https://dergipark.org.tr/tr/pub/ataunivbd
2020; 15(3): 251-256

Research Article/Araştırma Makalesi
DOI: 10.17094/ataunivbd.763496

Atatürk Üniversitesi Veteriner Bilimleri Dergisi
Atatürk University Journal of Veterinary Sciences

Comparison the Effect of Different Ratios of Ketamine and Propofol (Ketofol) Admixture on Anesthesia Induction in New Zealand White Rabbits

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Geliş Tarihi/Received	Kabul Tarihi/Accepted	Yayın Tarihi/Published
03.07.2020	20.09.2020	31.12.2020

Bu makaleye atıfta bulunmak için/To cite this article:
Yanmaz LE, Doğan E, Şenocak MG, Ersöz U, Okur S: The Effect of Anesthesia Induction with Ketamine and Propofol (ketofol) Admixture in New Zeland Rabbits. Atatürk University J. Vet. Sci., 15(3): 251-256, 2020. DOI: 10.17094/ataunivbd.763496

Abstract: This study was aimed to detect the effects of anesthesia induction with ketamine-propofol (ketofol) admixture in rabbits. Eight, healthy New Zealand white rabbits were randomly received ketofol admixture at the ratio of 1:1, 1:2, and 1:3 with one-week intervals. The length of surgical anesthesia was continuously evaluated until the presence of pedal withdrawal and ear-pinch reflexes. The recovery was assessed by the existence of the righting reflex. The heart rate and respiratory frequency values were recorded at pre-treatment, induction, and two minutes intervals until 20 minutes. There was no statistically significant difference between groups with respect to the ear-pinch reflex and pedal withdrawal reflex. The righting reflex returned earliest at the ratio of 1:1 (8.88 ± 0.63 minutes) which was significantly shorter than the ratio of 1:2 (10.50 ± 0.94 minutes) or 1:3 (13.62 ± 1.93 minutes). The animals receiving ketofol at the ratio of 1:3 had significantly lower respiratory frequency compared to 1:2 and 1:1 ratios at 0, 2, 4, 6, 8, and 12 minutes. The ketofol admixture at the ratio of 1:1 has less respiratory depression effects, and higher doses of propofol in ketofol admixture can be associated with anesthetic complication.

Keywords: Anaesthesia, Ketamine, Propofol, Rabbit.

Beyaz Yeni Zelanda Tavşanlarda Farklı Oranlarda Ketamine ve Propofol (Ketofol) Karışımının Anestezi İndüksiyonu Üzerine Etkilerinin Karşılaştırılması

Öz: Bu çalışma tavşanlarda üç farklı oranda hazırlanan ketamine-propofol (ketofol) karışımının anestezi indüksiyonu üzerine olan etkilerini karşılaştırmayı amaçladı. Sekiz, sağlıklı, Beyaz Yeni Zelanda tavşanına uygulamalar arasında 1 hafta olacak şekilde 1:1, 1:2 ve 1:3 oranında ketofol karışımı rastgele uygulandı. Cerrahi anestezi süresi kulak-çekme ve pedal geri çekme reflekslerinin varlığına bakarak sürekli olarak değerlendirildi. Tavşanların kendi başına doğrulabildiği zaman uyanma olarak kabul edildi. Kalp frekansı ve solunum sayısı, anestezi öncesinde, indüksiyonda ve ikişer dakika aralıklarla 20. dakikaya kadar kaydedildi. Kulak çekme refleksi ve pedal geri çekme refleksinde gruplar arasında istatistiksel olarak farklılık gözlenmemiştir. Tavşanların kendi başına doğrulma zamanı; 1:1 oranında (8.88 ± 0.63 dakika), 1:2 (10.50 ± 0.94 dakika) veya 1:3 (13.62 ± 1.93 dakika) oranlarından daha erken gerçekleşti. 1:3 oranında ketofol uygulanan hayvanların solunum sayısı 0, 2, 4, 6, 8 ve 12. dakikalarda 1:2 ve 1:1 oranlarına nazaran daha düşüktü. 1:1 oranında ketofol karışımı daha az solunum depresyonuna neden olmaktadır ve ketofol karışımı içerisindeki propofol oranını artması anestezik komplikasyon ile ilişkili olabilir.

Anahtar Kelimeler: Anestezi, Ketamine, Propofol, Tavşan.

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INTRODUCTION

Rabbits are some of the most frequently anesthetized animals for experimental researches but their anesthetic-related death rate is substantially higher than it is for other species. Even though several injectable anaesthetic agents have been used to induce anesthesia in rabbits, there is no safe anesthetic agent for this species (1).

Ketamine is a neuroleptic agent commonly used for the induction and maintenance of anaesthesia. It is an agent of choice in rabbits due to its rapid onset of action with minimal respiratory and cardiovascular effects (2). Propofol is a phenol-derived sedative-hypnotic anaesthetic agent with a short duration of action and rapid recovery. However, it causes cardiopulmonary depression, dose-dependent hypotension, and apnea (3).

Anaesthetic agents are commonly combined to enhance their therapeutic effects (4). The mixture of ketamine and propofol in the same syringe (ketofol) has been used in humans and veterinary patients (5-7). It has been reported that the advantages of this combination include reduced respiratory depression and intraoperative hemodynamic stability (8).

Propofol and ketamine at a 1:1 ratio have been used in dogs (7, 9) and cats (10). The aim of the current study was to compare the effects of anesthesia induction with 1:1, 1:2, and 1:3 ratio of ketofol admixture in rabbits.

MATERIALS and METHODS

Animals

The Atatürk University Local Board of Ethics Committee approved this study (HADYEK decision no: 2013/136).

Eight *New Zealand* white rabbits, 4 males, and 4 females, 8-10 months old and weighing between 2.9 and 3.4 kg, were used. Only rabbits that were clinically healthy according to physical examinations and biochemistry results were accepted in the study. The animals were maintained in individual cages with dimensions of 75x75x60 cm, where they were fed with commercial pellet food and water *ad libitum*. The rabbits were acclimatized for 2 weeks prior to the start of the study. The rabbits were not fasted before anesthesia. The left ear of each rabbit was clipped, and the skin cleaned with alcohol. A 22 G catheter was placed into the marginal ear vein for anesthetic injections. The body temperature of the animals was maintained at about 38°C by a heated operating table during anesthesia.

Study Design

Each rabbit received three different treatments in a randomized crossover design with a minimum washout period of 1 week between treatments. The drugs used were propofol (Propofol 10 mg/ml; Fresenius Kabi, Austria) and ketamine (Ketasol 100 mg/ml; Interhas, Richter Pharma AG, Wels, Austria). The animals received three ratios of the ketamine-propofol combination (1:1, 1:2, 1:3), which had been selected based on prior studies (8,11,12). An anaesthetist who was unaware of the experimental design prepared a propofol-ketamine admixture. To prepare the different ratios for ketofol mixture solution, a 5 ml sterile vial was used. The 1:1 combination of admixture contained 30 mg ketamine per ml and 30 mg propofol per ml (total 3.3 ml; 0.3 ml ketamine and 3 ml propofol per vial). The 1:2 combination of admixture contained 20 mg ketamine per ml and 40 mg propofol per ml (total 4.2 ml; 0.2 ml ketamine and 4 ml propofol per vial). The 1:3 combination of admixture contained 15 mg ketamine per ml and 45 mg propofol per ml (total 4.15 ml; 0.15 ml ketamine and 4 ml propofol per vial). Each vial of the mixture was kept for a maximum of 6 hours. Then, prepared vials that contain different ratios of ketofol admixture was diluted with sterile saline to achieve the final volume of 5 ml for administration. Anesthetics were administered slowly (over 60 s) by the anesthetist who was unaware of the prepared ratio until the disappearance of pedal withdrawal reflex and ear-pinch reflex. The total induction dose requirement of mixtures for each rabbit was recorded.

The length of surgical anesthesia was continuously evaluated until the presence of pedal withdrawal reflex and ear-pinch reflex. The recovery was assessed by the existence of the righting reflex (ability to return sternal position by own).

The heart rate and respiratory frequency values were recorded with a veterinary vital sign monitor (Cardell, 9404, Sharn Veterinary Inc, USA) and abdominal movements, respectively. Both rates were recorded at pre-treatment, immediately following anesthesia induction and two minutes intervals until 20 minutes.

Statistical Analysis

Differences among the three groups were evaluated with one-way ANOVA followed by Duncan's multiple range post-hoc test. An independent samples t-test was used to determine pre-treatment differences between groups. Post-treatment differences within each treatment group were evaluated using a paired samples t-test. All data were analyzed using the SPSS19 (IBM Company, Version 19.0, SPSS Inc, USA, 2010) statistical package. Statistical significance was declared at $P<0.05$. The data presented as mean ± SE.

RESULTS

There were no complications associated with using ketofol at the ratio of 1:1. The 1:2 ratio of ketofol caused apnoea in two rabbits. The ketofol at the ratio of 1:3 caused bradypnoea in two rabbits. Recovery was uneventful except one rabbit at the ratio of 1:3. Apnoea followed by cardiac arrest encountered in this rabbit. Cardiopulmonary resuscitation was attempted immediately but was unsuccessful.

The total induction dose requirement of ketofol at the ratio of 1:3 (6.12 ± 0.73 ml) was significantly ($P<0.05$) higher compared to the ratio of 1:1 (3.77 ± 0.33 ml) and 1:2 (3.58 ± 0.42 ml).

There was no statistically significant difference between groups with respect to the ear-pinch reflex and pedal withdrawal reflex. The righting reflex returned earliest at the 1:1 ratio of ketofol (8.88 ± 0.63 minutes) which was significantly ($P<0.05$) shorter than 1:2 (10.50 ± 0.94 minutes) or 1:3 ratio (13.63 ± 1.93 minutes) as shown in Table 1.

Table 1. Time to return of reflexes for each ketofol admixture (mean ± SE).
Tablo 1. Her ketofol karışımı için reflekslerin geri dönüş zamanı (ortalama ± SH).

	Groups		
Parameters	Ketofol 1:1	Ketofol 1:2	Ketofol 1:3
Pedal withdrawal reflex (minutes)	2.63 ± 0.18	3.13 ± 0.44	4.50 ± 0.88
Ear pinch reflex (minutes)	2.75 ± 0.16	3.25 ± 0.45	5.13 ± 1.71
Righting reflex (minutes)	8.88 ± 0.63^{b}	10.50 ± 2.67^{ab}	13.63 ± 5.47^{a}

[a-b] Different superscripts in the same rows indicates significant differences between groups ($P<0.05$).

There was no significant ($P>0.05$) difference among groups at the baseline parameters of heart rate and respiratory frequency. Increasing the propofol amount did not significantly affect heart rate at all time points (Figure 1). The animals receiving ketofol at the ratio of 1:3 had significantly ($P<0.05$) lower respiratory frequency compared to 1:2 and 1:1 ratios at 0, 2, 4, 6, 8, and 12 minutes (Figure 2).

The respiratory frequency value started to decrease at the induction phase in all groups. The respiratory frequency gradually increased earliest (6 minutes) in animals that received ketofol at the ratio of 1:2, and the latest at the ratio of 1:3 (14 minutes).

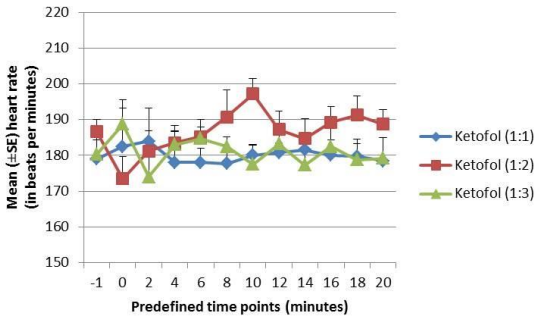

Figure 1. The heart rate (mean ± SE) for each ketofol admixture at predefined time points. -1: pretreatment; 0: Immediately following anaesthesia induction.
Şekil 1. Belirlenen zamanlarda her bir ketofol karışımı için kalp frekansı (ortalama ± SH). -1: tedavi öncesi; 0: anestezi indüksiyonunu takiben.

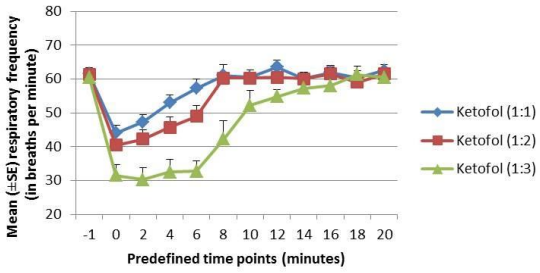

Fig 2. The respiratory frequency (mean ± SE) for each ketofol admixture at predefined time points. -1: pretreatment; 0: Immediately following anaesthesia induction.
Şekil 2. Belirlenen zamanlarda her ketofol karışımı için solunum sayısı (mean ± SH). -1: tedavi öncesi; 0: anestezi indüksiyonunu takiben.

DISCUSSION and CONCLUSION

The combination of ketamine and propofol, known as ketofol, can be prepared at any intended concentration. It has been mainly used extemporally ratios in the emergency department for procedural sedation (13). The previous study in humans has demonstrated that ketofol at the ratio of 1:3 has lower respiratory depression incidence compared to 1:1 and 1:2 ratios (14). However, in the present study ketofol at the ratio of 1:1 did not cause any adverse effects at the induction and recovery phase of anesthesia. This discrepancy could be possibly due to differences in the experimental subject or more likely total induction dose requirements of ketofol at the ratio of 1:3, which was significantly higher, compared to other ratios used in this study. It has been reported that higher propofol dosages are associated with respiratory depression and death in rabbits (15). Similarly, in the current study, respiratory depression was observed at the ratio of 1:2 and 1:3 during the induction of anesthesia. Based on our results, it can be proposed that augmenting the propofol ratio in ketofol admixture for anesthesia induction in rabbits is unnecessary.

In this study, the reflexes were used to determine the surgical plane of anaesthesia. The pedal withdrawal reflex and ear-pinch reflex are mainly used indicators to detect surgical anaesthesia in rabbits (16) while the righting reflex indicates recovery from anaesthesia in this species (17). In the current study, even though increasing the ratio of propofol in ketofol admixture resulted in longer periods absent of pedal withdrawal reflex and ear-pinch reflex, no statistically significant differences were observed between groups. However, the ketofol at the ratio of 1:3 caused a longer recovery period compared to 1:1 and 1:2 ratios.

Ketamine is a valuable anesthetic agent for hypotensive patients because it stimulates the cardiovascular system and increases the heart rate and arterial blood pressure (8). However, using propofol for induction of anesthesia may decrease the heart rate (18, 19). In the present study, even though different ratios of ketofol admixture were used, no significant heart rate alterations observed at all time intervals, which confirmed the previous report (6). As a result, it can be said that the combination of ketamine and propofol may be an agent of choice to ensure hemodynamic stability. The reduced respiratory rate was observed following the induction of anesthesia in all ratios. Previous studies have reported that ketofol anesthesia decreases the respiratory rate (5, 6). The ketofol at the ratio of 1:3 caused lower respiratory frequency compared to the ratio of 1:2 and 1:1. This finding confirms the previous study that shows respiratory depression is

related to the dose requirement of propofol for induction (20).

In cocnlusion, increasing the propofol ratio in ketofol admixture causes higher respiratory depression risks and results with a longer recovery period in rabbits. According to the present study, the ketamine and propofol admixture at the ratio of 1:1 has less respiratory depression effects, and higher doses of propofol in the ketofol admixture can be associated with anesthetic complication. However, more research regarding the detailed monitoring of pulmonary and hemodynamic effects of ketofol admixtures is needed to confirm our results.

Conflict of interest

The authors declare that they have no conflict of interest.

Acknowledgement

This study was financially supported by Ataturk University Scientific Research Projects (Project No: BAP 2015/301).

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