Abstract

Introduction
Fifty-two American Society of Anesthesiologists II-III patients undergoing elective coronary artery bypass surgery were included in the study.

Materials and methods
We examined haemodynamic and cerebral responses to induction and intubation in cardiac surgery using different doses of an opioid. Before induction, T1 values of systolic arterial pressure, mean arterial pressure, diastolic arterial pressure, heart rate, saturation, bispectral index, latencies of auditory evoked potential waves (V. wave, Na wave, Pa wave and Nb wave) and spectral edge frequency values were measured. The patients were divided into four groups, each comprising 13 individuals.

During induction, the patients were administered opioids as follows:
- Group 1: propofol 2.5 mg/kg + rocuronium 0.7 mg/kg
- Group 2: propofol 2.5 mg/kg + rocuronium 0.7 mg/kg + fentanyl 3 mcg/kg
- Group 3: propofol 2.5 mg/kg + rocuronium 0.7 mg/kg + fentanyl 6 mcg/kg
- Group 4: propofol 2.5 mg/kg + rocuronium 0.7 mg/kg + fentanyl 9 mcg/kg

Above-mentioned parameters were repeated in the first minute of induction (T2). Intubation was performed in the third minute of induction, then the measurements were repeated (T3).

Results
Demographics were similar among all four groups. According to the systolic arterial pressure, mean arterial pressure, diastolic arterial pressure and heart rate values, a significant increase was found in group 1 compared to group 4 at T3. There was also a significant difference between group 1 and group 3 in mean arterial pressure and heart rate measures. No significant difference was found between the groups in terms of bispectral index. There was also no significant difference between the groups in terms of spectral edge frequency 1-2. Auditory evoked potential wave latencies (V. wave, Na wave, Pa wave, Nb wave) were found to be different between the time intervals. Wave latencies were increased at T2 compared to T1 and decreased at T3 compared to T2 in all the groups. The statistically significant difference was found between fentanyl 0 group and fentanyl 9 mcg/kg group in terms of Nb wave latency values.

Conclusion
Auditory evoked potential is found to be more reliable than bispectral index and electroencephalogram with regards to the responses to induction and intubation using fentanyl. We also observed that Nb wave latency response is the most significant latency of auditory evoked potential waves.

Introduction
Recently, various techniques and tools have been introduced in order to be aware of the adverse haemodynamic effects that may arise due to insufficient or overdose of anaesthetic agents and also to avoid economic losses. Electroencephalogram (EEG), bispectral index (BIS) analysis and auditory evoked potentials (AEPs) are the monitoring methods developed to determine the intraoperative anaesthetic depth. In this study, haemodynamic and cerebral effects during induction and intubation were evaluated using BIS, AEP and EEG in patients who are undergoing coronary artery bypass surgery.

Materials and methods
This work conforms to the values laid down in the Declaration of Helsinki (1964). The protocol of this study has been approved by the relevant ethical committee related to our institution in which it was performed. All subjects gave full informed consent to participate in this study.

After local ethic committee approval, 52 patients aged >18 years, American Society of Anesthesiologists (ASA) II-III, undergoing elective coronary artery bypass surgery were included in the study.

Exclusion criteria were as follows: ejection fraction (EF) <40%, arrhythmia or absence of sinus rhythm on electrocardiogram (ECG), uncontrolled hypertension, severe major organ damage (creatinine >2 mg/dL, aspartate aminotransferase >40 U/L, alanine aminotransferase >40 U/L, hematocrit <30%), opioid and propofol

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allergy, active neuromuscular disease, history of cerebrovascular event, psychiatric or neurological drug use, occlusive disease in the carotid artery, hearing problems, possibility of a difficult intubation and patient refusal.

The study patients were assessed the night before the surgery, and were informed about the study and anaesthesia technique to be applied, and their written consents were received. Antihypertensive drugs were continued until the morning till the day of operation. Premedication was not performed. Besides routine cardiac surgery anaesthetic monitoring, each patient was monitored using BIS. BIS module (BIS, Inc. S/5 monitor module, DATEX-Ohmeda Madison, WI, USA) and BIS sensor (BISstmQuatro, Aspect Medical Systems, Inc., Newton, MA, USA) were used for BIS monitoring. Pre-induction BIS values were recorded in all the patients. Furthermore, four electrodes were inserted while the patients were awake. Two electrodes were inserted on both postauricular mastoids (A1 and A2), one electrode on the beginning of the scalp in the midline, and one electrode was placed anywhere in the frontal region as the earthing line. EEG and AEP modules were inserted into DATEX-Ohmeda USA monitors. Headsets were put on both ears, and a click stimulant of average 70–80 Db was given. For AEP set, a click stimulant of average 8.9Hz and average was 1000Db.

Module (BIS, Inc. S/5 monitor module, DATEX-Ohmeda Madison, WI, USA) and BIS sensor (BISstmQuatro, Aspect Medical Systems, Inc., Newton, MA, USA) were used for BIS monitoring. Pre-induction BIS values were recorded in all the patients. Furthermore, four electrodes were inserted while the patients were awake. Two electrodes were inserted on both postauricular mastoids (A1 and A2), one electrode on the beginning of the scalp in the midline, and one electrode was placed anywhere in the frontal region as the earthing line. EEG and AEP modules were inserted into DATEX-Ohmeda USA monitors. Headsets were put on both ears, and a click stimulant of average 70–80 Db was given. For AEP set, a click stimulant of average 8.9Hz and average was 1000Db.

Results

Demographics were similar among all the study groups (Table 1).

Haemodynamic results

SAP

Before induction (T1), SAP values were significantly higher in all the groups than the after induction (T2) values ($p < 0.001$). After induction (T2), SAP values were significantly lower in all the groups compared to after intubation (T3) values ($p < 0.001$). T3 SAP values were high in group 1 compared to T1, while SAP values at T3 were lower in groups 2, 3 and 4 compared to T1 values. SAP was found to be significantly higher at T3 in group 1 compared to group 4 ($p = 0.024$).

DAP

Before induction (T1), DAP values were significantly higher in all the groups than the after induction (T2) values ($p < 0.001$). After induction (T2), DAP values were significantly lower in all the groups compared to after intubation (T3) values ($p < 0.001$). T3 DAP values were high in group 1 compared to T1, while DAP values at T3 were lower in groups 2, 3 and 4 compared to T1 values. DAP was found to be significantly higher at T3 in group 1 compared to group 4 ($p = 0.003$).

MAP

Before induction (T1), MAP values were significantly higher in all the groups than the after induction (T2) values ($p < 0.001$). After induction (T2), MAP values were significantly lower in all the groups compared to after intubation (T3) values ($p < 0.001$). T3 MAP values were high in group 1 compared to T1, while MAP values at T3 were lower in groups 2, 3 and 4 compared to T1 values. DAP was found to be significantly higher at T3 in group 1 compared to groups 3 and 4 ($p = 0.004$ and $p = 0.008$, respectively). (Figure 1)

HR

Before induction (T1), HR values were significantly higher in all the groups than the after induction (T2) values ($p < 0.001$). After induction (T2), HR values were significantly lower in all the groups compared to after intubation (T3) values ($p < 0.001$).

Table 1 Demographic data of all the study patients

<table>
<thead>
<tr>
<th></th>
<th>Group 1 (n = 13)</th>
<th>Group 2 (n = 13)</th>
<th>Group 3 (n = 13)</th>
<th>Group 4 (n = 13)</th>
<th>p values</th>
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<tr>
<td>Age (years)</td>
<td>59.08 ± 7.95</td>
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<td>Gender (F/M)</td>
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<td>5/8</td>
<td>4/9</td>
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<td>Weight (kg)</td>
<td>75.76 ± 10.97</td>
<td>75.53 ± 9.11</td>
<td>77.76 ± 14.70</td>
<td>73.07 ± 14.70</td>
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<tr>
<td>Height (cm)</td>
<td>166.84 ± 10.29</td>
<td>169.76 ± 10.51</td>
<td>167.84 ± 7.05</td>
<td>169.84 ± 10.90</td>
<td>0.829</td>
</tr>
</tbody>
</table>

Figure 1: Change of MAP and HR according to the groups and time.

Figure 2: Change of BIS according to the groups and time.

Cerebral results

*BIS*
There was a statistically significant change in all the groups between the times ($p < 0.001$). T2 was significantly lower than T1 and T3 was significantly higher than T2 in all the groups. No significant difference was found between the groups in terms of BIS measures. (Figure 2)

*SEF*
(SEF1: left hemisphere and SEF2: right hemisphere)
No difference was found between SEF1 and SEF2 in all the groups. SEF1 and SEF2 were found to be significantly lower at T2 compared to T1 ($p < 0.001$), while T3 was significantly higher than T2 ($p < 0.001$). (Figure 3)

*AEP*
Brainstem response (V wave):
V. wave latencies were found to be significantly higher at T2 compared to T1 in all the groups ($p < 0.001$). V. wave latencies were found to be significantly lower at T3 than T2 ($p < 0.001$), while T3 values were higher than T1 values in all the groups. No significant difference was found between left and right (V1 and V2) in terms of V. wave latencies. No significant difference was found among the different groups.

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groups in terms of V1 wave latencies ($p = 0.338$). No significant difference was found among the groups in terms of V2 wave latencies ($p = 0.556$). (Figure 4)

Cortex responses:

**Na wave**

No significant difference was found between left and right (Na1 and Na2) in terms of Na wave latencies. No statistically significant difference was found among the groups in terms of Na1 and Na2 wave latencies ($p = 0.095$ and $p = 0.06$, respectively). Na1 and Na2 wave latencies were found to be higher at T2 than T1 ($p < 0.001$). Na wave latencies were significantly higher at T2 compared to T3 in all the groups ($p < 0.001$). T1 values were lower than T3 values. (Figure 5)

**Pa wave**

No difference was found between the left and right (Pa1 and Pa2) in terms of Pa wave latencies. No statistically significant difference was found between the groups in terms of Pa1 and Pa2 wave latencies ($p = 0.277$ and $p = 0.071$, respectively). Pa1 and Pa2 wave latencies were found to be higher at T2 than T1 in all the groups ($p < 0.001$). Pa1 and Pa2 wave latencies were significantly lower at T3 than T1 in all the groups ($p < 0.001$). T1 values were lower compared to T3 values. (Figure 6)

**Nb wave**

No difference was found between the left and right (Nb1 and Nb2) in terms of Nb wave latencies. Nb1 wave latencies were found to be statistically significantly higher at T3 in group 1 compared to group 4 ($p = 0.049$). Nb2 wave latencies were found to be statistically significantly higher at T3 in group 1 compared to group 4 ($p = 0.054$). Nb1 and Nb2 wave latencies were found to be significantly higher at T2 than T1 in all the groups ($p < 0.001$). Nb1 and Nb2 wave latencies were found to be significantly lower at T3 compared to T2 in all the groups ($p < 0.001$). T1 values were lower than T3 values. (Figure 7)

**Discussion**

**Haemodynamic discussion**

In the study, in which we examined the haemodynamic and cerebral responses to induction and intubation in cardiac surgery using different doses of opioids, we did not find any difference among 3 μg/kg, the minimal dose and 9 μg/kg, the maximum dose (Figure 3: Change of SEF 1-2 according to the groups and time. (Fen 0: Fentanyl 0 group Fen 3: Fentanyl 3mcg/kg group Fen 6: Fentanyl 6mcg/kg group Fen 9: Fentanyl 9 mcg/kg group, İ.O.; Pre-induction İ.S.; Post-induction E.S.; Post-intubation)

**Figure 4:** Change of V 1-2 wave latencies according to the groups and time. (V1: Left brain V. wave latency, V2: Right brain V. wave latency, Fen 0: Fentanyl 0 group Fen 3: Fentanyl 3mcg/kg group Fen 6: Fentanyl 6mcg/kg group Fen 9: Fentanyl 9 mcg/kg group, İ.O.; Pre-induction İ.S.; Post-induction E.S.; Post-intubation)

**Figure 5:** Change of Na 1-2 wave latencies according to the groups and time. (Na1; Left brain Na wave latency, Na2; Right brain Na wave latency, Fen 0: Fentanyl 0 group Fen 3: Fentanyl 3mcg/kg group Fen 6: Fentanyl 6mcg/kg group Fen 9: Fentanyl 9 mcg/kg group, İ.O.; Pre-induction İ.S.; Post-induction E.S.; Post-intubation)
Figure 6: Change of Pa 1-2 wave latencies according to the groups and time.

Figure 7: Change of Nb 1-2 wave latencies according to the groups and time.

Cerebral discussion

In the present study, decrease in the BIS values in the group of induction which was administered propofol alone without additional fentanyl was found to be similar to the decrease in other groups. An increase in BIS values after intubation was also found to be similar to other groups. A significant increase in the haemodynamic values in the group without additional fentanyl was not accompanied by the increase in BIS values. Impairment of the correlation between BIS and haemodynamic changes was attributed to the cortical activity to be assessed with BIS monitoring; while the haemodynamic response against painful stimuli under anaesthesia arose from the subcortical regions. Spectral edge frequency (SEF) values were decreased after induction in all the groups, while they were increased post intubation in all the groups. Increased haemodynamic changes in the group not administered fentanyl were not correlated with the SEF values. Similar to the symptoms frequently used in daily practice, such as tachycardia, hypertension and tears, feeling pain and amnesia could not be distinguished from each other with BIS and SEF as well. The problems related to BIS monitoring in cardiac anaesthesia have arisen from the use of opioid, benzodiazepine and inhalation anaesthetics together with different doses and concentrations, esmolol, esmolol, lidocaine, direct vasodilators, a-adrenergic blockers, magnesium or calcium channel blockers have been discussed in the literature. Undoubtedly, it is obvious that such an alternative would be helpful to avoid potential side-effects, such as hypotension, postoperative prolonged depression, muscle rigidity, nausea and vomiting, related to the use of high-dose opioids. In this study, we observed that sympathetic response is decreased by a reasonable degree with low-to-moderate doses of fentanyl.

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and each of these agents to have different hypnotic effects. BIS was demonstrated to be correlated with sedation, sensory loss and motor response to the skin incision in case of the isoflurane to be used alone as the anaesthetic agent. However, this correlation was reported to weaken when isoflurane is used along with opioids, and motor response against the incision was found to disappear in higher BIS values. It was reported that response to verbal stimulation disappears with low-to-moderate doses of fentanyl, and BIS values show large variations and therefore, BIS monitoring is unsuitable for the evaluation of hypnotic activity of fentanyl. Barr et al. observed that when the clinically sufficient anaesthetic depth is achieved with fentanyl and midazolam in coronary artery surgery, BIS values are above 60. It was reported that when more than one anaesthetic agents were used in combination, reliability of BIS in monitoring of the anaesthetic depth might be lost; wake up due to increase of anaesthetic agent used to decrease high BIS values might be delayed; and the haemodynamics might be impaired. Driessen et al. examined BIS and SAP responses against intubation and skin incision with fentanyl and midazolam in anaesthesia in coronary artery graft surgery and found post-sternotomy and post-incision BIS values between 59 and 70. BIS values were observed to be at the levels of alertness, although they did not observe an increase in SAP responses against sternotomy and incision. In conclusion, two important problems were observed in the BIS monitoring due to using opioids and anaesthetics in combination in cardiac anaesthesia: the first one is despite a sufficient anaesthetic seen with BIS, the level of analgesia cannot be defined because of the subcortical reflex sympathetic response received against painful stimuli, and the other problem is BIS values might be inconsistent with the clinical findings because of the different hypnotic and analgesic efficiencies of the agents used. In this study, all the wave latencies (V, Na, Pa and Nb wave) were increased after induction in all groups, while AEP wave latencies were decreased after intubation. The difference in shortening of Nb wave latency between the fentanyl 0 and fentanyl 9 μg/kg groups was found to be statistically significant after intubation. Higher Nb wave latency in group 1 compared to group 4 was consistent with increased haemodynamic changes after intubation. Analgesic effects of opioids are obtained with the central opioid receptors. These receptors are often intense in the subcortical regions. Nb wave latency occurs in about 40–50 ms. Nb is the closest wave to the mesencephalon in AEP data. Suppression of the haemodynamic response of the patients under anaesthesia against painful stimuli is thought to be associated with intense receptors in the subcortical regions. Therefore, the accordance between the haemodynamic changes and decreasing of Nb latency between group 1 and group 4 may be the Nb wave occurrence site after intubation. In a study conducted by Schwender et al., the groups were administered different doses of fentanyl and alfentanil and responses of the brainstem and middle latency-auditory evoked potentials (ML-AEP) against the skin incision were assessed. V wave latency responses were stable in all the groups, while responses of ML-AEP waves were found to be variable. In this study, ML-AEP wave latencies were increased after induction, while they were decreased after intubation. The most significant change occurred in Nb wave. Loveman et al. intubated 14 patients undergoing cardiac surgery by administering fentanyl and propofol and monitored the anaesthetic depth with AEP. They found Na, Pa and Nb wave latencies to be increasing after intubation and incision. In a study conducted by Musialowicz et al., 32 patients were anaesthetized with propofol or isoflurane. Nb latency after intubation and Pa and Nb latencies after sternotomy were observed to be decreased in the isoflurane group compared to the propofol group.

**Conclusion**

In this study, we used AEP, BIS and EEG methods to evaluate the cerebral response against induction and intubation with different doses of fentanyl. We concluded that among the AEP wave latencies, Nb is the most suitable monitoring method that evaluates haemodynamic responses to intubation. However, we encountered many challenges related to impractical use, measurement and interpretation of AEP. Although measurement and interpretation of BIS and EEG parameters were easier, we observed discordant results in the patients who were administered opioids.

**Abbreviations list**

AEP, auditory evoked potentials; ASA, American Society of Anaesthesiologists; BIS, bispectral index; DAP, diastolic arterial pressure; ECG, electrocardiography; EEG, electroencephalogram; EF, ejection fraction; HR, heart rate; MAP, mean arterial pressure; ML-AEP, middle-latency-auditory evoked potentials; MLR, middle latency response; SAP, systolic arterial pressure; SEF, spectral edge frequency.

**References**

3. Nicolson SC, Jobes DR, Quinlan JQ. Cardiovacsular effects of esmolol in patients anesthetized with...

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