Original Article

The effect of dexmedetomidine on wake-up test quality when muscle relaxants are not used: A randomized control trial

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ABSTRACT

Background and Aims: Stagnara wake-up test is a simple reproducible neuromonitoring method during spinal surgery which replaces the evoked potential monitoring in the absence of neuromonitoring facilities. Dexmedetomidine (DEX) effect on the intraoperative wake-up test is still unclear. The present study was conducted to evaluate the effectiveness of DEX on the quality of wake-up test during spinal correction surgery. **Methods:** A randomized controlled study was carried out over 62 patients randomized into two equal groups planned for elective minimally invasive corrective spine surgery. Instead of atracurium administration in the control group, patients in the experimental group were administered titrated continuous intravenous infusion of DEX at a dose of 0.2–0.7 μg/kg/hour. Lidocaine 2% spray around the vocal cords was done in both the groups to facilitate toleration of the endotracheal tube. **Results:** The DEX group showed statistically significant longer duration and better quality of the wake-up test. Statistically significant better haemodynamic state, a lower amount of intraoperative sedatives and higher amount of intraoperative analgesics were also evident in the DEX group. The postoperative Ramsay sedation scale was significantly lower in the DEX group just after extubation. **Conclusion:** The DEX use has shown an improving effect on the wake-up test quality, with slightly prolonged wake-up time. The present work supports the use of DEX as an adjuvant drug alleviating the need for the neuromuscular blockade, inducing a better haemodynamic profile, exhibiting better sedation and improving the awakening condition.

Key words: Corrective spine surgery, dexmedetomidine, wake-up test

INTRODUCTION

Scoliotic correction is a very challenging procedure and carries a lot of complications.[1] Both motor and sensory evoked potentials are used as surrogates for postoperative clinical wellbeing, but the wake-up test is more informative intraoperatively.[2] The Stagnara wake-up test was first described in 1973 and involves the intraoperative assessment of the spinal cord function by waking the patient up in the middle of surgery.[3]

Dexmedetomidine (DEX) is an α2 adrenergic receptor agonist with analgaesic, sedative and antisympathetic properties.[4] It is characterized by mild respiratory depression and easy wake-up effects.[5] DEX provides a neuropharmacological state that simulates the natural sleep pathways. Although the DEX effect on the intraoperative wake-up test quality has been assessed,[6] its safety and effectiveness are still controversial.

The primary outcome of this study was the wake-up test time and quality during minimally invasive spinal correction surgery, and the secondary outcome measures were the perioperative haemodynamic parameters and the amount of sedatives and analgaesic doses consumed by the patients. We hypothesized that

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using DEX is associated with better quality of wake-up test, which is ubiquitously available.

METHODS

This is a prospective double-blinded randomized controlled trial (RCT) that was conducted during the period from October 2020 to September 2021. The study was started after obtaining the approval of the research ethics committee provided by the Ethical Committee (approval number 10/2020 ANET 5 dated October 2020). It was prospectively registered in the Pan-African Clinical Trials Registry (PACTR202010818690380) and performed in accordance with the principles of Helsinki declaration.

The study included patients planned for elective minimally invasive corrective spine surgery during the study period. The patients who were of the physical status class I or II, according to the American Society of Anaesthesiologists (ASA), and generally fit for surgery under general anaesthesia were eligible for the study. All patients underwent thorough systemic examination and preoperative work-up.

Patients with neural or neuromuscular disorders, hearing problems, hypersensitivity to any of the study drugs and/or not willing to participate in the study were excluded. An informed written consent was obtained from each patient.

The eligible patients fulfilling all inclusion criteria and no exclusion criteria were allocated to their groups in a ratio of 1:1. Patient's allocation was implemented randomly based on a computer-created randomization list. The allocation was blinded for the participants, the trial investigators and the trial statistician who conducted the analyses. Patients were recruited to either the group I (DEX group), the experimental group; or group II (Atracurium group), the control group [CONSORT flow chart diagram].

Preparation and administration of the used drugs were accomplished by an independent anaesthesiologist. Before the surgery, the patients were taught about the wake-up test.

All patients were premedicated with oral bromazepam (1.5 mg) the night before surgery and 2 hours before being called to the operation theatre. On arrival at the operation theatre, continuous electrocardiography, non-invasive blood pressure (NIBP), pulse oximetry, train of four (TOF) guard and bispectral index (BIS) monitoring were applied. An 18-gauge cannula was placed in a peripheral vein, and a ringer lactate infusion (7 ml/kg/hour) was started. Pre-anaesthetic medications included I.V. glycopyrrolate (4 μg/kg) and I.V. midazolam (0.03 mg/kg). Anaesthesia was induced with I.V. propofol (2 mg/kg) and I.V. fentanyl (2 μg/kg). Endotracheal intubation was facilitated by I.V. injection of succinylcholine (1 mg/kg) and lidocaine 2% spray around the vocal cord. When the effect of succinylcholine wore off, patients were started on infusion of DEX at a dose of 0.2–0.7 μg/kg/hour in experimental group (group I), or atracurium at a dose of 0.3 mg/kg/hour guided by TOF guard in control group (group II).

Then, all patients were mechanically ventilated targeting an end-tidal CO_2 ($ETCO_2$) of 35–40 mmHg. Isoflurane minimum alveolar concentration (MAC) was adjusted to keep BIS at 40–50. If the haemodynamic values rose above the targeted figures in presence of accepted BIS, $ETCO_2$, oxygen saturation (SpO_2) and muscle relaxation, I.V. fentanyl (1 μg/kg) was given. Hypotension (mean arterial blood pressure less than 60 mmHg) was treated with incremental doses of ephedrine (5 mg). Thirty minutes prior to the surgeons' call for the intraoperative wake-up test, both infusions were stopped and recovery from the neuromuscular block was checked by transcutaneous TOF stimulation of the ulnar nerve at the wrist. If there was a residual neuromuscular blockade in the control group, this was antagonized with I.V. neostigmine (0.05 mg/kg) and glycopyrrolate (0.01 mg/kg), while in the experimental group, DEX infusion was stopped 30 minutes before surgeon call for wake-up test. Awakening was accomplished by withdrawing isoflurane 20 minutes before the test in both groups.

For the wake-up test, the patient's name was called repeatedly at 30-second intervals. This was followed by the patient's request to open and close hand fingers and then to flex both legs independently. Wake-up time (time from the interruption of anaesthesia till the patient responds by moving his fingers) was recorded in seconds using a stopwatch by an independent investigator not involved in the study. Midazolam (0.1 mg/kg) was given if the patient was anxious as in poor-quality wake-up test.

Anaesthesia maintenance was continued after completing the wake-up test. All patients received I.V.

paracetamol (15 mg/kg) 30 minutes before the end of surgery. After finishing the surgery, DEX infusion was stopped in the experimental group and the residual neuromuscular blockade was antagonized in the control group. Trachea were extubated and transferred to the postanaesthesia care unit.

The wake-up test time and quality were recorded. The test quality was graded on a 3-point scale (**Good**: quiet awakening, patient obeys orders and voluntary movements of hands and feet; **Satisfactory**: sudden awakening, patient seems confused, spontaneous movement of extremities not endangering spondylodesis; and **Poor**: dramatic awakening, patient is agitated, violent trunk movements threatening the stability of the device).[7] The intraoperative haemodynamic parameters were recorded eight times: before anaesthesia induction, after intubation, after surgical incision, at the test start, at the test end, after recovery and two times postoperatively (at the first and the second hours).

Postoperative sedation was assessed at 0, 15 and 30 minutes after extubation using the Ramsay sedation scale (RSS). This scale is graded from 1 to 6; patients had grade 1 if they were anxious, restless or both, grade 2 when cooperative, orientated and tranquil, grade 3 if they were responding to commands, grade 4 if there was a brisk response to stimulus, grade 5 if the response to the stimulus was sluggish and grade 6 if there was no response to the stimulus.[8]

The obtained data were recorded and analyzed using the SPSS statistical package, version 22 (IBM Corp., Armonk, NY, USA). After performing tests of normality, the Student's t-test and Mann–Whitney test were used to compare numerical data as appropriate, while the Chi-square test was used to compare categorical data. The level of significance was considered at *P* values less than 0.05.

RESULTS

This RCT included 62 patients, 31 in each group and both groups were matching in the basal demographic data [Table 1].

Statistically significant longer duration of the wake-up test was found in the DEX group; however, better test quality was evident as a good quality in 61.3% of patients in the DEX group compared to 19.4% of patients in the atracurium group [Table 2].

Statistically significant lower mean heart rate was observed in the DEX group compared with the atracurium group; this difference was found in the measures recorded after intubation, at the test beginning, at the test end, after recovery and postoperatively ($p < 0.001$) [Figure 1].

Likewise, the mean arterial blood pressure was significantly lower in the DEX group. This significant reduction was noted in the measures recorded at the test beginning, at the test end, after recovery and postoperatively ($p < 0.001$) [Figure 2].

Statistically significant lower amount of intraoperative sedatives (Midazolam) and higher amount of intraoperative analgesics (Fentanyl) were needed in the DEX group, compared to the atracurium group [Table 3].

Postoperative sedation RSS was significantly lower in the DEX group just after extubation; this statistically significant difference faded out at 15 and 30 minutes after extubation [Table 3].

DISCUSSION

In our study, DEX infusion improves the quality of wake-up test as DEX is particularly characterized by being sedative, anxiolytic and sympathetic inhibitor, with no respiratory depression effect.[4,5] DEX acts selectively on the α2 adrenergic receptors; therefore, it creates a condition that resembles normal sleep.[9]

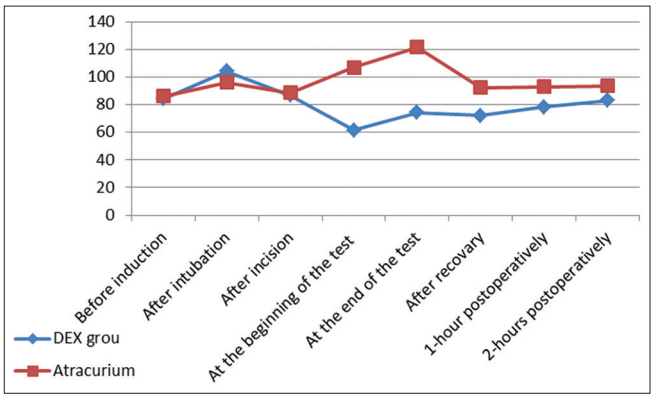


Figure 1: Heart rate measures in both groups

Table 1: Baseline data of the study patients

	Experimental group (*n*=31) Mean±SD	Control group (*n*=31) Mean±SD	*P*
Age (years)	15.6±2.6	15.9±2.4	0.57
BMI (kg/m^2)	26.1±1.4	26.3±1.8	0.63
Surgery duration (minutes)	265.6±35.3	269.7±36.1	0.66

Table 2: Wake-up test in the study patients

	Experimental group (*n*=31) Mean±SD			Control group (*n*=31) Mean±SD			*P*
Wake-up duration (seconds)	920.9±162.2			672.4±194.4			<0.001*
	Good *n*	Satisfactory *n*	Poor *n*	Good *n*	Satisfactory *n*	Poor *n*	
Wake-up quality	19	9	3	6	20	5	0.002*

Table 3: Peri-operative data in the study patients

	Experimental group (*n*=31) Mean±SD	Control group (*n*=31) Mean±SD	*P*
Midazolam (mg)	3.2±0.62	6.1±0.8	<0.001*
Fentanyl (µg)	220.5±29.7	180.5±16.6	<0.001*
Ramsay sedation scale (RSS)			
At 0 minutes	2.8±1.1	3.8±0.9	0.001*
At 15 minutes	2.3±0.8	2.6±0.9	0.16
At 30 minutes	1.6±0.6	1.9±0.7	0.13

In contrast to other sedatives working on the cerebral cortex, DEX is less likely to affect awakening during spinal surgery.[6]

Muscle relaxation is an important element of general anaesthesia. Routinely, neuromuscular blocking drugs (NMBs) are needed for tracheal intubation and are usually required in surgical patients under general anaesthesia.[10] However, the use of NMBs in general anaesthesia could be complicated by several adverse events, including delayed recovery, residual paralysis, release of histamine and even anaphylactic reactions.[11] All these events require reversal by antagonizing agents such as neostigmine/atropine.[12] In order to avoid NMBs side effects, efforts are exerted to preclude their use during general anaesthesia. It was presumed that some types of surgeries do not require continuous muscle paralysis during anaesthesia.[13-15] Few studies investigated this issue in spinal surgery, and they showed contradictory results.[16,17]

There are many limitations regarding the intraoperative neuromonitoring modalities as the somatosensorial evoked potentials (SSEPs) can be affected by anaesthetic agents (inhaled agents, thiopental, etomidate and narcotics), hypo-hyperthermia, hypotension, hypoxia, anemia and surgical stimulus while, the amplitude of motor evoked potentials (MEPs) is decreased with anaesthesia.[18]

This study assessed the effect of DEX on wake-up test during minimally invasive spinal surgery, and, as far as we know, this is the first study that compared the effect of DEX as an adjuvant drug during general anaesthesia induction with the neuromuscular blocking agent; atracurium in spinal corrective surgery.

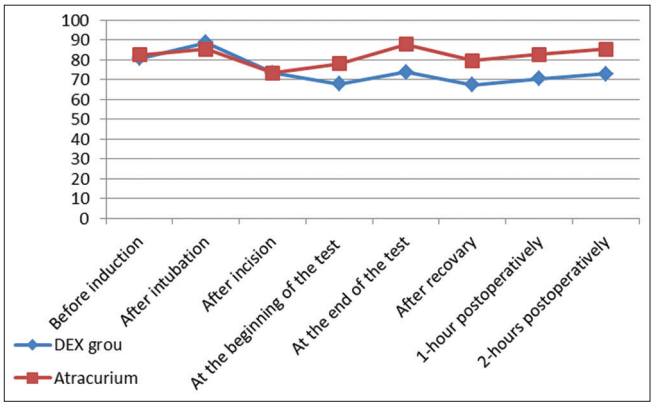
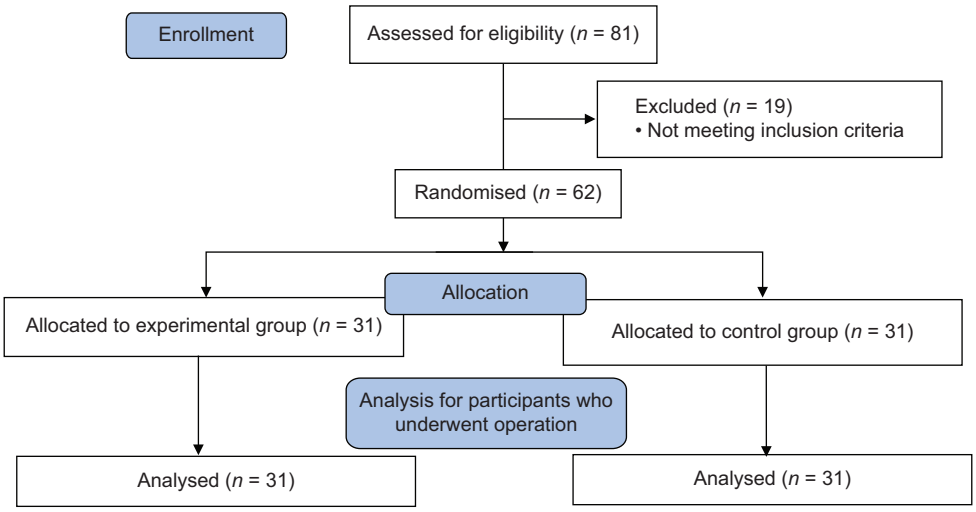


Figure 2: Mean arterial blood pressure in both groups

Owing to its simplicity, high specificity and reproducibility, the wake-up test has been widely adopted to monitor the neurologic integrity during spine surgeries.[19] To perform a successful wake-up test, ensuring proper time and quality is mandated. The wake-up time is preferred to be as short as possible. A wake-up test of a long duration would lead to prolonged surgery time, with subsequent increased risk of intraoperative bleeding and postoperative infection.[20] Concerning the wake-up test quality, considerable restlessness may lead to significant hemodynamic fluctuations or displacement of the operative fixation devices.[21]

Regarding the primary outcome of this study, the DEX group showed a statistically significant longer wake-up time. However, the difference was about 4 minutes. This difference seems to be of questionable clinical significance, particularly in view that no significant difference was found between the two groups in the surgery duration. In congruence with our findings, Cao *et al*.[6] found that the DEX group was associated with longer duration of wake-up. On the other hand, the wake-up test quality was found significantly better in the DEX group. This may be attributed to that the cortical functions of the patients in the atracurium group were more inhibited, while the subcortical central nervous system was temporarily disinhibited during awakening. This may result in a state in which the patient exhibits involuntary symptoms as restlessness or excitement. In contrast, the normal sleep-like state that occurs with DEX eliminates such



CONSORT flow chart diagram

symptoms. In line with the current work, previous studies demonstrated that DEX reduced restlessness during the awakening period.[6,20-22]

Regarding the secondary outcome, the present study showed that DEX was associated with a significantly better haemodynamic state in the form of less heart rate and mean arterial blood pressure, as in the absence of muscle relaxant, the dose of isoflurane must be higher which may be the reason of lower haemodynamic values. Also, it is postulated that DEX impedes the epinephrine and norepinephrine and relieves the perioperative stress.[23] By sympathetic inhibition, DEX alleviates the haemodynamic response to operative stress. A recent meta-analysis concluded that DEX has an efficient cardioprotective effect on patients undergoing cardiac surgery.[24] Similar findings were reported by Panse *et al*.[25] and Chen *et al*.[26] in their recent studies. They found that DEX use exhibited easiness in maintaining stable haemodynamics, when compared to fentanyl, in kyphoscoliosis correction surgeries. Similarly, Chen *et al*.[20] demonstrated that the use of DEX as an adjuvant agent with a propofol–remifentanil general anaesthesia regimen was related to significantly fewer fluctuations of the haemodynamic parameters.

In the current study, DEX was shown to reduce the amount of intraoperative sedatives. Moreover, it was associated with a significantly lower RSS scale immediately after the extubation, with higher number of patients in the DEX group were seen calm and able to cooperate with surgery. This is consistent with what was found by Goettel *et al*.[27] They indicated that DEX use during awakening made the patients quiet and kept them in a proper recovery state. Cao *et al*. (2019)[6] observed that DEX use for spinal surgery anaesthesia significantly improved the recovery quality with the intraoperative DEX pumping led to reduction of the amount of intraoperative sedatives and hindered postoperative anxiety. The sedative effect of DEX is explained by its nature as an α2 adrenergic receptor agonist. In adult volunteers, DEX has displayed reduction in the cortical networks mean strength, with modulatory effect on the functional connectivity within all resting networks,[28] and it has preserved the words processing.[29]

The present study, however, revealed significantly higher analgesics need in the DEX group, which could be the opposing aspect of the reduced sedatives need or may be explained by non-using a neuromuscular blockade agent. In harmony with our findings, Oh *et al*.[17] reported that postoperative analgesic consumption was significantly lower in the NMB group.

The strength of this study is being an RCT, and investigating, for the first time, the efficacy and safety of DEX use during general anaesthesia induction in spinal surgery. Also, the cost-effective management protocol for wake-up test during spinal correction surgery that could be easily applied in resource-limited areas. The study is, however, limited by the relatively small sample size. Larger multi-centric studies are recommended to attain a firm conclusion.

CONCLUSION

The use of DEX has shown an improving effect on the wake-up test quality, with slight prolongation. The

present work supports the use of DEX as an adjuvant drug alleviating the need for neuromuscular blockade, inducing better haemodynamic profile, exhibiting better sedation and improving the awakening condition.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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