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SCIENTIFIC ARTICLE

Comparison of propofol and midazolam on patients undergoing spinal surgery with intraoperative wake-up test: randomized clinical trial

Ozgur Canbay^a, Basak Altiparmak^{b,*}, Nalan Celebi^a, Heves Karagoz^a, Fatma Saricaoglu^a

^a Department of Anesthesiology and Reanimation, Hacettepe University Faculty of Medicine, Ankara, Turkey

^b Biga State Hospital, Canakkale, Turkey

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Wake-up test;
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Abstract

Background and objectives: Instrumentation in correction operations for spinal deformities carries a 0.5–5% risk of injuring the spinal cord. The wake-up test is used for early detection of these injuries. In this study we compared the effects of propofol and midazolam during wake-up test in scoliosis surgery.

Methods: Thirty patients were randomly assigned as group P and group M. Anesthesia was induced with propofol 2.5 mg kg⁻¹ for group P or midazolam 0.5 mg kg⁻¹ for group M with remifentanyl 0.5 µg kg⁻¹ and cisatracurium 0.15 mg kg⁻¹ for both groups. At the maintenance of anesthesia O₂/air and infusions of remifentanyl and cisatracurium were used. In group P, propofol 6–10 mg kg⁻¹ h⁻¹ and in group M, midazolam 0.5 mg mg kg⁻¹ were preferred. Approximately 15 min before the wake-up test, all drugs were discontinued. At the wake-up test, anesthesiologist asked the patients to open their eyes and squeeze his/her hand at every 30s until the patients responded. Then patients were told to wiggle their toes. Hemodynamic parameters, time of eye-opening, appropriate movement upon verbal command were evaluated. BIS frequency throughout the operation was recorded.

Results: The eye opening time was 9 ± 2.15 min in group P and 7 ± 3.15 min in group M. Motor movement time was 12 ± 2.55 min in group P and 21.25 ± 3.93 min in group M.

Conclusion: Propofol provided better wake-up conditions and conducted a better neurologic assessment within the same BIS values than midazolam.

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* Corresponding author.

E-mail: basakugurlu@me.com (B. Altiparmak).

PALAVRAS-CHAVE

Teste de despertar;
Propofol;
Midazolam;
BIS;
Cirurgia de coluna

Comparação de propofol e midazolam em pacientes submetidos à cirurgia de coluna vertebral com teste de despertar no intraoperatório: estudo clínico randomizado

Resumo

Justificativa e objetivos: A instrumentação em cirurgias de correção de deformidades da coluna vertebral tem risco de 0,5 a 5% de lesionar a medula espinhal. O teste de despertar é usado para a detecção precoce dessas lesões. Neste estudo comparamos os efeitos de propofol e midazolam durante o teste de despertar em cirurgia de escoliose.

Métodos: Trinta pacientes foram designados de forma aleatória para os grupos P e M. A anestesia foi induzida com propofol ($2,5 \text{ mg kg}^{-1}$) no grupo P ou midazolam ($0,5 \text{ mg kg}^{-1}$) no grupo M, com remifentanil ($0,5 \mu\text{g kg}^{-1}$) e cisatracúrio ($0,15 \text{ mg kg}^{-1}$) em ambos os grupos. A manutenção da anestesia foi feita com O_2/ar e infusões de remifentanil e cisatracúrio. Nos grupos P e M, respectivamente, doses de propofol ($6\text{--}10 \text{ mg kg}^{-1} \text{ h}^{-1}$) e de midazolam ($0,5 \text{ mg kg}^{-1}$) foram preferidas. Aproximadamente 15 min antes do teste de despertar, todos os medicamentos foram interrompidos. No teste de despertar, o anestesiológista pedia ao paciente que abrisse os olhos e apertasse sua mão a cada 30 s até que o paciente respondesse. Depois, o paciente era solicitado a mexer os dedos dos pés. Os parâmetros hemodinâmicos, o tempo de abertura dos olhos e o movimento apropriado sob comando verbal foram avaliados. A frequência do BIS foi registrada durante toda a cirurgia.

Resultados: O tempo de abertura dos olhos foi de $9 \pm 2,15$ min no grupo P e de $7 \pm 3,15$ min no grupo M. O tempo de movimento motor foi de $12 \pm 2,55$ min no grupo P e de $21,25 \pm 3,93$ min no grupo M.

Conclusão: Propofol proporcionou melhores condições de despertar e possibilitou uma melhor avaliação neurológica dentro dos mesmos valores do BIS que midazolam.

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Introduction

Instrumentation in correction operations for spinal deformities as vertebral fusion, congenital and traumatic scoliosis, carries a 0.5–5% risk of injuring the spinal cord during spinal surgery.¹ These complications are generally results of complex factors such as direct effects of compression on the spinal cord, distraction, the effects of spinal ischemia or arterial hypotension.^{2–4} The intraoperative monitoring of spinal cord function is necessary to prevent these series complications. The wake-up test is one of the methods used for early detection and possibly prevention of these spinal cord injuries⁵ and was performed for the first time successfully by Vauzella and Stagmara in 1973.⁶

Somatosensorial evoked potentials (SSEPs) and motor evoked potentials (MEPs) are more recent methods which give an idea about the spinal cord functions intraoperatively. But many factors may affect these kinds of neuromonitoring and yield erroneous results which necessitate the wake-up test to prevent long-term complications. A wake-up test is recommended for all cases in which threshold monitoring changes occur because spinal cord injury may exist even when monitored variables return to baseline.⁷

The purpose of the wake-up test is to monitor voluntary motor function of the lower limbs once the vertebrae have been instrumented and distracted. The depth of anesthesia is gradually lightened up to the point where patients are able to respond to verbal commands. As the voluntary movement of lower extremities is demonstrated, the depth of anesthesia is increased to complete the surgery.⁸ That is why during the wake-up test monitoring the depth of anesthesia carries additional importance. BIS values between 85 and 90 may also support superficial anesthesia or

wakefulness at which stage reliable neurological assessment can be made.

Nitrous oxide and halogenated anesthetics are known to have restraining effects on the MEPs from the lower extremities. TIVA (total intravenous anesthesia) has been recommended in the correction of scoliosis for several years because it may provide optimal conditions to monitor the spinal cord function reliably with rapid emergence during the wake-up test.^{9,10}

In this study our aim is to compare the effects of two different intravenous anesthetic agents during wake-up test in patients undergoing scoliosis surgery. Although TIVA is recommended, there is no study comparing the effects of propofol and midazolam together with remifentanil infusion during wake-up test under BIS monitoring.

Materials and methods

Thirty patients (between 10 and 30 years old, ASA physical status I–II) who had idiopathic spinal deformity but no neurologic deficit were enrolled in this randomized prospective study. Following local ethics committee approval and obtainment of informed consent from patients or the parents of the children, all patients were scheduled for posterior instrumentation operation. None of the patients had any history of drug allergy, mental retardation or psychiatric problems. After detailed specific information about the wake-up test was instructed, all the patients were told that during the wake-up test the anesthesiologist would first ask them to squeeze the anesthesiologist's hand, then wiggle their toes. Patients were randomly assigned for two groups as group P ($n = 15$) and group M ($n = 15$), using a computer-generated

table. Propofol or midazolam would be used as hypnotic agent for groups P or M respectively. No preoperative medication was given.

In the operating room, following preoxygenation for 3 min, anesthesia was induced with propofol 2.5 mg kg^{-1} for group P or midazolam 0.5 mg kg^{-1} for group M with remifentanyl $0.5 \mu\text{g kg}^{-1}$ (over 30–60s) and cisatracurium 0.15 mg kg^{-1} for both groups. At the maintenance of anesthesia O_2/air (50%/50%) and infusions of remifentanyl $0.025\text{--}0.2 \mu\text{g kg}^{-1} \text{ min}^{-1}$, cisatracurium $1\text{--}2 \mu\text{g kg}^{-1} \text{ min}^{-1}$ were used in both group. In the group P, propofol $6\text{--}10 \text{ mg kg}^{-1} \text{ h}^{-1}$ and in the group M, midazolam $0.5 \text{ mg kg}^{-1} \text{ h}^{-1}$ were preferred for maintenance of anesthesia. Intraoperative monitoring consisted of pulse oximetry, electrocardiogram, invasive arterial blood pressure, central venous pressure, end-tidal carbon dioxide, nasopharyngeal temperature and bispectral index. A disposable Bis Sensor (Aspect Medical Systems) was applied to patients' forehead prior to induction of anesthesia. Then the patients are placed in prone position. Anesthesia depth was monitored with BIS and hypnotic doses were titrated to keep BIS frequency approximately between 40 and 60. To minimize blood loss, controlled hypotension to maintain a mean blood pressure of 60–70 mm Hg was attempted in all of the patients with infusion of Nitroglycerin $0.1\text{--}4 \mu\text{g kg}^{-1} \text{ min}^{-1}$. The mean arterial pressure and heart rate were recorded at six different times as: before induction, after induction, at intubation, before surgical incision, at the beginning of the test and at the end of the test.

For the wake-up test, approximately 15 min before the predicted test time, all the drugs were discontinued. At the time of the wake-up test, anesthesiologist asked the patient to open his/her eyes and squeeze his/her hand at every 30s until the patient responded. Then patient was told to wiggle his/her toes. Hemodynamic parameters, time of eye-opening, appropriate movement upon verbal command were evaluated. BIS frequency before, during and at the end of the wake-up test were recorded. The wake-up test was ended after the appropriate motor responses were obtained and the patients were reanesthetized with repeated bolus propofol or midazolam doses for groups P and M respectively and anesthesia was maintained with the pretest medications. At the end of the surgical procedure, infusions were stopped and neuromuscular blockage was reversed with neostigmine 0.05 mg kg^{-1} . Patients were transported to PACU and extubated there. Neurologic examination was performed upon recovery. Postoperative analgesia was provided by intravenous morphine PCA with basal infusion of 0.1 mg kg^{-1} and bolus of 0.1 mg kg^{-1} with 15 min lock out period. Recall and pain during wake-up test were questioned at the second postoperative day by an anesthesiologist blind to the study.

Mann-Whitney *U* test was used for the comparison of numerical values between groups and Chi square test for the comparison of qualitative data between groups.

Results

Patient demographics were similar between groups ($p > 0.05$) (Table 1). Throughout the operation and during the wake-up tests hemodynamic parameters were similar in group P

Table 1 Patient and surgical characteristics.

	Group P	Group M
Age (year)	17 ± 7	14 ± 2.6
Gender (F/M)	9/3	9/3
Weight (kg)	49.6 ± 15.3	44.0
Height (cm)	148.5 ± 5	143.4 ± 4
Mean operation time (min)	214.1 ± 65.0	284.1 ± 93.9

and group M. There were no significant differences at mean arterial pressure and heart rate at each time points between groups (Figs. 1–4).

The mean time from the start of wake-up test to eye opening and motor movement upon verbal command (the wake-up time) was significantly lower in group P than group M (Table 2).

Neurologic deficits were revealed in two patients during their first wake-up tests and the deficits were found to be reversed in the second wake-up tests performed after loosening of screws.

There was statistically significant difference for recall of the wake-up test between the propofol and the midazolam groups ($p < 0.05$). Nine of the patients in the propofol group had memory of the wake-up test, but no recall of intraoperative pain whereas no patient had any memory of the wake-up test in midazolam group. Other intraoperative

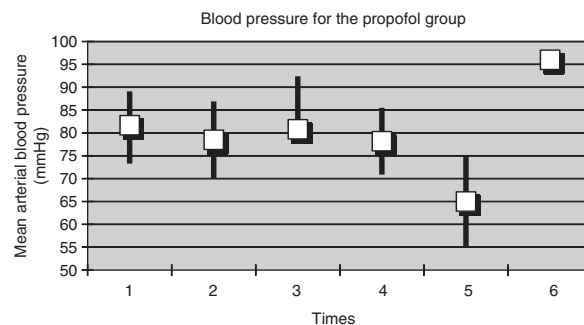


Figure 1 Mean arterial blood pressure values for Propofol Group (Times, 1: before induction, 2: after induction, 3: at intubation, 4: before surgical incision, 5: at the beginning of the test and 6: at the end of the test) (mean ± SD).

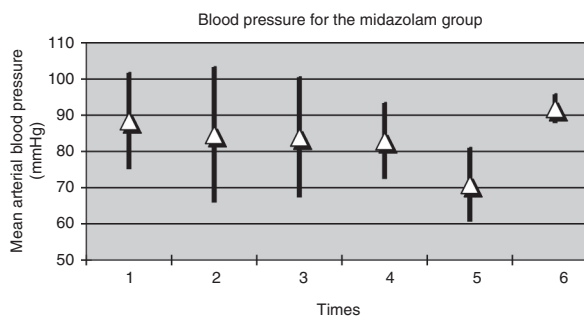


Figure 2 Mean arterial blood pressure values for Midazolam Group (Times, 1: before induction, 2: after induction, 3: at intubation, 4: before surgical incision, 5: at the beginning of the test and 6: at the end of the test) (mean ± SD).

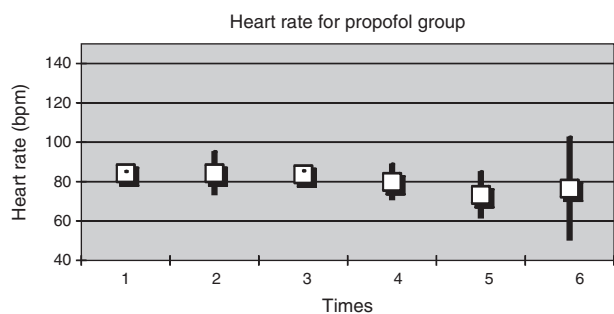


Figure 3 Heart rate (beat per minute) for Propofol Group (Times, 1: before induction, 2: after induction, 3: at intubation, 4: before surgical incision, 5: at the beginning of the test and 6: at the end of the test) (mean \pm SD).

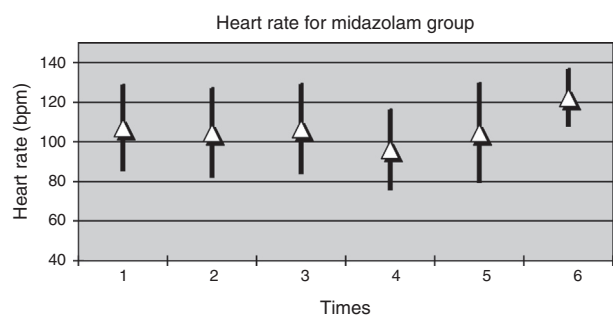


Figure 4 Heart rate (beat per minute) for Midazolam Group (Times, 1: before induction, 2: after induction, 3: at intubation, 4: before surgical incision, 5: at the beginning of the test and 6: at the end of the test) (mean \pm SD).

Table 2 Mean time for eye opening, motor movement and wake-up test for patients in group P and group M.

	Propofol	Midazolam
Eye opening time (min)	9 \pm 2.15 ^a	17.35 \pm 3.15
Motor movement time (min)	12 \pm 2.55 ^a	21.25 \pm 3.93
Wake-up test time (min)	13 \pm 3.35 ^a	24 \pm 4.21

^a $p < 0.05$.

events before and after the wake-up tests were not recalled by any patients in neither of the groups.

Discussion

Spinal cord injury is one of the most feared complications of scoliosis surgery. Neurologic complications during the repair of spinal deformities may result from complex factors such as direct effect of compression on the spinal cord, distraction, spinal ischemia or arterial hypotension. During "Harrington rod" instrumentation and posterior spinal fusion to correct scoliosis, excessive traction on the spinal cord can directly lead to vascular spasm or neuropraxia.² Prevention or early detection of neurologic complications necessitate neuromonitoring whether or not they are supported with intraoperative arousal tests.

As one of the intraoperative neuromonitoring modalities, somatosensory evoked potentials (SSEPs) show the posterior spinal cord function, but anesthetic agents

(inhaled agents, thiopental, etomidat and narcotics), hypothermia, hypotension, hypoxia, anemia and surgical stimulus decrease the amplitude of SSEPs and extend the latent period. Mean arterial pressure, particularly decrease below 60 mm Hg, can result in significant changes in SEPs, which may or may not be indicative of motor deficit.¹¹ Although motor evoked potentials (MEPs) give a better estimate of spinal cord function than SSEPs, they are also known to have a decreased amplitude with anesthesia.¹² It is recommended to perform wake-up test even if monitoring of the evoked potentials returns to baseline following interventions upon any sign of deterioration of spinal cord functions.⁷ With known limitations of these neuromonitoring modalities we used wake-up test for all our patients to detect any intraoperative spinal cord injury.

TIVA has been commonly used in the correction of scoliosis for wake-up tests to enable a rapid patient recovery and an immediate neurological examination. The development of propofol and remifentanyl as short-acting injectable anesthetics provides an opportunity to make an intraoperative wake-up test more reliable.¹³ As propofol has a rapid onset and rapid emergence, it has been commonly preferred for short procedures. In a study conducted by Dogan et al., propofol was used in electroconvulsive therapy and in this study eye opening time was found as 7.95 ± 1.27 min and time needed for obeying commands was 13.10 ± 1.97 min.¹⁴ In our study, in the propofol/remifentanyl group, eye opening time was 9 ± 2.15 min and motor movement time was 12 ± 2.55 min. These results are very similar with the study conducted by Blussé van Oud-Alblas et al. who compared composite auditory evoked potential index and BIS during wake-up test.¹⁵ In this study, propofol/remifentanyl infusion was used via conventional infusion pump technology for maintenance of anesthesia and the wake-up onset was reported as 9.4 ± 2.4 min. On the other hand, Grottko et al. reported shorter wake-up time than both of these studies. In their study, propofol/remifentanyl, propofol/sufentanyl and desflurane/remifentanyl combinations were compared.¹⁶ In the propofol/remifentanyl group time needed for head elevation was 9.3 ± 2.2 min and motion of feet took 9.4 ± 2.4 min. Although the onset of wake-up time seems similar in two studies, motor motion time is shorter in the study of Grottko et al. The delay in our study may result from the continuous infusion of neuromuscular blocking agent throughout the operation. In another study conducted by Imani et al., propofol/remifentanyl and propofol/alfentanil infusions were compared for posterior spinal fusion including wake-up test.¹⁷ In propofol/remifentanyl group, responding to verbal command was found only 4.1 ± 2 min whereas there was an extra preparation period (from discontinuation of anesthesia until start of spontaneous ventilation) for wake-up test in this study.

In our study, in midazolam/remifentanyl group, eye opening time was 7 ± 3.15 min and motor movement time was 21.25 ± 3.93 min. The test time of midazolam/remifentanyl group was significantly longer than propofol/remifentanyl group. In the light of this information, we can state that in our study propofol/remifentanyl combination provided a more rapid wake-up test than midazolam/remifentanyl. These results correlate with the study conducted by Eroğlu et al. in which propofol and midazolam groups combined with fentanyl infusion, instead of remifentanyl. In this study,

wake-up time for propofol group was shorter than midazolam group and propofol/fentanyl infusion provided a better quality of neurologic assessment during wake-up tests.¹⁸ On the other hand, in 2011 Kuruefe et al. conducted a study in which they compared midazolam/remifentanyl and midazolam/alfentanil in 38 patients undergoing scoliosis surgery with intraoperative wake-up test.¹⁹ In this study, in the midazolam/remifentanyl group wake-up test time was 5.8 ± 0.91 min and in the midazolam/alfentanil group 5.5 ± 0.68 min. Both results are significantly shorter than our study. In our study midazolam was infused based on a fixed dose ($0.5 \text{ mg kg}^{-1} \text{ h}^{-1}$) until 15 min before the wake-up test, although in the study by Kuruefe et al. midazolam infusion was arranged in a different manner. In this study, scoliosis operation was divided into 6 different stages and midazolam infusion was decreased gradually according to these stages. Difference between the wake-up test times may result from different ways of midazolam infusion.

In our study, no patient reported recall of wake-up test in midazolam group, although nine of the patients in propofol group had memory of the wake-up test. This significant difference between groups is probably due to the amnesic effect of midazolam. Likewise in the study of Kuruefe et al., only one patient out of 38 (2.6%) had recall of wake-up test.¹⁹ In another study conducted by McCann et al., 34 patients were premedicated with midazolam before operation and all patients received intermittent doses of midazolam before the wake-up test.²⁰ The incidence of explicit recall was found in 17.6% (6 patients) which was a smaller incidence than expected based on another voluntary adult study.²¹ In this study McCann et al. stated that BIS in the setting of a complex surgical procedure in which vasoactive drugs were used to modify hemodynamic responses and in which movement during an intraoperative wake-up test and postoperative recall could be used as discrete end points. They demonstrated a significant increase in BIS during the intraoperative wake-up test with a small incidence of explicit recall, which was independent of anesthetic technique.²⁰ As it is reported before, the depth of anesthesia assessment with BIS monitoring provides us an ability to inform the surgeon in time and to conduct a more reliable test.²² In our study we performed wake-up tests with effective results at the BIS values between 80 and 90. It also helped us to give more specific information to the surgeon about the reliability of the test. With these findings we suggest that especially in wake-up test BIS monitoring seems to be more useful than the other clinical signs of wakefulness.

In our study there was no statistical difference between the hemodynamic stability of the groups. Nitroglycerin infusion was needed to maintain controlled hypotension for 4 patients in group P and 5 patients in group M. The continuous remifentanyl infusion in both of the groups may probably lead to the hemodynamic stability in each group.

In conclusion, propofol provided better wake-up conditions and conducted a better neurologic assessment within the same BIS values than midazolam. We suggest that using propofol/remifentanyl infusion combined with BIS monitoring for depth of anesthesia increases the success of wake-up test in spinal surgery. However, it is necessary to conduct studies with more cases and also to evaluate the costs.

Conflicts of interest

The authors declare no conflicts of interest.

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