therefore, sugammadex, a neuromuscular blocker antagonist has been used in recent years to eliminate residual muscle relaxation [12].

It has been established that the TOF ratio, which is a neuromuscular recovery parameter in the adductor pollicis muscle, must be higher than 0.90 to lower the risk of aspiration after intubation and to avoid postoperative atelectasis and pneumonia [13,14]. However, Eriksson et al.[14] demonstrated that upper esophageal sphincter tonus decreased noticeably in 14 conscious patients when the TOF ratio was less than 0.90, and that muscle coordination also decreased when the TOF ratio was less than 0.60. Studies with humans found that it took 70 sec for TOF to reach 80% after administering sugammadex 2 mg/kg to reverse neuromuscular block induced with rocuronium (0.5 mg/kg) [15]. A study conducted on rabbits found that it took an average of 123 sec for TOF to reach 90% after administration of sugammadex 2 mg/kg to reverse neuromuscular block induced with rocuronium (0.6 mg/kg) [16]. It has been determined that TOF was 100% after approximately 73.6 sec following the administration of

Table 1. *Values for parameters measured on day 21 after mating*

Groups	Values Measured	Time					Statistical Measurements
		0th min.	5th min.	30th min.	60th min.	90th min.	
		Mean.±S.D.	Mean.±S.D.	Mean.±S.D.	Mean.±S.D.	Mean.±S.D.	P[b]
Control	P (min)	242.57±39.93	228±38.39	254±23.58	232.86±26.67	256.29±16.72	ns
	SAP (mmHg)	157.57±45.85	145.86±36.07	179.57±46.72	129±7.85	152.57±30.66	ns
	DAP (mmHg)	130.86±48.21	143.71±51.57	107.86±41.25	84.57±12.58	124±36.31	ns
	MAP (mmHg)	137.57±45.37	154.57±47.73	126.86±39.77	99.71±12.49	132.71±30.96	ns
	sPO_2 (%)	93.43±2.99	94.14±3.8	95.71±3.25	96.14±2.48	94.86±3.13	ns
	R (min)	18.86±4.56[a]	29.57±8.18[a]	31.86±6.41[a]	32.29±7.13[abc]	15.57±3.41[b]	a:b:0.000
	T (°C)	38.13±0.48[abx]	38.36±0.39[a]	37.83±0.56[ab]	37.66±0.59[b]	37.81±0.38[ab]	a:b:0.018
Group I	P (min)	258.29±31.9	248±25.92	248.57±20.15	241.86±8.51	237.57±27.64	ns
	SAP (mmHg)	144.86±23.86	154±36.1	152.14±25.63	134±27.17	157.14±23.41	ns
	DAP (mmHg)	120.29±29.49	112.86±37.48	115.43±48.17	88.71±34.09	124.43±29.63	ns
	MAP (mmHg)	128.57±22.11	125.57±30.22	130.29±46.95	103.14±32.06	133±26.2	ns
	sPO_2 (%)	95.71±2.29	96±2.94	95.71±2.69	95.86±2.61	94.43±2.76	ns
	R (min)	25±10.5	35.71±8.4[xy]	33.6±6.8[xy]	34.2±7.69[xy]	18.29±8.06	ns
	T (°C)	38.87±0.39[ay]	38.66±0.99[a]	38.36±0.57[ab]	37.94±0.53[b]	38.01±0.61[ab]	a:b:0.002
Group II	P (min)	250.86±16.07	264±31.3	239.71±17.17	230.71±11.57	261.86±36.29	ns
	SAP (mmHg)	123.43±19.05	147.43±22.31	155.71±31.53	131.43±22.91	161±35.57	ns
	DAP (mmHg)	100.86±16.47	110.71±43.34	105.86±25.96	94.86±31	134.14±36.24	ns
	MAP (mmHg)	112.57±18.95	129±34.18	105.29±47.11	105.29±28.34	138.86±35.8	ns
	sPO_2 (%)	95±1.63	94.71±1.5	94.14±2.73	95.86±2.67	93.14±2.48	ns
	R (min)	23.71±15.68[a]	43.14±6.6[ay]	41.71±0.49[a]	41.43±2.82[a]	14.14±3.72[b]	a:b:0.002
	T (°C)	38.56±0.49	38.63±0.83	38.5±0.76	38.31±0.6	38.3±0.43	ns
P[a]		x:y:0.027 (T)	x:y:0.043	x:y:0.029	x:y:0.041	ns	ns

P[a]: *Refers to comparisons between groups;* ***P[b]:*** *Refers to comparisons within groups. Pulse (P), Systolic Arterial Pressure (SAP), Diastolic Arterial Pressure (DAP), Median Arterial Pressure (MAP), Saturation (SPO_2), Respiratory Rate (R), Body Temperature/Centigrade degree (T/°C);* [a,b,c] *Refers to the statistical difference on each row;* ***ns:*** *non significant*

Table 2. *Distribution of progesterone levels on day 21 after mating*

Groups	Time					P
	0 min.	5th min.	30th min.	60th min.	90th min.	
	Mean.±S.D. (ng /mL)	Mean.±S.D. (ng /mL)	Mean.±S.D. (ng /mL)	Mean.±S.D. (ng /mL)	Mean.±S.D. (ng/mL)	
Control	5.77±0.17	5.72±0.36	5.76±0.38[a]	5.74±0.33[a]	5.79±0.23[a]	ns
Group I	5.51±0.14[x]	5.67±0.2[x]	6.71±0.32[by]	6.67±0.33[aby]	6.64±0.22[abxy]	x:y:0.001
Group II	5.66±0.37[xy]	5.61±0.19[xy]	6.59±0.29[bx]	4.62±0.23[acy]	4.59±0.2[acy]	x:y: 0.001
P	ns	ns	a:b: 0.003	b:c:0.001	b:c: 0.001	ns

[a,b,c] *Refers to the statistical difference in each column (P=0.001);* [x,y] *Refers to the statistical difference on each row (P=0.001);* ***ns:*** *non significant*

sugammadex (2 mg/kg), which was used in the process of reversing the neuromuscular block induced with rocuronium in Group II. It is considered that the fact that it takes less time for TOF to get to 100% might correlate with the dose of rocuronium.

All animal studies have shown that sugammadex effectively antagonizes the neuromuscular blockage caused by rocuronium without having any significant effect on arterial blood pressure or heart rate [5,17-19]. One study found that systolic, diastolic and mean arterial pressures and heart

rate were lower in the sugammadex group than in the neostigmine group, and the difference was statistically significant [20]. Our study did not find significant differences within groups with regard to pulse and systolic or diastolic arterial pressures on day 21 after mating. This suggests that rocuronium and sugammadex do not affect these parameters. The differences observed in parameters such as median arterial pressure, sPO_2, respiration values and body temperature are thought to be associated with changes expected in anesthesia.

It has been shown that the use of sugammadex (4 mg/kg) for contraceptive purposes in women reduces the amount of P4 by 34% and reduces its efficacy [21]. Progesterone is very important to pregnancy and continuation of pregnancy [8,9]. It ensures that desidual tissues develop, and it facilitates implantation following fertilization. Furthermore, it stimulates uterine growth and prevents the activity of factors that cause myometrial contractions [22]. If there is a significant decline in P4 levels, the pregnancy will be terminated [8,9]. Progesterone levels in rabbits gradually increase starting three days after mating. They peak in the middle of pregnancy and slowly decline towards the end [23,24]. Different results have been reported for P4 levels during pregnancy in rabbits. A study that investigated P4 levels in rabbits using the radioimmunoassay method found that the average was 5.3 ng/mL 3 days after mating and an average of 17-19 ng/mL on days 12-15 [23], but another study which used the chemiluminescent enzyme immunoassay method found P4 was 8.6 ng/mL on day six after mating, 15 ng/mL on day thirteen, 9.8 ng/mL on day 18 and 11.7 ng/mL on day 25 [25]. In our study, the average P4 level on day 21 after mating was 5.65 ng/mL. This difference in P4 levels is thought to be due to the day of pregnancy, as well as the brand of kit and the measuring technique that were used.

In recent years, there has been a significant increase in sedation performed on pregnant women in anesthesia procedures outside of the operating room [26]. It is not known whether or not rocuronium, which is used as a neuromuscular relaxant, poses a risk to the fetus during pregnancy [27]. No complication has been reported in an infant born during the normal gestational week to a woman who was given rocuronium for neuromuscular blockage when she was known to be pregnant [26]. Insufficient data are available from animal studies [27]. In our study, the administration of rocuronium at 21 day after mating was found to significantly increase P4 levels compared to the other groups (control, Group II). This finding is the most important conclusion of our study. These results suggest that in pregnant rabbits rocuronium supports the corpus luteum that secretes P4.

Serious complications can result due to the risk of residual curarization. Sugammadex is widely used to eliminate residual neuromuscular muscle relaxation [12]. Studies have reported that sugammadex interacts with and binds to externally administered medicinal products, thus reducing the medicines' effect [12,28]. It is not recommended for use in women during pregnancy because there is no clinical data and minimal placental transfer is possible [29]. Animal studies have demonstrated that the use of sugammadex has no harmful effect, either directly or indirectly, on pregnancy, embryonic/fetal development and birth or during the post-natal period [21].

A study by Et et al.[6] investigated the effect of administering rocuronium and sugammadex on P4 levels in rats on day 12 of pregnancy. They found that administering rocuronium followed by sugammadex did not change P4 levels, and that administration of sugammadex only lowered serum P4 levels in rats numerically. However, this decline was not statistically significant. The fact that pregnancy continued to develop normally without abortus or stillbirth suggests that sugammadex can be used safely on day 12 of pregnancy. A different study, however, reported that administration of sugammadex had no effect on serum P4 levels [12]. Because endogenous steroids similar to P4, like rocuronium, do not contain the ammonium compounds found in steroidal neuromuscular blockers, sugammadex reportedly demonstrates low affinity for these steroids [30,31]. Furthermore, steroidal hormones contribute to this low affinity because they bind strongly to special transporter proteins [12,31]. In our study, on day 21 of pregnancy, there was a significant decline in serum P4 levels at 60 and 90 min in Group II compared to levels prior to sugammadex administration. Gunduz Gul et al.[12] found that there was a temporary decline in P4 levels after using sugammadex, but that levels rose again when measured 4 h later. None of the rabbits in our study experienced abortus or stillbirth during pregnancy in spite of the decline in P4 levels. This suggests that the P4 levels rose again some h later.

In conclusion, our study did not find that the use of the neuromuscular blocker rocuronium and its antagonist sugammadex in rabbits on day 21 of pregnancy had a negative effect on serum P4 levels during pregnancy.

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