Comparison of the Depth of Anesthesia Produced with Dexmedetomidine-Sevoflurane or Medetomidine-Sevoflurane by Using Bispectral Index Monitoring

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ABSTRACT

Background: Bispectral index (BIS) monitor was developed to utilize the depth of anesthesia by estimating electroencephalogram (EEG) signals. BIS, which is the numerical value of EEG derivative, is used for evaluation of depression of central nervous system (CNS) in human medicine. The depressive effect of sedative and anaesthetic agents on CNS in human is correlated to BIS. Dexmedetomidine (DEX) is administered as continuous infusion during anesthesia and surgery in humans. DEX is a hypnotic with high selectivity for α2-adrenergic receptors.

Materials, Methods & Results: Adult female New Zealand rabbits (mean ± SD body weight 3.8 ± 0.5 kg) were procured from a certified commercial source to use in medical researches. The animal number in each of the two study groups was four, for a total of eight. The rabbits were randomly divided into two equal groups (n = 4). The rabbits DEX group were administered 20 mcg/kg of i.v. DEX HCI for premedication. Medetomidine (MED) group was administered 20 mcg/kg of iv MED for premedication. Induction was provided by 5% of sevoflurane + 4 L/min oxygen via glove mask in the both groups. General anesthesia was maintained with 3% of sevoflurane + oxygen on spontaneous respiration for 30 min. The animals’ temporomandibular region was shaved; its fat was eliminated with ether before the study. Human sensors were used as BIS sensor consisted of 5 electrodes. Three were placed into frontal area as the remaining two into the preauricular area. After ensuring the connection of the sensor to the BIS monitor, BIS value was continuously followed and recorded at 0 min (T0), 1st (T1), 5th (T5), 7th (T7), 9th (T9), 15th (T15) 20th (T20), 25th (T25) and at 30th min (T30) in both groups while the rabbits were awake. At T1 measure point, DEX and MED were applied; sedation was produced at T5; 5% of sevoflurane was administered through glove-mask method at T7 for induction; general anesthesia was obtained at T9 and continued during T15, T20, T25 and T30; they were awakened at the end of 30th min. On the day preceding the study, they were sedated; their femoral arteries were localized and catheterized under local anesthesia following sedation. At T0, T1, T5, T7, T9, T15, T20, T25 and T30 measure time points, the catheter-transducer connection was established for mean arterial blood pressure (MAP) measurement; for ECG monitoring, ECG electrodes were attached to all four extremities of the subjects and, ECG tracings from lead II were monitored and recorded on the multi-channel monitor. The pH was kept between 7.35 - 7.45, as PCO2 between 35 - 45 mmHg. All animals in both groups were documented during the study for Anesthesia Score (AS). MAP and BIS decline in DEX group at the end of 1st min at statistical significance (P < 0.05). At the same time point, AS was recorded higher in DEX group (P < 0.05). In the comparison of DEX group with MED group at T5; HR, MAP and BIS markedly declined in DEX group (P < 0.05); however, AS was found higher in DEX group as being statistically significant at the same time point (P < 0.05). As it was at T5, Heart Rate (HR), MAP and BIS were also found statistically significantly low in DEX group at T7 and T9; while AS was found higher as compared to MED group (P < 0.05). BIS value in MED group was low at a statistical significance level at T15, T20, T25 and T30 time points (P < 0.05).

Discussion: In present study, sevoflurane administration with glove mask method provides sufficient anesthesia in the rabbits which were premedicated with DEX and MED in experimental studies or surgical procedures during veterinary practice. Besides the vital parameters and AS monitoring, BIS monitoring is also an effective method in determination of the depth of anesthesia in rabbits.

Keywords: bispectral index, rabbits, dexmedetomidine, medetomidine, sevoflurane, hemodynamic parameters.
INTRODUCTION

BIS monitor was developed to utilize the depth of anesthesia by estimating EEG signals [3,5,19,20]. BIS, which is the numerical value of EEG derivative, is used for evaluation of depression of central nervous system (CNS) in human medicine. The depressive effect of sedative and anaesthetic agents on CNS in human is correlated to BIS [15,19,20].

Inhalational anesthetics are widely used in both human and veterinary anesthetic medicine; their main advantages include being independent from hepatic or renal elimination. This reduces their biotransformation [15,19,23]. Therefore, the biotransformation of inhalational anesthetics and morbidity and mortality are very low, as compared to other anesthetics [15,20,23].

DEX is administered as continuous infusion during anesthesia and surgery in humans. There is limited number of publication about the use of DEX in animals. DEX is a hypnotic with high selectivity for \( \alpha_2 \)-adrenergic receptors [18,19]. Its advantages include reduced respiratory depression, good quality of sedation, and anti-delirium, anti-agitation, anesthetic and analgesic features [19,22]. MED is also in reaction with \( \alpha_2 \)-adrenergic receptors [1].

In this study, we aimed to determine the depth of anesthesia produced by this anesthesia protocol by using the BIS monitoring and certain vital parameters after maintaining sevoflurane anesthesia through glove mask in rabbits in which DEX and MED were administered for pre-medication.

MATERIALS AND METHODS

Animals

Adult female New Zealand rabbits (mean ± SD body weight 3.8 ± 0.5 kg) were procured from a certified commercial source to use in medical researches. The animal number in each of the two study groups was four, for a total of eight.

Anesthesia

No restriction of food or water was applied until 2 h prior to the study. The rabbits were allowed to drink water until the start of study. The rabbits were randomly divided into two equal groups (n = 4). A 22G intracath\textsuperscript{®} was placed into marginal auricular vein of rabbits in both groups for drug and serum administration. The rabbits in DEX group were administered 20 mcg/kg of i.v. DEX HCl for premedication. MED group was administered 20 mcg/kg of iv MED\textsuperscript{2} for premedication. Induction was provided by 5% of sevoflurane\textsuperscript{3} + 4 L/min oxygen via glove mask in the both groups. General anesthesia was maintained with 3% of sevoflurane + oxygen on spontaneous respiration for 30 min.

Bispectral index measure

The animals’ temporomandibular region was shaved; its fat was eliminated with ether before the study. Human sensors were used as BIS sensor\textsuperscript{4}. Sensors consisted of 5 electrodes. Three were placed into frontal area as the remaining two into the pre-auricular area [19]. After ensuring the connection of the sensor to the BIS monitor, BIS value was continuously followed and recorded at 0 min (T0), 1\textsuperscript{st} (T1), 5\textsuperscript{th} (T5), 7\textsuperscript{th} (T7), 9\textsuperscript{th} (T9), 15\textsuperscript{th} (T15) 20\textsuperscript{th} (T20), 25\textsuperscript{th} (T25) and at 30\textsuperscript{th} min (T30) in both groups while the rabbits were awake. At T1 measure point, DEX and MED were applied; sedation was produced at T5; 5% of sevoflurane was administered through glove-mask method at T7 for induction; general anesthesia was obtained at T9 and continued during T15, T20, T25 and T30; they were awakened at the end of 30\textsuperscript{th} min.

Measure of Vital Parameters

On the day preceding the study, they were sedated; their femoral arteries were localized and catheterized under local anesthesia following sedation. At T0, T1, T5, T7, T9, T15, T20, T25 and T30 measure time points, the catheter-transducer connection was established for MAP measurement; MAP monitored on multi-channel monitor\textsuperscript{5}. For ECG monitoring, ECG electrodes were attached to all four extremities of the subjects and, ECG tracings from lead II were monitored and recorded on the multi-channel monitor. The pH\textsuperscript{6} was kept between 7.35 - 7.45, as PCO\textsubscript{2} between 35 - 45 mmHg.

All animals in both groups were documented during the study for AS according to the report by Saritas et al. [19], like 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 software package. A one-way ANOVA test was used to compare both groups. Test significance levels within and between the groups were checked using Duncan’s test. Descriptive results are expressed as mean ± standard deviation. For all comparative tests, a value of \( P < 0.05 \) was considered significant.

RESULTS

Anesthesia induction was occurred favorable in all rabbits without excitations. The values for MAP, HR, AS and BIS at different time points are indicated in Table 1. MAP and BIS decline in DEX group at the end of 1st min at statistical significance \( (P < 0.05) \) [Figures 1 & 2]. At the same time point, AS was recorded higher in DEX group \( (P < 0.05) \) [Table 1].

In the comparison of DEX group with MED group at T5; HR, MAP and BIS markedly declined in DEX group \( (P < 0.05) \); however, AS was found higher in DEX group as being statistically significant at the same time point \( (P < 0.05) \) [Table 1].

As it was at T5, HR (Figure 3), MAP and BIS were also found statistically significantly low in DEX group at T7 and T9; while AS was found higher as compared to MED group \( (P < 0.05) \). BIS value in MED group was low at a statistical significance level at T15, T20, T25 and T30 time points. \( (P < 0.05) \) [Table 1].

<table>
<thead>
<tr>
<th>Time (min)</th>
<th>Group</th>
<th>HR (Pulse/min)</th>
<th>MAP (mmHg)</th>
<th>BIS</th>
<th>AS</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>DEX</td>
<td>176.5 ± 13.3</td>
<td>92.2 ± 2.2</td>
<td>100 ± 0(^{a})</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>MED</td>
<td>179.2 ± 1.7</td>
<td>93.2 ± 2.2</td>
<td>100 ± 0(^{a})</td>
<td>0</td>
</tr>
<tr>
<td>1(^{a})</td>
<td>DEX</td>
<td>160.5 ± 6.6</td>
<td>88.2±1.7(^{*})</td>
<td>90 ± 3.7(^{*})</td>
<td>2.5 ± 0.5(^{*})</td>
</tr>
<tr>
<td></td>
<td>MED</td>
<td>173.5 ± 5.8</td>
<td>89 ± 1.4</td>
<td>97 ± 0.8(^{a})</td>
<td>0</td>
</tr>
<tr>
<td>5</td>
<td>DEX</td>
<td>152.5 ± 5(^{*})</td>
<td>78.1 ± 2.1(^{*})</td>
<td>82.2 ± 5.4(^{c})</td>
<td>3.25 ± 0.5(^{*})</td>
</tr>
<tr>
<td></td>
<td>MED</td>
<td>169.5 ± 2.8</td>
<td>83.2 ± 2.9</td>
<td>86 ± 0.8(^{b})</td>
<td>0</td>
</tr>
<tr>
<td>7(^{c})</td>
<td>DEX</td>
<td>149.0 ± 6.2(^{*})</td>
<td>72 ± 1.8(^{*})</td>
<td>70.0 ± 6.3(^{d*})</td>
<td>4.2 ± 0.5(^{*})</td>
</tr>
<tr>
<td></td>
<td>MED</td>
<td>165.1 ± 3.9</td>
<td>79.7 ± 1.5</td>
<td>78.2 ± 3.3(^{c})</td>
<td>1.7 ± 0.5</td>
</tr>
<tr>
<td>9</td>
<td>DEX</td>
<td>145.5 ± 5(^{*})</td>
<td>70.5 ± 1.2(^{*})</td>
<td>52.5 ± 8.7(^{c})</td>
<td>5.0 ± 0</td>
</tr>
<tr>
<td></td>
<td>MED</td>
<td>172.1 ± 8.6</td>
<td>75.7 ± 2.6</td>
<td>68.2 ± 2.5(^{d})</td>
<td>4.5 ± 0.5</td>
</tr>
<tr>
<td>15</td>
<td>DEX</td>
<td>159.0 ± 5.7</td>
<td>70.5 ± 1.2</td>
<td>61.5 ± 4.4(^{a})</td>
<td>5 ± 0</td>
</tr>
<tr>
<td></td>
<td>MED</td>
<td>160.2 ± 6.3</td>
<td>67.7 ± 1.7</td>
<td>48.5 ± 2.9(^{a})</td>
<td>4.7 ± 0.5</td>
</tr>
<tr>
<td>20</td>
<td>DEX</td>
<td>155.0 ± 7.3</td>
<td>70 ± 1.4</td>
<td>64.0 ± 2.8(^{d*})</td>
<td>5 ± 0</td>
</tr>
<tr>
<td></td>
<td>MED</td>
<td>157.7 ± 6.9</td>
<td>66.7 ± 1.7</td>
<td>45.5 ± 1.2(^{b})</td>
<td>5 ± 0</td>
</tr>
<tr>
<td>25</td>
<td>DEX</td>
<td>156.5 ± 6.6</td>
<td>68 ± 1.8</td>
<td>64.5 ± 6.2(^{a})</td>
<td>5 ± 0</td>
</tr>
<tr>
<td></td>
<td>MED</td>
<td>161.1 ± 4.6</td>
<td>66.5 ± 2.9</td>
<td>43.7 ± 3.5(^{d})</td>
<td>5 ± 0</td>
</tr>
<tr>
<td>30</td>
<td>DEX</td>
<td>157.5 ± 5.7</td>
<td>67.2 ± 1.9</td>
<td>62.2 ± 5.4(^{d})</td>
<td>5 ± 0</td>
</tr>
<tr>
<td></td>
<td>MED</td>
<td>160.7 ± 3.5</td>
<td>67.2 ± 2.5</td>
<td>44 ± 3.1(^{c})</td>
<td>4.7 ± 0.5</td>
</tr>
</tbody>
</table>

\(^{a}\)There is significant difference between groups \( (P < 0.05) \). The values with different letters in the same column have significant difference \( (P < 0.05) \). \(^{b}\)Administration time of medetomidine ve dexmedetomidine. \(^{c}\)Administration time of sevoflurane.
DISCUSSION

The reasons for commonly the use of DEX as a selective alfa-2 adrenergic agonist in intensive care units are sedation and causing to less respiratory depression [12,21]. Another reason of popularity of it is decreasing the opioid need in intensive care units. In their animal study, Hayashi et al. [10] reported that it eliminates the arrhythmia caused by epinephrine in dogs anesthetized with halothane. The reason of this anti-arrhythmic effect of alfa-2 adrenergic agonist is vagal activation [10,21].

MED is a racemic mixture of two stereoisomers, DEX and levomedetomidine. On the other hand, it was reported that levomedetomidine has no effects over cardiovascular parameters and do not produce marked sedation and analgesia [13,24]. It is mentioned that the pharmacokinetic effects of DEX and racemic MED are very similar [21]. MED is a potent 2-adrenoceptor agonist with sedative and analgesic features, commonly used as a pre-anesthetic agent in dogs. MAC-reducing effects of MED and the active racemate, DEX, on inhaled anesthetics were reported [4,8,17,24]. Thus, relatively greater CNS depression is expected at a given MAC of inhaled anaesthetic with co-administration of MED, compared to the same MAC of inhaled anaesthetic alone. In human anesthesiology, alpha-2 adrenergic agonists are used at low doses at a progressively increasing level to provide cardiovascular stability and tachycardia [11].

Sevoflurane is a volatile anesthetic providing rapid and smooth induction and recovery [2,7]. The effect of sevoflurane over HR is variable. It causes systemic vasodilatation and dose related declines in MAP can be seen [7,16].

Rabbits are the third most commonly used experimental animals in European countries. Rabbits carry high risk in terms of anesthesia and mortality risk is 14 times higher as compared to dogs [11]. Intubation of rabbits is difficult and they show reaction against mask induction. Rabbits are widely used in biomedical researches; major surgical procedures are performed on them. Nevertheless, it’s been reported that minimum alveolar concentration (MAC) does not represent the depth of anesthesia correctly in rabbits due to the individual response to anes-
thetics. Thus, an objective and reliable system showing the depth of anesthesia is very crucial [14].

Hypotension can occur during the use of inhalational anesthetics in rabbits. This situation may be caused by the cardiovascular depressive effects of anesthetics and sedatives [9,19].

In this study, we aimed to contribute to few numbers of rabbit anesthesia studies. From this point, these rabbits were premedicated with MED, which is commonly used in veterinary practice recently, and DEX, which its use has been gradually increased in intensive care units in human medicine as mentioned above; general anesthesia was produced with sevoflurane; the depth of anesthesia was determined with BIS monitoring.

In this presented study, HR declined in both groups at the 1st min of pre-medication. Moreover, decline in MAP levels in DEX group was found significant. Similarly to MAP, BIS also declined in DEX group. In light of these data, it was understood that DEX produces faster sedation as compared to MED. Additionally, the decline in HR, MAP and BIS at 5th min of premedication continued in DEX group, it was observed that the rabbits in which DEX was administered sedatized faster.

At the time point of T7, induction was provided in all rabbits from both groups with 5% sevoflurane through glove mask method under spontaneous respiration. During the measurements at the mentioned time points, HR, MAP and BIS continued to decline in DEX group samples. This was considered as a sign for which DEX group became anesthetized faster and increase in AS was recorded, as parallel to BIS. The rabbits in DEX group became anesthetized when we looked at AS. Nevertheless, BIS was recorded around 70 at the same time point.

At the time point of T9, anesthesia was maintained by inhalation of 3% of sevoflurane and oxygen mixture after induction maintenance in both groups. Anesthesia produced in both group was assured with both vital parameters and BIS and AS. However, data at T15 showed the occurrence of deeper anesthesia in MED group. Assessment of obtained data shows that MED provides long term deep sedation, as it is in dogs, and MED deepens the sevoflurane anesthesia as compared to bolus infused DEX.

As mentioned above, sevoflurane decreases the HR and arterial blood pressure as related to the dose. According to BIS, MAP and AS, deep anesthesia occurred in MED group at the time of points of T15, T20, T25 and T30. BIS and MAP remained stable in DEX group during the mentioned time points. AS showed that the rabbits in both groups were under deep anesthesia at the mentioned time points.

In our previously published rabbit study [19], both group were premedicated with DEX, induction was maintained with propofol; general anesthesia was provided with propofol infusion in one group and with isoflurane in the other. In this study, BIS was found around 60 in both propofol and isoflurane groups and deeper anesthesia was produced in propofol group. In this current study, the depth of anesthesia in the rabbits in DEX group is consistent with the findings of previous study.

CONCLUSION

In conclusion, sevoflurane administration with glove mask method provides sufficient anesthesia in the rabbits which were premedicated with DEX and MED in experimental studies or surgical procedures during veterinary practice. Besides the vital parameters and AS monitoring, BIS monitoring is also an effective method in determination of the depth of anesthesia in rabbits.

SOURCES AND MANUFACTURERS

1 Precedex, Abbot, Istanbul, Turkey.
2 Domitor, Pfizer, Istanbul, Turkey.
3 Sevorane, Abbot, Istanbul, Turkey.
4 Covidien, Complete Monitoring System, Norwood, MA, USA
5 KMA Petas-800 Multi-Channel Monitor, Petas Ltd., Istanbul, Turkey.
6 Gastat Mini, Yokohama, Japan.

Ethical approval. The study was approved by the animal local Ethics Committee (AKU, HADYEK Date: 21.11.2013. Number: 294 - 13), Afyon Kocatepe University.

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

REFERENCES


