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ORIGINAL RESEARCH PEDIATRIC ANESTHESIA

# Effect of propofol infusion vs ketamine plus dexmedetomidine infusion on the amplitude of motor evoked potential in pediatric patients undergoing tethered spinal cord surgeries; a randomized, double blind controlled study

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## ABSTRACT

**Background & objective**: The use of intraoperative neurophysiologic monitoring (IOM) has increased over the past two decades for the detection and prevention of iatrogenic neurologic injuries. Motor evoked potentials (MEP) are extremely sensitive to changes in physiological variables and inhalational agents reduce MEPs in a dose dependent manner. So IV anesthetics (propofol or ketamine) and opioids (fentanyl or remifentanil), are frequently used in spinal surgeries under MEPs monitoring. We compared the effects of propofol and fentanyl to those of ketamine, dexmedetomidine, and fentanyl in terms of minimizing their effects on MEP amplitude and hemodynamic stability during surgery

**Methodology:** This double blind, randomized, prospective study was conducted on 46 children, who were randomly allocated into 2 groups Ketamine–dexmedetomidine group: (n = 23) Maintenance throughout the procedure, by infusing Dexmedetomidine (0.4 -0.6 µg/.kg /.hr) ketamine, (1 -2m/.kg/.hr.) and giving bolus of fentanyl, (1-2µg/.kg/ ). Propofol-group:(n = 23) Maintenance throughout the procedure, By infusing propofol (100 ug L/kg/min) and giving bolus of fentanyl, (1-2µg/.kg/ ), with keeping mean arterial blood pressure changes within 25% of the baseline in both groups.

**Results:** Right and left quadriceps muscle measurements were insignificantly different between both groups at base line and were significantly higher in Group KD than Group P at skin incision, surgical manipulation and surgical closure. Right and left adductor hallucis muscle measurements were insignificantly different between both groups at base line and were significantly higher in Group KD than Group P at 5 mins, 10 mins, 15 mins, skin incision, surgical manipulation and surgical closure (P value <0.001). Intraoperative fentanyl consumption was significantly lower in Group KD than Group P.

**Conclusion:** The combination of dexmedetomidine and ketamine infusion is efficacious, safe, and has minimal effect on evoked potentials compared with the propofol-based TIVA group during spine pediatrics surgery. In addition, this combination increases the reliability and accuracy of MEP monitoring with hemodynamic stability and adequate post-operative pain relief. Using dexmedetomidine and ketamine infusions during pediatric spine surgery might successfully replace the typical propofol-based TIVA, although more studies are required .

**Registration:** ClinicalTrials.gov registration number NCT05591001.

 

**Keywords:** Motor evoked potential, dexmedetomidine, ketamine, propofol.

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# 1. INTRODUCTION

Tethered spinal cord in pediatric patients may develop as a part of several spinal dysraphism or may be an isolated pathology. It is characterized by a lower-lying conus medullaris and a thick or fatty filum. To release the cord, it may be necessary to cut the filum terminale, remove a lipoma, or remove broad-based scar tissue that is affecting the conus or cauda equina roots. When temporary difficulties were considered after surgery for cord untethering, the incidence of long-term neurological issues rose to 10.9% from up to 4.5%.[1-3]

Intraoperative neurophysiologic monitoring (IOM) is increasingly being used for the past two decades in detection and prevention of iatrogenic neurologic injuries. IOM is frequently employed in adults and, in their concepts, can be used in pediatrics.[4] Inhalational agents reduce Motor Evoked Potentials (MEPs) in a dose dependent manner and are in potentially conflict with accurate neurophysiological monitoring.[5] Because of this, total intravenous anesthesia (TIVA), using IV anesthetics (propofol or ketamine) and opioids (fentanyl or remifentanil), is frequently being used in spinal surgeries under MEPs monitoring.[6]

Because of rapid metabolism of propofol, it is possible to rapidly alter the anesthetic depth and its effects on evoked potential monitoring. Multi-pulse stimulation can compensate for the MEP amplitude reduction brought on by propofol usage. Opioids activate specific opioid receptors (μ, κ, and δ) are usually used with propofol as they have little impact on Somatosensory Evoked Potentials (SSEPs) and MEPs.[7]

If used as a continuous infusion intraoperatively, ketamine differs from other anesthetic drugs in that it improves MEP amplitude and cortical SSEPs without altering latency, thus allowing an acceptable monitoring environment.[8.]

Dexmedetomidine is increasingly being used during TIVA as an adjuvant to IV anesthesia. Depending on the specific study, its impact on MEPs has been observed to either dramatically reduce the amplitude of MEPs or not have a negative impact on MEP monitoring.[9-10] Ketamine and dexmedetomidine make a good combination to maintain hemodynamic parameters. Dexmedetomidine may also reduce ketamine's effects such as increased blood pressure, heart rate, salivation and emergence phenomenon.[11]

Except for a case report by Rozzana Penny, who utilized dexmedetomidine and ketamine infusion during scoliosis correction surgery with SSEP and MEP monitoring in a 15-year-old female patient, this combination had not been used in this sort of surgery before.[10] Evoked potentials are extremely sensitive to changes in physiological variables including hematocrit, arterial blood pressure, core and peripheral temperatures, etc.[9] With the aforementioned criteria in mind, we conducted this study to compare the effects of propofol and fentanyl to those of ketamine, dexmedetomidine, and fentanyl in terms of minimizing their effects on MEP amplitude and hemodynamic stability during spinal surgery in pediatric patients.

# 2. METHODOLOGY

After approval by the institutional ethical committee (No. N-83-2022) and ClinicalTrials.gov registration (No. NCT05591001), this prospective randomized double-blind trial was conducted in the Abu El Reesh Hospital at Cairo University. We enrolled 64 children, ASA I-II, aged between 3-8 y with tethered spinal cord, scheduled for surgical repair in the study. Parents' or guardians' written informed consents were obtained.

Children who underwent growing rod distraction surgery, had congenital scoliosis or neuromuscular diseases, were in physical status III or IV according to the American Society of Anesthesiologists (ASA), were taking antidepressants or anticonvulsants prior to surgery, or had a known history of drug allergies were removed from the study.

Using computer generated randomization tables, children were sorted into two equal groups. Serially numbered, opaque, sealed envelopes were used to hide the results. The group assignment was sent to the investigators in a number of sealed envelopes with only the case number printed on the outside of each, and the investigators were not aware of the specifics of the series.

Patients were evaluated by preoperative history taking, clinical examination and investigations; complete blood

 

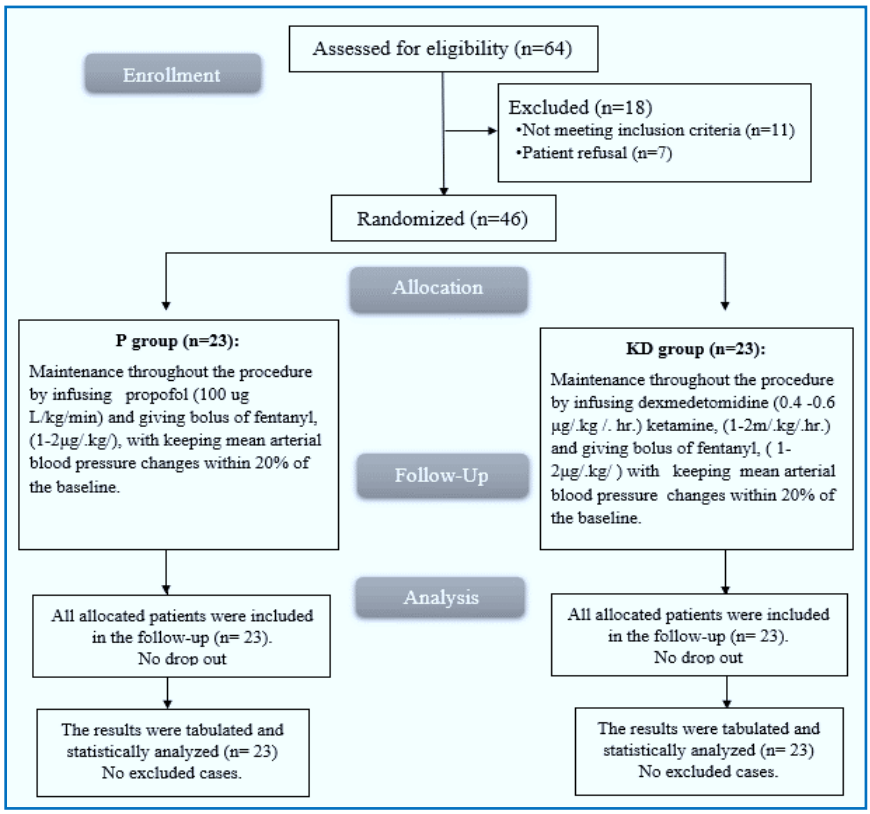


**Figure 1: CONSORT flowchart of the enrolled patients**

count (CBC), coagulation profile and kidney and liver function tests. Preoperative fasting was ensured for 6 h for solid food and minimum of 2 h for water and clear fluids.

All children were continuously monitored with electrocardiography, non-invasive blood pressure, and pulse oximetry and end tidal carbon dioxide throughout the duration of the surgery. The children were randomly assigned into two equal groups according to the type of drug injected; ketamine–dexmedetomidine (Group KD) and in group propofol (Group P).

Anesthesia was induced with mask inhalation of 6% sevoflurane in a air:oxygen mixture. Two peripheral IV cannulas, as well as a radial arterial catheter were inserted after induction. Fentanyl 1 µg/kg, rocuronium 0.6 mg/kg, and tranexamic acid 20 mg/kg were administered IV. The patient was turned prone after being intubated. The neurophysiologist recorded a train of four from the left and right abductor hallucis (AH) muscles in the foot while the subject was lying on his or her back to check that the muscle relaxation had subsided by stimulation of left and right posterior tibial nerves at the medial malleolus.

Dexmedetomidine 0.4-0.6 µg/kg/h and ketamine 1-2 mg/kg/h were infused. A bolus of fentanyl 1-2 µg/kg was given. Mean arterial blood pressure and heart rates were maintained within 25% of the baseline.

Maintenance throughout the procedure was done by infusing propofol (100 µg/kg/min) –giving bolus of fentanyl, (1-2 µg/kg) with keeping mean arterial blood pressure and heart rate changes within 25% of the baseline.

Heart rate (HR) and mean arterial pressure (MBP) were measured at the baseline, once the patient was prone, during the surgical incision, after the spine had been exposed, during spinal manipulation, and at the end of the surgery.

Hypotension (MAP less than 25% from the baseline reading) was managed by intravenous fluid; if not responded, ephedrine 0.1 mg/kg was given. Bradycardia (less than 25% of baseline) was controlled by atropine sulphate 0.5mg increments. Hypertension (MBP > 25% of basal value or tachycardia (HR > 25% of base line) was managed through a bolus dose of fentanyl 1µg/kg in both groups.

The MEP monitoring equipment was set up by the neurologic monitoring technician, who also ran a baseline test.
The neurophysiologist inserted two sub-dermal needle electrodes into the tibialis anterior (TA), AH, and first dorsal interosseous muscles of the left and right feet. The completion of the 10-20 measurement system (11) required the insertion of needle electrodes over the motor cortex 1 cm anterior to C1-C2. The left and right dorsal interosseous (DI), TA, and AH muscles, as well as the skeletal muscle of the anal sphincter were the muscle groups examined.

Muscle relaxant was not reversed but was worn off, as shown by 4/4 twitches on train-of-four. Added doses of neuromuscular relaxant were not administered once the surgeon started the procedure.

MEP peak-to-peak amplitudes were obtained by delivering a train of five, 50-µsec, constant voltage, anodal pulses with a 1.1-msec interstimulus interval (909 Hz), alternating over each hemisphere (using Nicolet Endeavor CR). Stepwise increases in stimulus intensity between 250 and 500 volts were made until each muscle

 

group responded with its maximal amplitude. A 30-1500 Hz filter was used to record the MEP amplitudes, which were then exhibited over a 100-msec window with a screen sensitivity 200 µV.

Retrospective measurements and documentation of the MEPs' maximum amplitudes from each of the three muscle groups were conducted by a neurophysiologist. The time points for recording MEPs were at baseline once the patient was prone, 3 readings at 5 min intervals for 15 min before surgical incision, at skin incision, once exposure of the spine was completed, during spinal manipulation and by the end of the surgery. After removing all patient identification information, measurements were taken, leaving only a timeline of the stacked MEPs collected during each case.

At the end of the surgery, all infusions were discontinued five minutes before the surgery was scheduled to end. After exhibiting adequate motor and sensory responses, the patient was extubated and transferred to the pediatric intensive care unit (PICU).

Our primary outcome was the average of three MEP measures taken at 5-min intervals at the AH muscle prior to skin incision.

Secondary outcomes were; total intraoperative fentanyl consumption, measurement of MEP at baseline once the patient was in prone position, at surgical incision, and once exposure of the spine was completed and during spinal manipulation and at the end of the surgery.

BP and HR measurements were noted at base line T1, induction (T2), positioning (T3), skin incision (T4), during spinal manipulation (T5) and at the end of the surgery (T6).

First rescue analgesia (0.1 mg/kg morphine sulphate IM was given once the patient experienced pain. Side effects, e.g., hypotension, bradycardia, sedation, and respiratory depression were noted. Any complication e.g., hematoma formation or propofol infusion syndrome were also noted.

**Table 2: Demographic data of the groups**

| Parameter | | Group P (n = 23) | Group KD (n = 23) | P value |
|---|---|---|---|---|
| **Age (y)** | | 4 ± 1 | 3.9 ± 1.06 | 0.887 |
| **Sex** | **Male** | 14 (60.87) | 16 (69.57) | 0.536 |
| | **Female** | 9 (39.13) | 7 (30.43) | |
| **Weight (kg)** | | 21.3 ± 4.13 | 22 ± 4.87 | 0.650 |

*Data were presented as mean ± SD or frequency (%)*

## Statistical Analysis

The mean MEPs at AH in pediatric patients receiving TIVA was 57 ± 28 Mv in a previous study.[11] A minimum of 21 patients in each group was required to achieve a study power of 80% and an alpha error of 0.05 to detect a difference of 25 mV between the two study groups. To compensate for possible dropouts the number of envelopes were increased to 46 envelops (23 in each group). MedCalc V 14.1 (MedCalc Software bvba, Belgium) was used for calculating the sample size.

The SPSS v26 (IBM Inc., Armonk, NY, USA) statistical analysis programme was used. Using an unpaired Student's t-test, quantitative variables were given as mean, standard deviation (SD), and range and were compared between the two groups. The Chi-square test or Fisher's exact test was used to examine qualitative variables that were reported as frequency and percentage (%). Statistical significance was defined as a two tailed P value 0.05.

# 3. RESULTS

In this study, 64 patients were evaluated for eligibility, eleven patients did not fulfil the requirements and seven patients refused to share in the study. The remaining 46

**Table 1: Comparative quadriceps muscle MEP amplitudes in the studied groups**

| Quadriceps | Measuring Time | Group P (n = 23) | Group KD (n = 23) | P value |
|---|---|---|---|---|
| **Right** | **Base line** | 502.87 ± 41.89 | 515.39 ± 56.61 | 0.398 |
| | **Skin incision** | 299.09 ± 90.87 | 491 ± 94.88 | **< 0.001*** |
| | **Surgical manipulation** | 182.91 ± 72.24 | 427.52 ± 126.93 | **< 0.001*** |
| | **Surgical closure** | 341.87 ± 86.31 | 495.78 ± 87.63 | **< 0.001*** |
| **Left** | **Base line** | 500.87 ± 57.87 | 531.74 ± 49 | 0.057 |
| | **Skin incision** | 274.13 ± 102.74 | 502.43 ± 118.1 | **< 0.001*** |
| | **Surgical manipulation** | 182.91 ± 72.24 | 460.78 ± 146.75 | **< 0.001*** |
| | **Surgical closure** | 341.87 ± 86.31 | 529.74 ± 56.6 | **< 0.001*** |

*Data are presented as mean ± SD; * Significant P value ≤ 0.05; MEP amplitude are displayed in µV.*

 

patients were randomly allocated into two equal groups (23 patients in each). All allocated patients were followed-up and analyzed statistically (Figure 1).

Age, sex and weight were comparable between both groups (Table 2).

Right and left quadriceps muscle measurements were higher in Group KD compared to Group P at baseline but the differences were not significant. The measurements were significantly higher in Group KD than Group P at skin incision, surgical manipulation and surgical closure ($P < 0.001$) (**Error! Reference source not found.**).

Right and left tibialis anterior measurements higher in Group KD compared to Group P at baseline but the differences were not significant. The measurements were significantly higher in Group KD than Group P at skin incision, surgical closure and surgical manipulation ($P < 0.001$)(**Error! Reference source not found.**).

Right and left adductor hallucis measurements were insignificantly different between both groups at baseline, and were significantly higher in Group KD than Group P at 5 min, 10 min, 15 min, at skin incision, surgical manipulation and surgical closure ($P < 0.001$) (Figure 2 and 3).

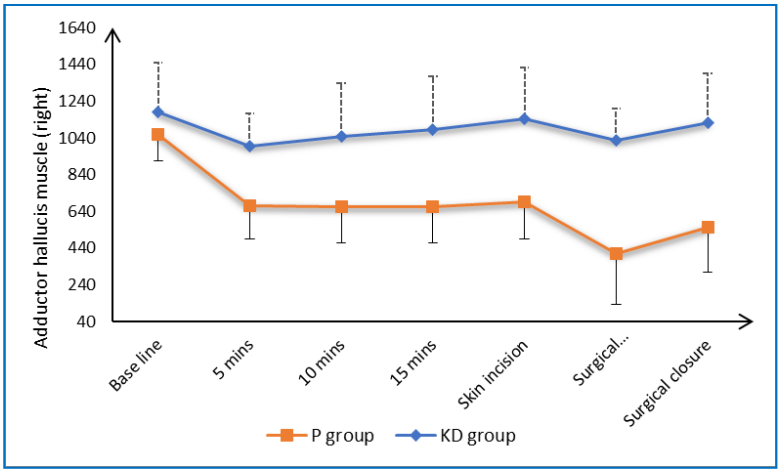


**Figure 2: Right adductor hallucis measurements of the two groups**

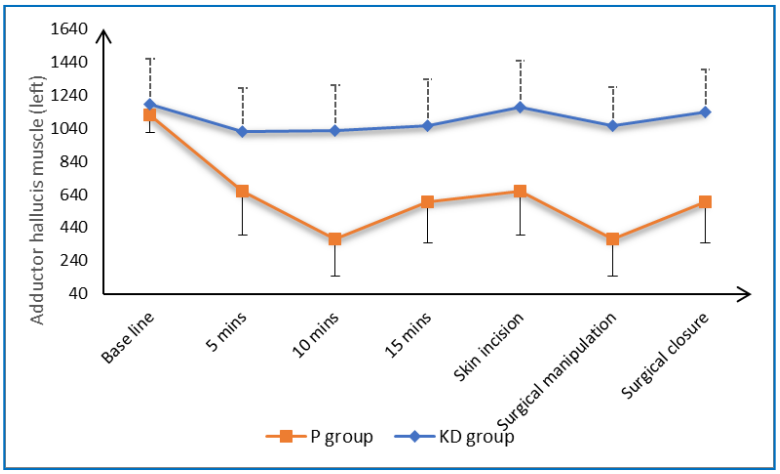


**Figure 3: Left adductor hallucis measurements of the two groups**

Anal sphincter measurements were insignificantly different between both groups at base line and were significantly higher in Group KD than Group P at skin incision, surgical manipulation and surgical closure ($P = 0.017$ and $< 0.001$ respectively) (Table 4).

Mean blood pressure measurements were insignificantly different between both groups at base line, surgical manipulation and surgical closure and were significantly lower in Group KD than Group P at skin incision ($P < 0.001$) (Figure 4).

Heart rate measurements were insignificantly different between both groups at base line and surgical closure and were significantly lower in Group KD than Group P at skin incision and surgical manipulation ($P < 0.001$ and 0.007 respectively) (Figure 5).

ntraoperative fentanyl consumption was significantly lower in Group KD than Group P ($P < 0.001$). Time to

**Table 4: Comparative anal sphincter MEP amplitudes in the studied groups**

| Measuring time | Group P (n = 23) | Group KD (n = 23) | P value |
|---|---|---|---|
| **Base line** | 200.74 ± 13 | 205.13 ± 18.06 | 0.349 |
| **Skin incision** | 150.22 ± 76.46 | 191.74 ± 24.68 | **0.017*** |
| **Surgical manipulation** | 89.7 ± 49.73 | 169.39 ± 26.5 | **< 0.001*** |
| **Surgical closure** | 132.78 ± 43.75 | 196.52 ± 20.93 | **< 0.001*** |

*Data are presented as mean ± SD; * Significant P ≤ 0.05; MEP amplitudes are displayed in μV*

 

first rescue analgesia and extubation time were insignificantly different between both groups (Table 5).

Regarding complications, only 3 patients of Group KD experienced irritability and respiratory depression,

**Table 5: Intraoperative fentanyl consumption, time to 1st rescue analgesia and extubation time of the studied groups**

| Variable | Group P (n = 23) | Group KD (n = 23) | P value |
|---|---|---|---|
| **Intraoperative fentanyl consumption (µg/kg)** | 2.1 ± 0.43 | 0.9 ± 0.29 | **< 0.001*** |
| **Time to 1st rescue analgesia (min)** | 46.8 ± 11.89 | 45.9 ± 8.07 | 0.762 |
| **Extubation time (min)** | 16 ± 2.98 | 17 ± 3.28 | 0.285 |

*Data are presented as mean ± SD; * P ≤ 0.05 significant*

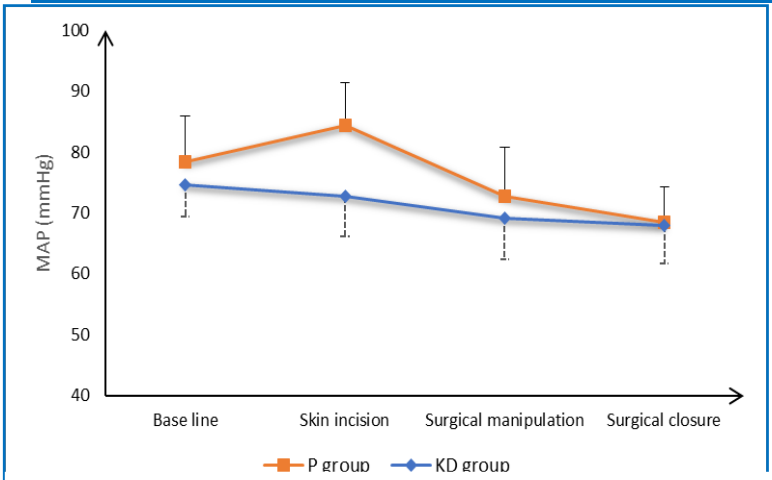


**Figure 4: Comparative mean arterial pressures (mmHg) in the studied groups**

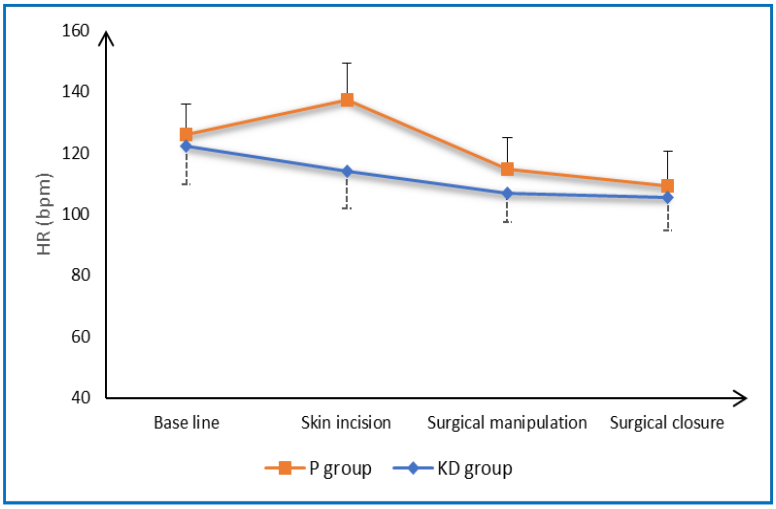


**Figure 5: Comparative mean heart rates (bpm) of the studied groups**

while 10 patients of Group P experienced hypotension.

# 4. DISCUSSION

Our study found that the combination of dexmedetomidine plus ketamine infusion and a bolus of fentanyl 1-2 µg/kg has significantly higher MEP amplitude compared with propofol group during spine surgery. This was clinically detected when the alarm criteria decreased by 60% or more in muscles tested increases the reliability of MEP monitoring.

MEPs are more susceptible to a reduced blood flow secondary to vascular injury or hypotension. Moreover, it changes earlier than SSEP allowing early detection of potential spinal cord injury. After the implementation of routine MEP monitoring, a decline was found in both new and permanent neurological damage / deficits following spinal fusion surgery.[12,13]

Guidelines suggest using a major warning criterion in spine deformity surgery with a drop in MEP signal of > 60%. Unfortunately, one of the biggest restrictions on the use of MEPs continues to be the absence of specific warning criteria. This restriction is in part due to the high anesthetic sensitivity of MEPs and the significant trial-to-trial variability in outcomes.[13,14]

Inhalational anesthetics in therapeutic concentration result in a dose-dependent increase in latency and decrease in amplitude during SSEP monitoring and are potent MEP depressants.[15] Many authors advocate that avoiding inhalational agents is the ideal anesthetic policy for best

 

monitoring of MEPs even when utilizing a high-frequency stimulation method.[16] Propofol and barbiturates produce synaptic inhibition by stimulating the inhibitory effect of Gamma Amino Butyric Acid (GABA). Nevertheless, propofol has a very quick metabolism, making it possible to quickly modify the degree of anesthesia and the way it affects evoked potential monitoring.[16]

Opioids have little impact on SSEPs and MEPs and are commonly used with propofol.[16.] Ketamine, a dissociative anesthetic drug and N-Methyl-D-Aspartate (NMDA) receptor antagonist, is known for its potent analgesic effects. When used intraoperatively as a continuous infusion, it improves MEP amplitude and cortical SSEP without altering latency and offers appropriate monitoring circumstances.[8.] Dexmedetomidine does not affect the SSEP or MEP monitoring when used as an anesthetic adjunct. As the Alpha2 adrenoreceptors are situated in presynaptic, postsynaptic, and extrasynaptic regions of the CNS as well as the peripheral nervous system.[17-18]

Our most specific tested muscles, right and left adductor hallucis measurements were statistically insignificantly different between both groups at baseline, but were higher in the ketamine group than propofol group at all other measuring time spots with statistical significance. Then, right and left quadriceps muscle measurements were insignificantly different between both groups at baseline and were higher in the ketamine-dexmedetomidine group than the propofol group at skin incision, surgical manipulation, and surgical closure with statistical significance.

Our results agree with those of Erb et al, who noticed that intraoperative SSEP and MEP monitoring were successful when using the combination of ketamine at dose of 0.4 to 0.6 mg/kg/h (lower dose than in our trial) and dexmedetomidine at 0.9 to 1.2 g/kg/h (higher dose than ours).[8]

In contrast, Holtet et al. showed that dexmedetomidine infusion in the doses of 0.5 µg/kg/h and 0.3 µg/kg/h significantly decreased the amplitude of MEP relative to control before instrumentation of the spine in both the upper and lower muscle groups studied.[19] A study by Tobias et al. reported no significant difference in MEP or SSEPs before or after administration of the dexmedetomidine loading dose once propofol was adjusted for BIS, although one additional patient had an abnormal response secondary to a brachial plexus injury.[20]

Iyer et al. discussed a case of a child 4 years old who had congenital scoliosis and was scheduled for an expansion thoracoplasty. The child was induced by a 20 mg bolus of ketamine then followed by an infusion of ketamine (4 mg/kg/h) and remifentanil (2 µg/kg/min). MEP responses were recorded in the upper and lower extremities through the surgery, and spatial facilitation was used for the lower extremities. The report stated ketamine's ability to maintain MEP recording in a patient. Therefore, taking into account the patient's age is crucial when designing the anesthetic strategy for EP-monitored procedures. Ketamine may be especially useful when MEP monitoring was used in pediatric patients.[21]

Furmaga et al. investigated the effects of ketamine and propofol on MEPs in rodents with and without a conditioned deep brain stimulus. The findings showed that ketamine was able to increase MEP amplitude while propofol administration gradually decreased MEP amplitude.[22] According to Kalkman et al., ketamine alone was capable of "increasing elicitation" of evoked myogenic responses in the tibialis anterior. There has been an amplitude increase of 150–250%.[23]

The differences in hemodynamic measurements were non-significant between both groups at baseline and surgical closure but were significantly lower in the ketamine group than in the propofol group at skin incision. Dexmedetomidine sympatholytic effects were counterbalanced by the sympathomimetic effects of ketamine. In addition, dexmedetomidine is known for its cardiovascular stabilizing properties.[10] when it comes to spinal deformity surgery, MAP 60 mmHg is a significant risk factor for spinal cord injury. With the added strain that corrective surgery puts on the spinal cord, autoregulation might not guarantee adequate spinal-cord perfusion, so avoiding low MAP intraoperatively and post-operatively is important for pediatrics.[24]

Patients between the ages of 8 and 14 who were scheduled for posterior spinal fusion in the study by Negemi et al. were divided into two equal groups and randomly assigned to receive either a remifentanil infusion at a dose of 0.2 ug/kg/min or the same dose of remifentanil infusion combined with ketamine at a dose of 1 µg/kg/min. The two group times for extubation were comparable. Monitoring of the electrophysiology, recovery time and score were insignificant. The group receiving remifentanil experienced considerably lower intraoperative heart rate and arterial blood pressure. The remifentanil-ketamine group experienced a longer first rescue time for analgesia. Remifentanil-ketamine groups consumed considerably less morphine throughout the first 24 hours.[25]

## 5. LIMITATIONS

This study had some limitations concerning the group of age and the small number of patients. In addition, this

 

trial was placed in a single medical center undergoing one type of spine surgery.

# 6. CONCLUSION

To conclude, the combination of dexmedetomidine and ketamine infusion is efficacious, safe, and has minimal effect on evoked potentials compared with the propofol-based TIVA group during spine surgery in pediatric patients. In addition, this combination increases the reliability and accuracy of MEP monitoring with hemodynamic stability and adequate post-operative pain relief. Using dexmedetomidine and ketamine infusions during pediatric spine surgery might successfully replace the typical propofol-based TIVA.

## 7. Data availability

The numerical data generated during this research is available with the authors.

## 8. Acknowledgement

We gratefully thank Faculty of Medicine, Cairo University, Cairo, Egypt

## 9. Conflict of interest

The study utilized the hospital resources only, and no external or industry funding was involved.

## 10. Authors' contribution

AH: concept, conduct of the study work, writing and editing of the manuscript.

IS: concept, interpretation of data, writing and revising of the manuscript.

PH: drafting the work and revising it for intellectual content, interpretation of data and manuscript editing

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