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Comparison of Bispectral Index and Vital Parameters in Rabbits Receiving Propofol or Isoflurane Anesthesia

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ABSTRACT

***Background*:** Reflexes, muscle tonus, heart rate, respiratory frequency and blood pressure are parameters that can be used to evaluate the depth of anesthesia. Bispectral index (BIS) was developed with the objective of evaluating quantitatively the sedative and hypnotic effects of anesthetic drugs. It is widely used to assess central nervous system depression levels. The objective of this study was to compare changes in BIS and several vital parameters during general anesthesia achieved with either propofol or isoflurane, following premedication with dexmedetomidine.

***Materials, Methods & Results*:** Adult female New Zealand rabbits (Mean ± SD body weight 3.6 ± 0.4 kg) were procured from a commercial source certified for medical experimentation. The animal number in each of the two study groups was four, for a total of eight. The animals were checked before the study to ascertain their good health. The animals, randomly allocated to either of two study groups, were given dexmedetomidine, 20 µg/kg i.v. Induction was realized by means of propofol, 8 mg/kg i.v. in the propofol group (n = 4), and by administration through a glove mask of isoflurane, 4%, in the isoflurane group (n = 4). Anesthesia maintenance was assured by propofol, 0.6 mg/kg/min or 2% isoflurane with oxygen, respectively. Both anesthetic applications were well tolerated by the rabbits. Before premedication (T0), at the time points of 1 (T1) and 5 min (T2) after dexmedetomidine injection, 1 min into anesthesia induction (T3), and 10 (T4), 30 (T5) and 60 min (T6) after start of maintenance, the following were recorded: BIS, systolic, diastolic and mean arterial blood pressure, heart rate and Anesthesia Score (AS). Blood gas analysis, serum sodium and potassium, blood glucose level, hemoglobin and hematocrit were measured at time points T0 and T6. MAP dropped significantly lower in the propofol group at times T_2, T_3 and T_4 ($P < 0.05$). Under BIS monitoring, BIS values were also found to be relatively lower in the propofol group at times T_1, T_2 and T_4, corresponding in this to AS. At T_4, the BIS values were, respectively, 69.5 ± 6.24 and 68.25 ± 3.59 in the isoflurane and propofol groups ($P < 0.05$). In summary, premedication with dexmedetomidine did not, differently than with humans, assure deep sedation; BIS values, in parallel with our AS evaluation, reached levels of deep anesthesia in the maintenance stage both in the propofol and isoflurane groups. BGA results in arterial blood (pH, PaO_2, $PaCO_2$, BE, HCO_3) as well as hematocrit (Hct), Na^+, K^+, glucose, hemoglobin (Hb) were recorded and reported in Table 2. A significant increase in pH was noted at T_6 ($P < 0.05$) in the propofol groups compared to animals given isoflurane (7.39 ± 0.01 *vs* 7.35 ± 0.003, respectively), all measurements remaining within the normal values.

***Discussion*:** Vital parameters showed parallelism with the values of both our AS and BIS in this study, in which we administered general anesthesia with either propofol or isoflurane to rabbits premedicated with dexmedetomidine. Publications on humans show that surgical anesthesia is realized at BIS values under 60; BIS fell in rabbits in parallel to MBP at 10, 30 and 60 min of anesthesia, and AS also showed that the depth of anesthesia was adequate. No surgery having been performed in this study, we think that the parameters noted in this paper should be investigated in future studies that include surgery.

Keywords: bispectral index, rabbits, dexmedetomidine, propofol, isoflurane, mean arterial blood pressure, heart rate, blood gas analysis.

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INTRODUCTION

Determining the depth of anesthesia during a surgical procedure is not easy. Reflexes, muscle tonus, heart rate, respiratory frequency and blood pressure are parameters that can be used to evaluate the depth of anesthesia [15,16]. Evaluating the depth of anesthesia during its induction and maintenance is a complicated, as yet unsolved problem.

It has been observed, since the discovery of electrical potentials produced by the brain, that anesthetic drugs modify the electroencephalography (EEG) recording. Therefore interest in EEG to monitor anesthesia increased; it was proposed by numerous publications as a valuable method for evaluating the depth of anesthesia [3,22]. The Bispectral Index monitor (BIS®), which allows to assess quantitatively the EEG signal, has been used in recent years to evaluate depth of anesthesia.

BIS was developed with the objective of evaluating quantitatively the sedative and hypnotic effects of anesthetic drugs [1]. It is widely used to assess central nervous system (CNS) depression levels [15].

Inhalant anesthetics are widely used in both human and veterinary medicine; their main advantages consist of not being dependent on hepatic or renal elimination. This reduces their biotransformation [15,23].

During propofol anesthesia, too deep a sedation is correlated with clinically manifest cardiovascular and respiratory depression, while light sedation is known to cause intra-operative awakening [13,21].

The objective of this study was to determine the depth of anesthesia with isoflurane or propofol by BIS and vital signs in rabbits.

MATERIALS AND METHODS

Animals

Adult female New Zealand rabbits (Mean ± SD body weight 3.6 ± 0.4 kg) were procured from a commercial source certified for medical experimentation. The animal number in each of the two study groups was four, for a total of eight. The animals were checked before the study to ascertain their good health.

Anesthesia

The rabbits had feed and water *ad libitum* until 2 h before start of the study. They were allowed to drink water up to the start of study. The rabbits were randomly assigned to wither of two groups (n = 4). A 22 G Intracath® catheter was placed in the marginal auricular vein of animals in both groups to allow administration of anesthetics and fluids. Dexmedetomidine HCl[1], 20 µg/kg i.v. premedication was administered to all animals. Once sedation was achieved, the animals in one of the groups (ISO Group, n = 4) were given 4% isoflurane[2] using an SMS Classic 2000 anesthesia device with automatic ventilator[3] and a glove mask, with oxygen, 4 L/min. Anesthesia was then maintained by 2% isoflurane in the ISO group. The second study group (PROP Group, n = 4) was given propofol[4], 8 mg/kg body weight i.v. Anesthesia maintenance was ensured by continuous infusion of propofol, 0.6 mg/kg/min (Infusion pump make). Anesthesia was administered for a total duration of 60 min.

BIS measurement

The animals' temporofrontal areas were shaved prior to the study. The shaved area was defatted with ether immediately preceding the application. BIS sensors[5] used in humans were employed in this animal study. The BIS sensors consisted of five electrodes. Of these, three were applied to the frontal area and the two others to each pre-auricular temporal area. After connecting the sensor to the BIS monitor[6], the BIS values were continually followed on the monitor and noted. BIS measurements were noted, for all animals in both groups, before sedation (0 min, T_0); 1 min following dexmedetomidine administration (T_1); 5 min following dexmedetomidine administration (T_2) after start of induction at 1 min (T_3); during anesthesia maintenance at 10 min (T_4), 30 min (T_5) and 60 min (T_6).

Vital Parameter Measurements

On the day preceding the study, were sedated and the femoral artery of all was isolated and catheterized under local anesthesia following sedation. At times T_0, T_1, T_2, T_3, T_4, T_5 and T_6 the catheter-transducer connection was re-established to note the systolic, diastolic and mean arterial pressure (SAP, DAP and MAP, respectively) on a multi-channel monitor[7] Electrodes secured to the extremities were also connected to the monitor, allowing to note heart rate (HR) at the mentioned time points. Arterial blood samples drawn through the femoral artery catheter at times T_0 and T_6 were examined in a Blood Gas Analysis (BGA) device[8] for pH, partial carbon dioxide and oxygen pressure (pCO_2 and pO_2), bicarbonate (HCO_3), base excess, sodium (Na^+), potassium (K^+), glucose, hemoglobin (Hb) and hematocrit (Hct) levels and recorded.

All animals in both groups were documented during the study for depth of anesthesia according to the following scale of Anesthesia: 0 = Awake, mobile, stops when held; 1 = Awake, mobile, stops without being held. Moves in response to stimulus; 2 = Awake, stops without being held. Does not move in response to stimulus; 3 = Asleep. Partially responds to painful stimulus; 4 = Asleep. No response to painful stimulus; 5 = Anesthesia.

Statistical Analysis

Data were analyzed with the SPSS 16.0 (SPSS Inc, for Windows) software package. A one-way ANOVA test was used to compare the groups. Test significance levels within and between groups were checked using Duncan's test. Descriptive results are expressed as means ±1 standard deviation. For all comparative tests, a value of $P < 0.05$ was considered significant.

RESULTS

The values for SAP, DAP, MAP, HR, Anesthesia Score (AS) and BIS at the different time points are indicated in Table 1. A fall in SBP in the propofol group at time points T4, T5 and T6 was statistically significant ($P < 0.05$).

Table 1. Systolic, diastolic and mean arterial blood pressure, heart rate, anesthesia score and BIS values in rabbits in the the propofol and isoflurane groups (n = 4). [Mean ± Standard Deviation].

Groups - Time Points	Systolic Arterial Pressure (mmHg)	Diastolic Arterial Pressure (mmHg)	Mean Arterial Pressure (mmHg)	Heart Rate (Beats/Minute)	Anesthesia Score	BIS
T_0 Propofol	91 ± 2.1*	74 ± 2.82	83.5 ± 3.69*	183 ± 6.48*	0 ± 0	100 ± 0
Isoflurane	92.25 ± 3.5	71 ± 7.16	77.75 ± 5.56	180 ± 4.34	0 ± 0	100 ± 0
T_1 Propofol	86 ± 3.55	69.25 ± 2.06*	77.5 ± 2.38*	168 ± 6.24*	1.75 ± 0.95	85 ± 2.16*
Isoflurane	87 ± 2.58	72.25 ± 3.5	80.25 ± 3.30	180 ± 3.59	1.75 ± 0.5	92.2 ± 2.98
T_2 Propofol	86.75 ± 1.89	64.5 ± 3.1*	76 ± 1.82*	173 ± 7.24*	2 ± 0.81	88.5 ± 1.29*
Isoflurane	85.75 ± 2.62	71 ± 2.58	78.5 ± 1.29	172 ± 3.87	2 ± 0.81	84.5 ± 3.41
T_3 Propofol	87 ± 7.78	59.25 ± 4.27*	67.5 ± 3.87*	164 ± 5.06	3.25 ± 1.25	80.75 ± 8.42
Isoflurane	84.5 ± 3.69	63.50 ± 4.5	70.75 ± 3.86	162 ± 2.16	2.25 ± 1.25	82.25 ± 6.65
T_4 Propofol	71.25 ± 3.77*	50 ± 2.82*	59.5 ± 4.35*	156 ± 8.77	4.75 ± 0.5	69.5 ± 6.24*
Isoflurane	77.5 ± 2.38	57.75 ± 1.7	64 ± 2.58	165 ± 3.55	4 ± 1.15	68.25 ± 3.59
T_5 Propofol	67.5 ± 3.78*	50.5 ± 3.41*	58.25 ± 3.3	163 ± 6.65*	4.25 ± 0.9	62.5 ± 5
Isoflurane	74.25 ± 2.98	55.50 ± 3.10	61.5 ± 2.64	167 ± 8.04	4.5 ± 0.5	60.75 ± 1.7
T_6 Propofol	65 ± 6.21*	49.25 ± 5.37	55.75 ± 6.94	183 ± 7.87	4.5 ± 0.5	64.5 ± 4.12
Isoflurane	73.5 ± 3.51	50 ± 2.16	57.50 ± 1.29	162 ± 3.1	4 ± 0.8	65.75 ± 3.3

*There is significant difference between groups ($P < 0.05$).

DAP values fell in both groups over the measurement period. At times T_1, T_2, T_3, T_4, T_5 the fall in DAP in the propofol group subjects was significantly different than in the isoflurane group. MAP was significantly lower in the propofol group at times T_2, T_3 and T_4 (at the latter time point the MAP values were 59.5 ± 4.35 mm Hg for the propofol subjects vs 64 ± 2.58 mm Hg in the isoflurane group ($P < 0.05$). MAP remained stable over T_5 and T_6 (Figure 1).

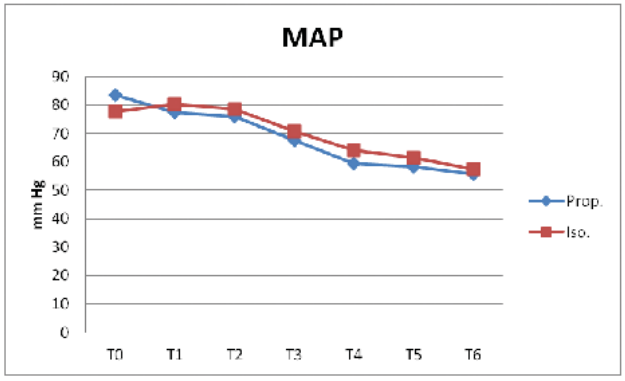

Figure 1. Mean arterial blood pressure in the propofol and isuflorane group rabbits.

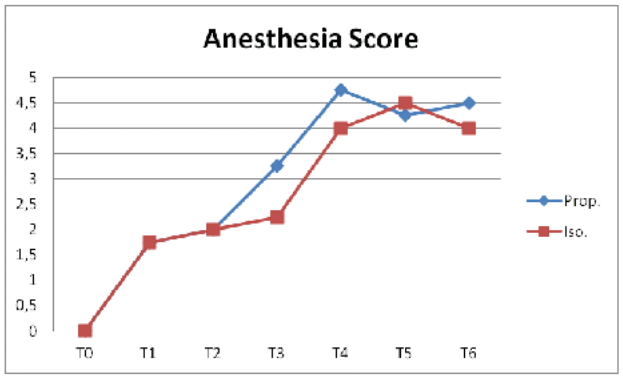

Figure 2. Mean anesthesia scores in the propofol and isuflorane group rabbits.

The anesthesia grading performed by ourselves (AS) was significantly increased at T_4, T_5 and T_6 in the propofol animals when compared to the isoflurane group ($P < 0.05$). Depth of anesthesia score was 4.5 ± 0.5 and 4 ± 0.8, respectively, for the propofol and isoflurane groups at T_6; the increase in the former group was statistically significant ($P < 0.05$) [Figure 2].

Under BIS monitoring, BIS values were also found to be relatively lower in the propofol group at times T_1, T_2 and T_4, corresponding in this to AS. At T_4, the BIS values were, respectively, 69.5 ± 6.24 and 68.25 ± 3.59 in the isoflurane and propofol groups. Depth of anesthesia as scored at time points T_4, T_5 and T_6 were in the deep anesthesia zone according to BIS (Figure 3).

When comparing HR between groups, values in the propofol group fell lower than in isoflurane animals as recorded at T_1, T_2 and ,T5 ($P < 0.05$) [Figure 4].

BGA results in arterial blood (pH, PaO_2, $PaCO_2$, BE, HCO_3) as well as Hct, Na^+, K^+, glucose, Hb were recorded and reported in Table 1. A significant increase in pH was noted at T_6 ($P < 0.05$) in the propofol groups compared to animals given isoflurane (7.39 ± 0.01 vs 7.35 ± 0.003, respectively), all measurements remaining within the normal values. In the within-group comparison of PaO_2 in the propofol animals, the T_6 value was significantly higher than at T_0 ($P < 0.05$) while remaining within the normal range. Propofol and isoflurane group blood glucose values were, respectively, 113.33 ± 5,.4 mg/dL and 114.16 ± 4.92 mg/dL at T0 and 85.66 ± mg/dL and 88 ± 2.38 mg/dL at T_6, a significant reduction ($P < 0.05$).

No statistical significance could be established in the changes observed in the other parameters between their T_0 and T_6; such changes remained within their respective normal ranges (Table 2).

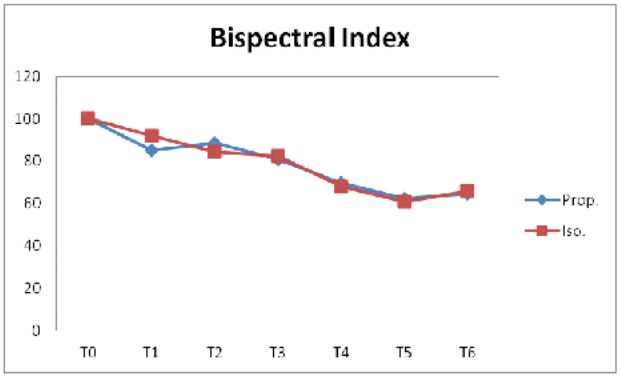

Figure 3. Bispectral index in the propofol and isuflorane group rabbits.

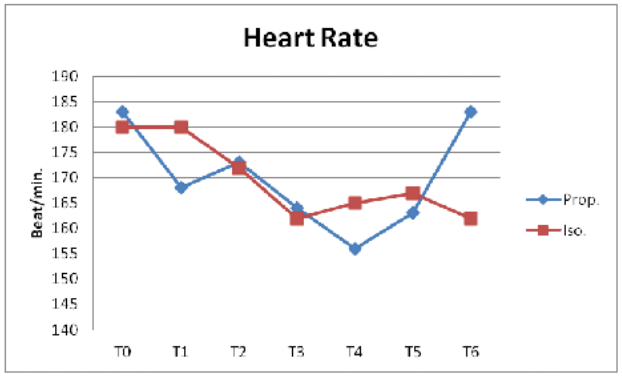

Figure 4. Heart rate in the propofol and isuflorane group rabbits.

Table 2. Blood gases and other parameters for the animals in the propofol and isoflurane groups (n = 4). [Mean ± standard deviation].

Groups	pH (-log 10^7)	PaO_2 (mmHg)	$PaCO_2$ (mmHg)	BE (mmol/L)	HCO_3 (mmol/L)	Hct (%)	Na^+ (mmol/L)	K^+ (mmol/L)	Glucose (mg/dL)	Hgb (g/dL)
T_0										
Propofol	7.36 ± 0.007	87 ± 3.15	35.5 ± 1.43	-1.7 ± 0.80	24.95 ± 2.39	29.08 ± 1.66	142.16 ± 0.64	3.88 ± 0.11	113.33 ± 5.14	9.08 ± 0.28
Isoflurane	7.36 ± 0.004	82.83 ± 1.55	38.16 ± 0.94	-2.21 ± 0.34	25.53 ± 0.52	28.01 ± 0.72	142.66 ± 0.61	4 ± 0.11	114.16 ± 4.92	9.05 ± 0.30
T_6										
Propofol	7.39 ± 0.01*	91.33 ± 1.35*	38.83 ± 1.13	0.48 ± 1.00	22.61 ± 0.51	27.83 ± 1.86	140.86 ± 0.32	3.86 ± 0.08	85.66 ± 7.95*	8.78 ± 0.18
Isoflurane	7.35 ± 0.003	86.4 ± 0.97	38 ± 0.7	-1.9 ± 0.29	25.8 ± 0.37	27.04 ± 0.37	141.4 ± 0.50	3.86 ± 0.09	88 ± 2.38	8.62 ± 0.17

*There is significant difference between groups ($P < 0.05$).

DISCUSSION

The objective of the study was to evaluate the depth of anesthesia by BIS and several vital parameters under general anesthesia achieved with either propofol or isoflurane, following premedication with dexmedetomidine, a drug increasingly used in human medicine.

The use of the rabbit model when necessary in biomedical experimentation is recognized in the attempt to reduce to a minimum the interaction between anesthetic drugs, an important endpoint. Earlier studies in rabbits have showed that a combination of isoflurane or halothane for induction is poorly tolerated [5]. Dexmedetomidine and propofol are often used to assure sufficient sedation in intensive care patients. Some animal and human studies, however, evidence that these agents cause respiratory depression [4]. In this study, dexmedetomidine was used as premedication; for induction and maintenance isoflurane was used in the ISO group and propofol in the PROP group. BGA showed a PaO_2 below normal values in both groups, an observation supported by the findings of Chang *et al*. [4]. On the other hand, both isoflurane and propofol induction were well tolerated, a result different than that reported by Flecknell *et al*. [5].

Hypotension may develop in rabbits during the use of inhalant anesthetic agents. This condition may develop as a result of cardiovascular depression by anesthetic and sedative drugs. Surgical bleeding may worsen hypotension [11]. Propofol is an intravenous anesthetic agent that allows good control of depth of anesthesia. Due to its lack of analgesic potential, it is not used as a single drug for anesthesia. Earlier publications have reported its combined use with sedative and analgesic agents [17-19]; the use of alpha-agonist drugs as sedatives or anesthetics has also been studied. Dexmedetomidine, a hypnotic with high selectivity for α2-adrenergic receptors, is often used in humans in intensive care units [17]. Its advantages consist in reduced respiratory depression, good quality of sedation, and its anti-delirium, anti-agitation, anesthetic and analgesic properties [20]. Dexmedetomidine was well tolerated in our study in rabbits, achieving a sedation of comparable grade on both BIS and AS.

Propofol is an intravenous anesthetic agent that allows good control of depth of anesthesia. Its advantages are the rapid onset of action and the rapid recovary from anesthesia [21]. In humans, BIS is used to evaluate the degree of hypnosis relative to the amount of anesthetic used [12]. It has also been characterized in

the dog and other species [2,9,10,13]. In the human, a BIS value of 90 or higher indicates wakefulness, while a score under 50 is ideal for surgical procedures [8]. A dog study shows that the scores over 95 correspond to a condition in the dog that is not different than that in the human. In this study, the animals were awake and responded to stimuli in the period following sedation.

A study in rabbits [5] indicated that induction with halothane and isoflurane was similar to that in earlier reports [6]. The rabbits in our study were premedicated with dexmedetomidine. Although BIS values fell at the 1st and 5th minutes during sedation, response to stimuli persisted. No important difference from our own AS was observed.

The protocol for induction in rabbits using a facial mask was developed by Flecknell *et al*. in 1995 [6]. The glove mask method was used in our earlier studies in rabbit; no hypoxia was observed. The glove masked was applied to rabbits in this study, too; anesthesia induction and maintenance was performed with this mask attached to an anesthesia device. Flecknell *et al*. [6] reported the development of apnea and tachypnea in rabbits being administered isoflurane and sevoflurane induction and maintenance. Apnea did not develop during our study. As for tachypnea, it was observed but no reduction in oxygen saturation was noted.

When comparing PaO_2 values at T_6 to T_0, results in the propofol group were higher than for the isoflurane animals. We have suggested above that such a reduction may be due to the use of the glove mask. The last mentioned authors also report the development of apnea-associated bradycardia; they also indicate that no arrhythmia or hypotension had been observed. The fall in SAP, DAP and MAP at the different measurement time points in our study was both statistically and clinically significant. The fall in MAP shows some parallelism with both BIS and AS.

There are only few reports of the use of BIS to characterize anesthesia depth in rabbits. Studies are available, however, measuring the depth of anesthesia by EEG for anesthesia with combinations of injectable anesthesia agents [14,24]. According to the report published by Martin-Cancho *et al*. [14] on BIS and hemodynamic parameters in propofol or sevoflurane anesthesia, an inverse correlation of HR is to be found with BIS and a direct correlation with BP. The same study indicated a marked decrease of BIS in both groups following induction. HR was reported to increase, in comparison to the baseline value, immediately after propofol induction in both groups. In our study, a parallel, significant fall in both BP and BIS values was found in the propofol group 10 at min. This is in accord with the published studies. HR was not, however, observed in either group, thanks to the good hydration of the animals. In fact, it showed a slowing.

BGA performed before anesthesia and after 1 h of general anesthesia showed variation within normal limits for pH, $PaCO_2$, BE and HCO_3. PaO_2 values at T_6 compared to T_0, showed a higher increase in the propofol group than for the isoflurane animals. These values, however, remained within the normal range.

In a study in which comparing Na^+ and K^+ levels during halothane and isoflurane anesthesia were compared to the baseline, serum Na^+ was found to be significantly higher 1 min after intubation in the isoflurane animals than in the halothane group. The authors report that the serum K^+ level fell significantly at the 1 and 60 min time points post intubation [7]. In our study in which samples were collected at the start and after 60 min of anesthesia, the levels of both electrolytes were within the normal interval in both groups. Blood glucose values fell at 60 min in both groups; the fall in the propofol group reached statistical significance.

HB and Hct were within the normal range at T_0 and T_6 in our study.

In summary, vital parameters showed parallelism with the values of both our AS and BIS in this study, in which we administered general anesthesia with either propofol or isoflurane to rabbits premedicated with dexmedetomidine. Publications on humans show that surgical anesthesia is realized at BIS values under 60; BIS fell in rabbits in parallel to MBP at 10, 30 and 60 min of anesthesia, and AS also showed that the depth of anesthesia was adequate. No surgery having been performed in this study, we think that the parameters noted in this paper should be investigated in future studies that include surgery.

SOURCES AND MANUFACTURERS

[1]Precedex® 100 µg/mL, Abbott, USA.

[2]Forane Likit®, Abbott Ltd, Turkey.

[3]SMS 2000 Classic, SMS, Turkey.

[4]Propofol 1%, Fresenius Kabi, Germany.

[5]BIS Quatro, Aspect Medical Systems International B.V., Netherlands.

[6]Bispectral Index Monitor, A-2000 PIN: 185-0070, BIS XP Platform Aspect Medical Systems Inc., USA.

[7]PETAŞ KMA 800 Multi-Channel Monitor, Turkey.

[8]Gastat Mini, Japan.

***Ethical approval*.** The study was authorized before it started by the Local Ethical Committee for Experimental Animals, Afyon Kocatepe University (Protocol Number: AKUHADYEK 35-11).

***Declaration of interest*.** The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

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