

Susceptibility of Transcranial Electric Motor-evoked Potentials to Varying Targeted Blood Levels of Dexmedetomidine during Spine Surgery

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ABSTRACT

Background: Dexmedetomidine has been increasingly used as an adjunct to opioid-propofol total intravenous anesthesia (TIVA). The authors tested the hypothesis and found that clinically relevant blood levels of dexmedetomidine do not produce significant attenuation of the amplitude of transcranial electric motor-evoked potentials either independently or by interaction with propofol in a dose-dependent manner.

Methods: The authors planned to recruit 72 patients with idiopathic scoliosis who had posterior spine fusion surgery during propofol and remifentanyl TIVA with dexmedetomidine as an adjunct. However, the authors terminated the study after enrolling 44 patients because of change in surgical technique. Before administering dexmedetomidine, baseline transcranial electric motor-evoked potentials were acquired during TIVA with remifentanyl and propofol. Patients were randomized to varying targeted blood levels of dexmedetomidine (0.4, 0.6, and 0.8 ng/ml) and propofol (2.5, 3.75, and 5 μ g/ml) using a factorial design. The primary outcome variable was amplitude of transcranial electric motor-evoked potential. The secondary outcome was amplitude of cortical somatosensory-evoked potentials.

Results: Of the 44 recruited patients, 40 completed the study, and their data were analyzed. The administration of dexmedetomidine in increasing doses as an adjunct to propofol-based TIVA caused a clinically and statistically significant attenuation of amplitudes of transcranial electric motor-evoked potentials.

Conclusion: The authors conclude that under the stimulation conditions used, dexmedetomidine as an anesthetic adjunct to propofol-based TIVA at clinically relevant target plasma concentrations (0.6–0.8 ng/ml) can significantly attenuate the amplitude of transcranial electric motor-evoked potentials.

What We Already Know about This Topic

- ❖ Transcranial electric motor-evoked potentials, used to assess spinal cord function during surgery, can be affected by many anesthetics
- ❖ Whether dexmedetomidine affects this monitoring is not known

What This Article Tells Us That Is New

- ❖ In 40 subjects undergoing spine surgery, dexmedetomidine infusion significantly reduced the amplitude of transcranial electric motor-evoked potentials when combined with a propofol-based anesthetic

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INTRAOPERATIVE neurophysiologic monitoring using transcranial electric motor-evoked potentials (tceMEPs) has been used increasingly to reduce the risk of spinal cord injury during corrective spine surgery.^{1,2} In most centers, neurophysiologic monitoring using somatosensory-evoked potentials (SSEPs) and tceMEPs has become an integral component of the intraoperative care of patients undergoing posterior spinal fusion. SSEPs and tceMEPs are mediated by different neural pathways, and the monitoring of both can provide a more complete assessment of cord sensory and motor function than either modality alone. Using both modalities facilitates early intraoperative detection of evolving intraoperative spinal cord compromise,¹⁻⁴ thereby allowing for prompt therapeutic intervention.

Understanding the effects of available anesthetics on tceMEPs is required to avoid the erroneous conclusion that changes in amplitude represent neurologic injury during surgical manipulations rather than known anesthetic effects. Most commonly used anesthetic agents produce dose-related changes in the amplitude of tceMEP. Inhalational anesthetic agents significantly depress tceMEP amplitude in a dose-dependent manner^{5,6} because of interference with alpha motor neuron excitability⁷⁻⁹; therefore, total intravenous anesthesia (TIVA) techniques with propofol as the hypnotic agent have been advocated to optimize tceMEP monitoring during spine surgery.¹⁰

Dexmedetomidine (Precedex®; Hospira, Lake Forest, IL), an α -2 adrenergic agonist, is routinely used to provide analgesia and sedation without respiratory depression in critically ill patients. It has been increasingly used as an adjunct to TIVA in procedures requiring intraoperative neurophysiologic monitoring because of its sedative, analgesic, and neuroprotective properties.¹¹⁻¹³ Recently, authors of a relatively smaller study in adults undergoing spine surgery reported that use of dexmedetomidine as an anesthetic adjunct at target plasma concentrations up to 0.6 ng/ml does not cause any significant change in somatosensory or motor-evoked potential responses during complex spine surgery by any clinically significant amount.¹⁴ However, we recently experienced and reported two pediatric patients having deterioration of tceMEP signal with intraoperative use of dexmedetomidine as an adjunct to propofol-based TIVA during spine surgeries.¹⁵ Therefore, we tested the hypothesis and found that clinically relevant target blood levels of dexmedetomidine will not significantly depress the amplitude of tceMEP either independently or by interaction with propofol.

Materials and Methods

After obtaining approval from the institutional review board of Cincinnati Children's Hospital Medical Center, Cincinnati, Ohio, we enrolled patients with idiopathic scoliosis who presented for posterior spinal fusion surgery with appropriate written informed consent and assent. Patients were between the ages of 10 and 25 yr and of both genders. Patients were excluded from the study if they had any of the following: neuromuscular scoliosis, allergy to, or contraindication to dexmedetomidine or propofol, morbid obesity (body mass index > 40 kg/m²), existing sensory or motor neurologic deficits, and history of severe cardiopulmonary disease (pulmonary hypertension, cardiomyopathy, mechanical ventilation, and American Society of Anesthesiologists physical status greater than II).

Protocol

After establishing an intravenous access with or without inhalation of 70% nitrous oxide in oxygen, anesthesia was induced by intravenous propofol (2–3 mg/kg). Alternatively, some subjects were induced with sevoflurane followed by the placement of intravenous access. After induction, tracheal intubation was facilitated with cisatracurium (0.1 mg/kg)

and fentanyl (3 μ g/kg). Subjects who did not receive preoperative oral midazolam (0.5 mg/kg to a maximum dose of 20 mg) were given midazolam (2 mg) intravenously during induction. After tracheal intubation, intravenous infusions of propofol at 110 μ g \cdot kg⁻¹ \cdot min⁻¹ and remifentanyl at 0.5–1.0 μ g \cdot kg⁻¹ \cdot min⁻¹ were started, and the use of volatile anesthetic agents was discontinued. Remifentanyl was titrated at a dose range (0.5–1.0 μ g \cdot kg⁻¹ \cdot min⁻¹) to control the hemodynamic responses (blood pressure and heart rate) to the surgical procedure. For subjects induced with sevoflurane, no data were collected until the measured end-tidal concentration was less than 0.1%.

Intraoperative monitoring included continuous electrocardiography, pulse oximetry, blood pressure (*via* arterial line and blood pressure cuff), and core temperature *via* rectal or esophageal probe. Mean arterial blood pressure was tightly controlled and maintained within 20% of the preoperative measurement by using vasoactive agents, if necessary. Core temperature was kept between 35.5° and 37°C, and end-tidal carbon dioxide was kept in the 35–45 mmHg range. The spinal cord is routinely monitored for major spinal surgery in our institution by recording both upper and lower extremity tceMEPs and SSEPs. Upper extremity positioning also is monitored during these procedures, with upper extremity tceMEPs and SSEPs. Neuromonitoring subdermal needle electrodes were positioned and secured after intubation by a neurophysiologist who was blinded to the study doses of dexmedetomidine and propofol. All subjects received reversal of residual muscle relaxant by administering 50 μ g/kg neostigmine and 10 μ g/kg glycopyrrolate. Once the patient was turned to prone position, baseline tceMEP was obtained after confirming adequate reversal of neuromuscular blockade with the presence of tetany at 50 Hz and by return of muscles twitches from abductor hallucis muscle to train-of-four electrical stimulation of the posterior tibial nerve (T4/T1 > 0.7).

The primary outcome measure of the study was tceMEP amplitude relative to baseline at one of the five dose combinations of dexmedetomidine and propofol. A factorial design with a center point was used to dissect the independent contributions from the interactions of dexmedetomidine and propofol blood levels. Subjects were randomized to one of five dexmedetomidine and propofol combination groups. For each group, the targeted blood levels of the two drugs are shown in table 1. To achieve the target levels, propofol dos-

Table 1. Experimental Groups and Corresponding Target Levels of Dexmedetomidine and Propofol

Group	Target Plasma DEX Level (ng/ml)	Target Effect Site Propofol Level (μ g/ml)
1	0.4	2.5
2	0.8	2.5
3	0.4	5.0
4	0.8	5.0
5	0.6	3.75

DEX = dexmedetomidine.

ing was based on the model of Marsh *et al.*¹⁶ Dexmedetomidine dosing was based on the data of Petroz *et al.*¹⁷ using a two-compartment mammillary model.

tceMEPs were obtained at the following intervals: (1) at baseline, before dexmedetomidine administration while receiving propofol (target level 2.5 $\mu\text{g}/\text{ml}$) and remifentanyl ($0.5\text{--}1.0 \mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$) (referred to as baseline); (2) after loading with dexmedetomidine (more than 15 min) and propofol (if required) to achieve the designated target plasma concentration (referred to as loading phase); and (3) after 15 min at the new target concentration (referred to as steady-state phase). If the amplitude of the tceMEPs was significantly reduced at anytime after the dexmedetomidine load, dexmedetomidine was discontinued. In addition, the tceMEP stimulation parameters were altered for clinical purposes to obtain a usable signal. The parameters were kept constant for study-related measurements until amplitude returned to 70% of baseline.

tceMEP amplitude was measured peak to trough (microvolts). Four tceMEPs were acquired at 15-s intervals at each of the intervals described earlier. After acquisition of these data, the dexmedetomidine infusion was decreased to $0.3 \mu\text{g} \cdot \text{kg}^{-1} \cdot \text{h}^{-1}$ provided that tceMEP amplitude was not completely lost or significantly reduced. If the amplitude of tceMEP was significantly attenuated or lost, the dexmedetomidine infusion was paused and only resumed at $0.3 \mu\text{g} \cdot \text{kg}^{-1} \cdot \text{h}^{-1}$ when tceMEP amplitude had returned to at least 70% of baseline.

The measurements of actual dexmedetomidine blood levels were used to calculate the bias of the pharmacokinetic models that predicted blood levels for the study. Eleven subjects were randomly selected to have blood drawn (5 ml) from the existing arterial catheter. The sample was withdrawn immediately after the dexmedetomidine loading dose. The blood samples were then centrifuged at 4,150 revolutions per minute for 5 min, and the plasma from each sample was divided into 3-ml SP brand polystyrene aliquot tubes (Cardinal Health, Dublin, OH). The samples were then placed in a -70°C freezer until further analysis. Liquid chromatography–tandem mass spectrometry method was used for quantitation of dexmedetomidine.¹⁸

Acquisition of Evoked Potentials

tceMEPs were acquired by stimulating at the scalp and recording the peripheral responses from target muscle groups. Motor-evoked potentials were triggered using a Digitimer D-185 transcranial stimulator (Digitimer Ltd., Welwyn Garden City, United Kingdom) that delivered (300–700 V) electrical stimulus pulse trains (pulse width = 50 μs , $N = 4\text{--}9$, interpulse interval = 1–4 ms) between two corkscrew-type electrodes (A Gram Co., Glenn Rock, NJ) placed over the motor cortex region at C1 and C2 (International 10–20 system).^{19–21} The optimal interpulse interval and the number of pulses in the stimulus train were adjusted to achieve maximum tceMEP amplitude for a given stimulating voltage. Recording of the tceMEP was accomplished by placing

pairs of subdermal needle electrodes in target muscle groups in all the four extremities and by observing the electromyographic responses time locked to the stimulation at the head. tceMEPs were recorded using pairs of subdermal needle electrodes inserted into bilateral (right and left) quadriceps, tibialis anterior (TA), and abductor hallucis muscles in the lower extremities and into bilateral first dorsal interosseous (FDI) muscles in the upper extremities. TA and FDI muscles were used for the study because these muscles generally produce robust tceMEPs because of their rich innervation by the corticospinal tract. The stimulus intensity and other stimulation parameters were adjusted to obtain the optimal baseline responses for each patient and then were kept constant until all study-related data were obtained. The optimal baseline amplitude response was obtained by increasing the tceMEP stimulus intensity from a starting value of 250 V by 25 V increments until muscle action potentials of at least 150 μV were acquired from all muscle groups. Significant response attenuation was defined as a 75% reduction in amplitude at each individual target muscle group when compared with that patient's baseline tceMEP.

Cervical or brainstem and cortical SSEPs were recorded to interleaved stimulation of the left and right posterior tibial nerves at a rate of 3.1/s and to interleaved stimulation of the left and right ulnar nerves at a rate of 4.7/s. SSEPs also were recorded to simultaneous stimulation of the left and right posterior tibial nerves at a rate of 4.7/s. Stimulus pulse duration was 300 μs . Stimulation intensity (20–40 mA) was optimized for each patient. SSEP stimulus parameters were set to optimize signal-to-noise ratio, so that a reproducible signal was acquired with a few hundred stimulations. The stimulus intensity was supramaximal, as evidenced by a 1–2-cm visible movement of the fingers or foot and maximal SSEP amplitude recorded from the scalp. Upper extremity cortical SSEPs were recorded from subdermal needles placed at Cp3 and Cp4 using Fpz (International 10–20 system) as a reference. Lower extremity cortical potentials were recorded from a subdermal electrode affixed to Cpz and referenced to Fpz. Subcortical potentials were recorded between electrodes over the second or third cervical vertebra and Fpz. A single ground needle electrode in the left or right thigh was used for all neurophysiologic recordings.

Neurophysiologic signals were recorded using a commercially available neuromonitoring system (Axon Systems Inc., Hauppauge, NY). The band-pass filters for cervical brainstem and cortical SSEPs were 30–500 Hz and 30–300 Hz, respectively. The band-pass filter for myogenic tceMEPs was 10–1500 Hz, with a sampling rate of 10 kHz.

Statistical Analysis

The primary null hypothesis was that dexmedetomidine would not produce significant depression of the amplitude of tceMEPs at any target blood level tested. We estimated that a sample size of 15 subjects for each of the four dexmedetomidine–propofol groups and 12 subjects for the center point (table 1) would be needed to have a statistical power of 85% to detect an effect of 0.80 standard deviations in the percent

of change in the amplitude of tceMEP for the primary effect of interests: dexmedetomidine effect, propofol effect, and dexmedetomidine \times propofol interaction effect. Design-Expert version 7.0 (Stat-Ease Inc; Minneapolis, MN) was used for the power analysis. We were unable to fulfill our prestudy plan, to recruit 72 patients total. The study design included a provision that there be a minimum of 90 min between the conclusion of the dexmedetomidine bolus and the time at which the surgeon would request tceMEPs because of surgical manipulation of the spine. A change in surgical technique necessitated termination of the study because the minimum time provision could no longer be met. A total of 44 subjects were enrolled at the time the study was terminated. No interim data analysis had been performed before study termination. The group of 44 subjects yielded a sample of 40 patients who were evaluable, which is 56% of the planned sample size.

Only the loading phase data are completely analyzed as data at the end of the steady-state phase were not recorded for 17 subjects. These subjects were deemed to have experienced loss or significant depression of the tceMEPs by the neurophysiologist and by study protocol the dexmedetomidine postload infusion was not started. The data recording for these subjects consisted of single tceMEPs every 15 min until the amplitude returned to 70% of baseline. The steady-state phase data were examined to determine whether any subject who was not affected at the end of the loading phase was found to have significant depression of tceMEP amplitude.

The planned factorial analysis was undertaken using a mixed-effects factorial model with restricted maximum likelihood estimation. Because of the early termination of the study resulting in a reduced sample size, we in addition performed equivalence testing.²² For the equivalence testing, the null hypothesis was changed to H_0 : dexmedetomidine causes significant depression of tceMEP amplitude. The hypothesis was tested as described under dichotomous outcome.

Continuous Outcomes: Primary Analyses

The FDI and TA muscles were analyzed separately using a two-level mixed-effects factorial model. The statistical model included the main effects: dexmedetomidine at two levels (0.4 and 0.8 ng/ml) and propofol at two levels (2.5 and 5.0 μ g/ml), the interaction between the dexmedetomidine and propofol levels, and two covariates: baseline tceMEP amplitude and side (left *vs.* right). These covariates were included to account for the variation in baseline measurements between subjects.

The primary outcome variable was the ratio of the post-drug tceMEP amplitude to the baseline amplitude. For each muscle within a subject, the median of the 14 ratios was used. The natural logarithm transformation of the ratio was used for the analysis. This transformation allowed us to interpret the data as percent change from baseline and not absolute change from baseline. The results of the analysis are presented as the percent change from baseline based on the geometric mean of the ratios and their respective 97.25%

CI. SAS[®] Proc MIXED (version 9.2; SAS[®], Cary, NC), and the Kenward–Roger option for the degrees of freedom was used for analysis. All tests were two-sided. For each of the two muscles, P values ≤ 0.025 were considered statistically significant. The significance levels were not adjusted for the unexpected early termination of the study.

Continuous Outcomes: Secondary Analyses

The secondary outcome variables including arterial blood pressure and heart rate were analyzed as described earlier. To compare the dexmedetomidine plasma levels with the predicted target levels, the matched-pair Wilcoxon signed-rank test was used. A regression analysis was also performed using the measured plasma levels as a function of the predicted levels. For all secondary outcomes, two-sided tests were performed, and P values ≤ 0.05 were considered statistically significant.

Dichotomous Outcome

The dichotomous variable had the values “affected” and “unaffected.” For each muscle within a subject, the set of joint probabilities of pre-dexmedetomidine load baseline tceMEP amplitudes and postload amplitudes were defined. The highest and lowest ratios were discarded, all ratio values were log transformed, and a 95% CI was defined. Equivalence testing was performed by using null hypothesis: subjects are significantly affected by dexmedetomidine. A muscle was considered affected if the 95% CI included -1.386 (corresponds to a 75% reduction in amplitude). A subject was classified as affected if three or more of the four muscle groups were identified as affected. The effects of systemic influences such as drugs on muscle groups are highly correlated within a subject²³; therefore, muscle groups were not considered as independent for the purpose of setting the 95% CIs. The interval was set conservatively assuming two tails when in fact we were only testing for one tail. Once subjects were assigned to affected or nonaffected, the percentage of affected subjects in an experimental group was determined. In addition, the dichotomized data were used to determine the significance of the dexmedetomidine effect using Fisher exact test. To maintain an experiment-wise significance level of 0.05, the significance level was set to 0.025 for the Fisher exact test. No additional adjustment was made for the unexpected early termination of the study. Chi-square tests and logistic regression analysis were performed using STATA[®] 10.1, for Mac (STATA Corp, College Station, TX), whereas Mathematica[®] (Wolfram Research Inc., Champaign, IL) was used to compute the geometric means, 95% CI, and perform tests for normality. Details of the methods to classify subjects and the analysis are described in Appendix 1.

Results

Forty-four patients were initially enrolled in the study and randomized to five treatment groups. Of the 44 patients, four patients did not complete the study protocol and were excluded from the statistical analysis. In two of these patients, a prone positioning baseline tceMEP was required (devi-

Table 2. Patient Demographics by Treatment Group

Group	Age (yr), Mean \pm SD	Weight (kg), Mean \pm SD	Height (cm), Mean \pm SD	BMI (kg/m ²), Mean \pm SD	Gender (%), Male:Female
1 = low DEX, low propofol	16.6 \pm 2.3	64 \pm 9	175 \pm 12	21 \pm 3	50:50
2 = high DEX, low propofol	15.0 \pm 1.9	60 \pm 7	168 \pm 8	21 \pm 2	71:29
3 = low DEX, high propofol	15.1 \pm 1.8	52 \pm 13	157 \pm 7	21 \pm 5	100:0
4 = high DEX, high propofol	15.3 \pm 1.9	54 \pm 11	161 \pm 6	21 \pm 3	88:12
5 = intermediate DEX, intermediate propofol	14.8 \pm 1.8	56 \pm 10	160 \pm 8	22 \pm 4	83:7

DEX = dexmedetomidine.

ation from study protocol). The third excluded subject experienced severe bradycardia during the loading dose of dexmedetomidine requiring immediate discontinuation of the dexmedetomidine loading dose and treatment with atropine. The fourth subject was excluded because of an incomplete dataset secondary to technical problems with data acquisition. The subject demographics are shown in table 2.

Fourteen of 40 patients (40%) were found to have experienced either loss or significant reductions in the amplitudes of tceMEP (three or four of four muscles affected) after the loading dose of dexmedetomidine. The median time to recovery of tceMEP to 70% of baseline for these participants was 68 min (range, 29–208 min). Subjects who did not have a loss or significant reduction of tceMEP amplitude during the loading phase did not experience a loss or significant reduction during the steady-state phase.

The results of the factorial analysis are shown in table 3. As expected, there was a significant between-subject variation in baseline tceMEP amplitude for both muscles. The main effect of dexmedetomidine was significant in both muscles ($P = 0.0148$ and 0.0120 for the FDI and TA muscles, respectively). For the FDI muscle, there was a 54% decrease (97.25% CI, -73 to -22) in the amplitude of tceMEP from baseline in the 0.8 ng/ml dexmedetomidine group compared with a 3% increase (97.25% CI, -38 to 72) in the 0.4 ng/ml dexmedetomidine group (table 3). The CI specifies a range within which we expect the estimated effect to lie. The CI

provides us with a measure of the reliability of the estimated effect. A negative sign indicates a decrease from baseline, and a positive sign indicates an increase. If zero is within the lower and upper limits, then there is no change from baseline.

The results were similar for the TA muscle, with a 57% decrease (97.25% CI, -75 to -25) from baseline in the 0.8 ng/ml dexmedetomidine group compared with a 3% increase (97.25% CI, -39 to 73) in the 0.4 ng/ml group. The main effects of propofol, interaction of propofol and dexmedetomidine, and side effect (right *vs.* left) were found to be nonsignificant. The 97.25% CIs for both muscles, for the main effect of propofol, contain zero, indicating no significant effect (table 3).

The final number of evaluable subjects in each group who had significant reductions in tceMEPs in three or four muscles is shown in table 4. There were no significant changes in the SSEP amplitudes or latencies for any subject, after the administration of the dexmedetomidine loading dose. An example of a set of tceMEP traces from a subject who had significant reductions in motor response amplitude compared with baseline is shown in figure 1. For comparison, a set of traces from a subject who did not have a statistically significant reduction in tceMEP amplitude is shown in figure 2.

The results of the analysis of the preinfusion and postinfusion amplitude ratios indicated that a total of 23 subjects (57.5%) had a significant attenuation of tceMEP amplitude (null hypothesis could not be rejected) for one or more mus-

Table 3. Percent Change from Baseline in tceMEP Amplitude (97.25% CL)

Muscle	Effect	Level	Percent Difference (97.5% CL)	<i>P</i> Value	
First dorsal interosseous	Side	Left	-30 (-54 to 5)	0.0477	
		Right	-32 (-52 to -2)	0.0186	
	DEX	0.4	3 (-38 to 72)	0.8785	
		0.8	-54 (-73 to -22)	0.0015	
		Propofol	2.5	-30 (-58 to 19)	0.1235
			5.0	-32 (-59 to 13)	0.0808
Tibialis anterior	Side	Left	-32 (-53 to 0)	0.0240	
		Right	-35 (-58 to 1)	0.0297	
	DEX	0.4	3 (-39 to 73)	0.9054	
		0.8	-57 (-75 to -25)	0.0010	
		Propofol	2.5	-31 (-60 to 18)	0.1090
			5.0	-35 (-61 to 10)	0.0632

The percentage change and respective confidence limits (CL) are calculated using $100(e^{\text{change}} - 1)$, where e is exponential e , and the change is provided by the analysis of the \log_e ([tceMEP at postloading] $-$ [tceMEP at baseline]).

DEX = dexmedetomidine; tceMEP = transcranial electric motor-evoked potentials.

Table 4. Patient Disposition by Treatment Group

Group	Enrolled (n)	Completed and Evaluable (n)	tceMEP Amplitude Lost/Significantly Reduced (Patients with ≥ 3 Affected Muscles), n (%)
1 = low DEX, low propofol	9	8	1 (12.5)
2 = high DEX, low propofol	8	8	3 (37.5)
3 = low DEX, high propofol	9	9	1 (11.1)
4 = high DEX, high propofol	10	8	4 (50.0)
5 = intermediate DEX, intermediate propofol	8	7	4 (57.1)
Total	44	40	13 (32.5)

DEX = dexmedetomidine; tceMEP = transcranial electric motor-evoked potentials.

cles. Seven subjects (17.5%) had involvement of all four muscles, six (15%) had three muscles involved, five (12.5%) had two muscles involved, and five (12.5%) had a single muscle involved. The number of subjects having a significant reduction in tceMEP by muscle group was 12 for the left FDI, 17 for the right, 15 for the left TA, and 17 for the right. The differences in subjects affected within a muscle group are not significant. The conditional probability of three or four muscles affected by dexmedetomidine given a significant depression of tceMEP amplitude in either FDI is 76%; the conditional probability increases to 100% if significant depression occurs in the FDI bilaterally. If either TA is significantly depressed, the conditional probability of three or four muscles affected is 75%; the probability is 100% if significant depression occurs in the TA bilaterally.

As shown in table 4, 11 of 23 patients (47.8%) who received the high dose or intermediate loading dose of dexmedetomidine (groups 2, 4, and 5) experienced significant at-

tenuation or loss of tceMEP amplitude (in three or four muscles) compared with 2 of 17 patients who received low loading dose of dexmedetomidine (groups 1 and 3).

Fisher exact test was used to determine the influence of dexmedetomidine. The incidence of the affected subjects in groups 2, 4, and 5 was compared with that in groups 1 and 3. The intermediate and high target level dexmedetomidine groups had a significantly greater proportion of affected subjects than the low target level dexmedetomidine groups (Fisher exact test; $P = 0.020$; significance here is $P < 0.025$).

The secondary outcomes such as systolic blood pressure, diastolic blood pressure, mean arterial pressure, heart rate, temperature, and end-tidal carbon dioxide were assessed for significant changes between baseline and postdrug load, with dexmedetomidine and propofol as continuous covariates. The only statistically significant effects were from dexmedetomidine on systolic blood pressure ($P = 0.03$), diastolic blood pressure ($P = 0.04$) at the loading stage, and mean

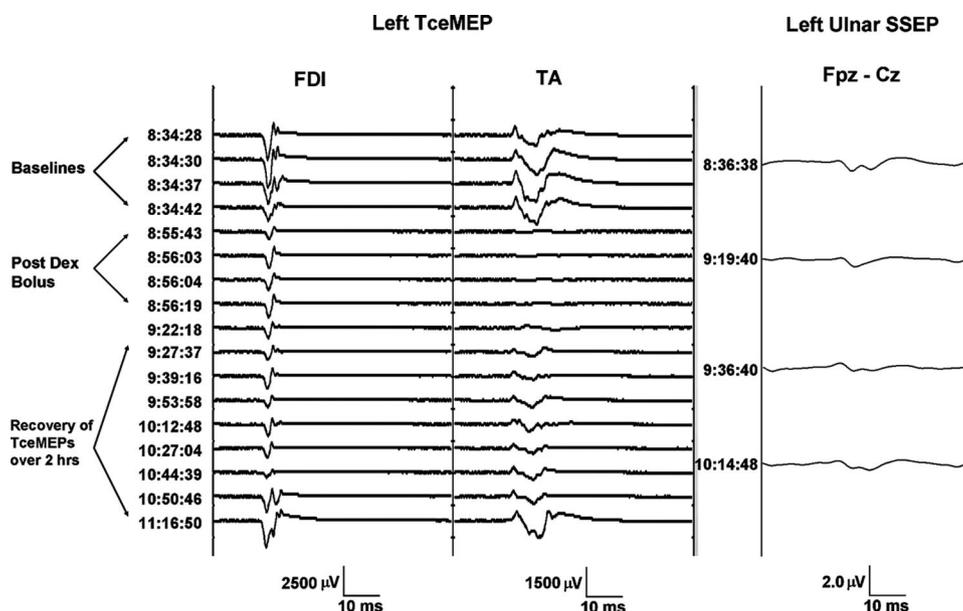


Fig. 1. Significant reductions in motor response amplitude. Traces on the *left* show representative transcranial electric motor-evoked potentials (tceMEPs) recorded from left first dorsal interosseous (FDI) and tibialis anterior (TA) muscles from a patient who had significant reductions in motor response amplitude from baseline after loading dose infusion of dexmedetomidine (Dex) (target plasma level = 0.8 ng/ml). Responses gradually recovered during a 2-h period after discontinuation of Dex infusion. Traces on the *right* show representative cortical somatosensory-evoked potentials (SSEPs) to stimulation of the left ulnar nerve during the same time periods. There were no significant changes in SSEP amplitude. Fpz-Cz = designation for specific locations on the scalp.

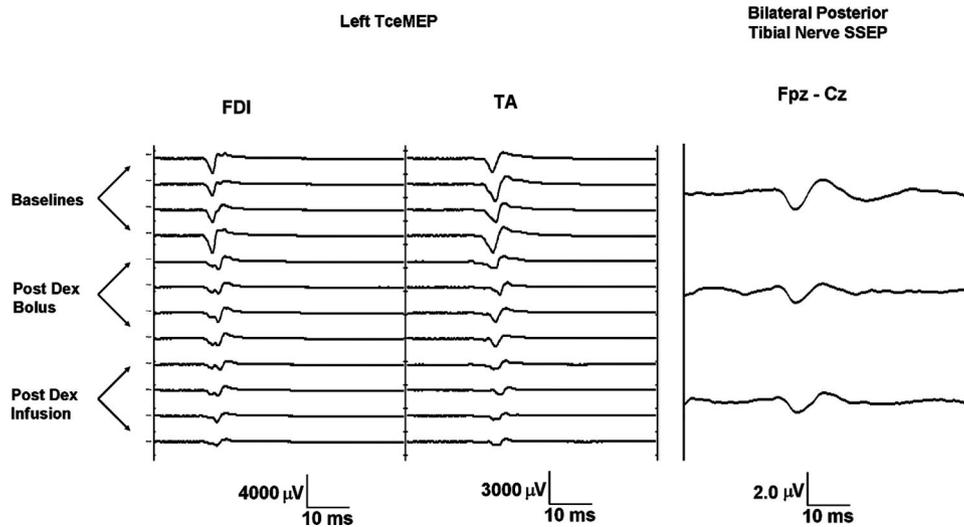


Fig. 2. Stable motor response amplitude. Traces on the *left* show representative transcranial electric motor evoked potentials (tceMEPs) recorded from left first dorsal interosseous (FDI) and tibialis anterior (TA) muscles from a patient who did not have any statistically significant reductions in motor response amplitude from baseline after a loading dose infusion of dexmedetomidine (Dex) or during the steady-state phase of the study (target plasma level = 0.8 ng/ml). Traces on the *right* show representative cortical somatosensory-evoked potentials (SSEPs) to bilateral stimulation of the posterior tibial nerves, which remained stable during the same time periods. Fpz-Cz = designation for specific locations on the scalp.

arterial pressure at both the loading and infusion stages ($P = 0.03$ and $P = 0.05$). The means and standard deviations of the blood pressure values are presented in table 5.

The dexmedetomidine plasma levels ($n = 10$) were compared with the predicted target levels using the matched-pair Wilcoxon signed-rank test. The predicted levels were not significantly different from the measured levels ($z = 1.172$, $P = 0.241$). A regression analysis was also performed using the measured plasma levels as a function of the predicted levels. The regression was significant ($F_{1,8} = 5.36$, $P = 0.049$, adjusted $r^2 = 0.33$). The constant was nonsignificant

and of the estimated slope was 1.33 (SE = 0.5786, $t = 2.32$, $P = 0.049$). The regression does suggest the possibility that the predicted dexmedetomidine levels may be lower than measured at higher levels.

In a majority of subjects who experienced significant tceMEP attenuation, the amplitude returned to 70% of baseline before spine instrumentation, and the neurophysiologist was able to adequately monitor tceMEPs during the procedure using original stimulation parameters. In the few cases where tceMEP amplitudes did not return to 70% of baseline before instrumentation, stimulation parameters had to be adjusted to

Table 5. Mean (SD) of Blood Pressure Readings

Group	Baseline	Loading Stage	Infusion Stage
1 = low DEX, low propofol			
Systolic BP	88.0 (15.6)	103.6 (5.8)	100.2 (5.5)
Diastolic BP	50.2 (10.7)	61.6 (7.2)	59.4 (5.2)
MAP	62.8 (12.2)	75.5 (6.2)	73.0 (4.6)
2 = high DEX, low propofol			
Systolic BP	88.0 (10.7)	118.1 (15.2)	113.0 (10.9)
Diastolic BP	48.9 (6.2)	69.3 (9.0)	66.1 (5.0)
MAP	61.9 (7.4)	85.5 (10.8)	81.9 (7.0)
3 = low DEX, high propofol			
Systolic BP	92.9 (9.8)	111.9 (15.1)	106.0 (10.9)
Diastolic BP	53.2 (16.6)	64.6 (10.4)	59.4 (7.2)
MAP	66.4 (14.1)	80.3 (11.3)	74.8 (7.3)
4 = high DEX, high propofol			
Systolic BP	92.6 (15.3)	114.4 (17.2)	107.5 (15.0)
Diastolic BP	47.8 (7.1)	60.6 (8.8)	59.9 (7.6)
MAP	62.7 (8.8)	78.6 (10.2)	75.8 (9.3)
5 = intermediate DEX, intermediate propofol			
Systolic BP	96.0 (12.6)	115.3 (12.3)	110.5 (10.0)
Diastolic BP	51.1 (8.2)	64.6 (8.0)	58.5 (6.6)
MAP	66.1 (9.2)	81.4 (9.0)	75.9 (7.6)

BP = blood pressure; DEX = dexmedetomidine; MAP = mean arterial pressure.

facilitate reliable monitoring. Ulnar and posterior tibial nerve cortical SSEP amplitudes and latencies remained within baseline range after administration of dexmedetomidine.

Discussion

Dexmedetomidine is a highly selective α -2 adrenergic agonist that has been used as an adjunct to TIVA in the perioperative regimen in the care of adolescents undergoing posterior spine fusion because it permits dose reduction in propofol and the inhalational anesthetic agents because of the anesthetic-sparing effects.^{24,25} Reducing the infusion rate of propofol in turn facilitates emergence from anesthesia for the intraoperative wake-up test (when requested) and at the completion of surgery. Even though the use of dexmedetomidine is desirable, the dose-response effects of dexmedetomidine on the tceMEP must be considered before use as an adjunct to TIVA in these procedures.

The results of the analyses indicated that dexmedetomidine as an anesthetic adjunct to propofol at target plasma concentrations of 0.6–0.8 ng/ml can significantly attenuate the amplitude of transcranial electric motor-evoked potentials. Despite the early termination of the study for reasons of change in surgical technique, we were able to demonstrate a definite dexmedetomidine effect using the originally planned factorial analysis and using equivalence testing. In both instances, the dexmedetomidine effect is highly significant. In contrast, increasing the target level of propofol from 2.5 to 5 μ g/ml without increasing the level of dexmedetomidine had no significant effect on the amplitude of the tceMEPs. In the factorial analysis, the propofol–dexmedetomidine interaction was not significant.

Other factors that could contribute to the differences between the baseline tceMEP amplitudes and the tceMEP amplitudes after drug loading doses were controlled. The stimulation parameters required to obtain the optimal response in each condition were not changed throughout the study period; each patient served as his or her own control; remifentanyl has negligible effect on motor-evoked potentials²⁶ in the dose range used; and the hemodynamics were tightly controlled. The only factors that changed between the baseline measurement and the subsequent tceMEP measurements were the dexmedetomidine in some groups and the propofol concentration(s) in plasma.

The influence of propofol concentrations on tceMEP has been evaluated by Nathan *et al.*,²⁷ who concluded that increasing propofol reduced tceMEP amplitude, with no effect on the latency. The propofol target value in their study ranged between 4 and 8 mg/l, and other authors found that motoneurone excitability is markedly impaired when the target propofol concentrations reached 9 mg/l.⁷ By comparison, propofol target values in the current study were generally lower, varying between 2.5 and 5 mg/l.¹

One of the limitations in our study is its early termination, which can produce a biased estimate of the drug effect and reduce the generalizability of the results. Normally with planned interim analyses, adjustments are made to the sig-

nificance to be conservative about stopping early. However, we have chosen not to adjust the significance level for the unexpected termination of the study. The CIs are presented to account for the variability of the estimate for the drug effect. When a study is terminated early, the CIs tend to be wider because of the reduced sample size. The width of the CI is inversely related to the amount of information available to interpret the results and is the reliability of the estimate.

Our results agreed with other recent studies that examined the effects of dexmedetomidine on tceMEP and SSEP in spinal surgery with instrumentation.^{14,28} We did not find any significant change in cortical SSEP amplitudes, even at target plasma concentrations of 0.8 ng/ml. The persistence of cortical SSEPs in the presence of marked tceMEP attenuation suggests a differential effect of dexmedetomidine on the respective neural pathways that mediate these two signals. Action at the level of spinal cord interneurons or alpha motor neurons would be consistent with the observed differential effect of dexmedetomidine.

In contrast to SSEP monitoring where identical responses are elicited by consecutive stimulations, compound muscle action potentials elicited by transcranial electric stimulation can show significant intertrial variability. The effect of response variability on the ability to interpret tceMEPs was evident in a study by Bala *et al.*,¹⁴ who examined the effect of dexmedetomidine on tceMEP and SSEPs during desflurane and remifentanyl anesthesia. Upper- and lower-extremity transcranial motor-evoked potentials and SSEPs were recorded during four defined periods: baseline without dexmedetomidine; two periods with dexmedetomidine (0.3 and 0.6 ng/ml), in a randomly determined order; and a final period 1 h after drug discontinuation. The primary outcomes were amplitude and latency of P37/N20, and amplitude, area under the curve, and voltage threshold for transcranial motor-evoked potential stimulation. Their results indicated that dexmedetomidine up to 0.6 ng/ml has no effect on SSEPs, but the area under the curve of the motor-evoked responses was too variable to claim response equivalence in the presence and absence of dexmedetomidine. Despite the fact that the authors were unable to reject the hypothesis that dexmedetomidine attenuates motor-evoked responses by more than 50%, they concluded that dexmedetomidine did not change tceMEPs in any clinically significant way because tceMEPs continued to be recorded in the presence of dexmedetomidine. The authors did not address the effects of large tceMEP variability on the clinical interpretability of these responses.

It is difficult to compare the current results with those of Bala *et al.* because of important differences in anesthesia and tceMEP stimulation conditions. The current study used a total intravenous anesthetic protocol with propofol, selected to optimize tceMEP amplitudes and stability.¹⁰ Bala *et al.* investigated the effects of dexmedetomidine in the presence of desflurane, which can depress tceMEP amplitudes even at relatively low concentrations.¹⁴ The interactive effects of propofol and dexmedetomidine on the neural circuitry involved in generating tceMEPs may be different from that of dexmedetomidine and desflurane. Stable, large-amplitude motor-evoked potentials are

generally more difficult to record in the presence of volatile anesthetic agents than with propofol, perhaps because of differential effects of these agents within the spinal cord. For example, recent evidence suggests that the volatile agent sevoflurane has a greater effect than propofol on the motor neurons of the anterior horn.²⁹

A second critical difference between the studies centers on the stimulation protocol used in each to elicit tceMEPs. In the current study, the average stimulating voltage was 525 V, delivered using a commercially available constant voltage stimulator. Stimulus parameters, including voltage, were adjusted for each patient in the baseline condition to produce a maximal response. Assuming a 600-ohm impedance, a typical value for the stimulation leads used, and given the 50- μ s pulse duration, the delivered charge per pulse was approximately 45 microcoulombs. In the study by Bala *et al.*, a constant current stimulator was used to deliver seven 500- μ s pulses at intensities up to 500 mA. A comparable charge calculation for the study by Bala *et al.* yields a per pulse charge of 132 microcoulombs. (It should be noted that certain brands of instrumentation are capable of generating only pulses of 50 μ s. To achieve a 130-microcoulomb charge, the voltage is more than 1,500 V and beyond the safety limits of these devices.)¹ The greater delivered charge per pulse in the study by Bala *et al.* may have been sufficient to prevent total obliteration of responses in their high dexmedetomidine concentration condition (0.6 ng/ml); however, the presence of some persisting response does not preclude the possibility that response interpretability was nonetheless affected by dexmedetomidine in this condition.

Our results confirm the conclusion of a recent study by Tobias *et al.*,²⁸ who evaluated the effect of dexmedetomidine on tceMEPs and SSEPs in nine patients (age, 12–17 yr) undergoing posterior spine fusion. SSEPs and tceMEPs were measured before and after the administration of dexmedetomidine. Dexmedetomidine (1 μ g/kg) over 20 min followed by an infusion of (0.5 μ g \cdot kg⁻¹ \cdot h⁻¹) was administered at the completion of the surgical procedure but before wound closure as an adjunct to TIVA, which included propofol and remifentanyl, adjusted to maintain a constant depth of anesthesia as measured by a bispectral index of 45–60. The results showed that in the first patient, dexmedetomidine administered in conjunction with propofol at 110 μ g \cdot kg⁻¹ \cdot min⁻¹ resulted in a decrease in the bispectral index from 58 to 31. Although no significant effect was noted on the SSEPs (amplitude or latency) or tceMEP duration, there was a decrease in tceMEP amplitude. The protocol was modified so that the propofol infusion was incrementally decreased during the dexmedetomidine infusion to achieve the same depth of anesthesia. As noted in their study, significant MEP amplitude changes were evident in their first patient when dexmedetomidine was administered without adjusting the propofol infusion rate. The expected blood level of dexmedetomidine after the load is 0.84 ng/ml; the expected propofol effect site concentration is 2.5 μ g/ml for the 100 μ g \cdot kg⁻¹ \cdot min⁻¹ infusion and 1.8 μ g/ml for a 78 μ g \cdot kg⁻¹ \cdot min⁻¹ infusion. The first patient of Tobias *et al.*

fits into our group 2, whereas the other eight patients do not fit into any of our experimental groups as the computed propofol effect site concentration is less than that targeted in our group 2. The decreased tceMEPs in the first patient is not unexpected given that we observed a significant decrease in tceMEP amplitude in 37.5% of our group 2 subjects.

It is important to note that the targeted blood levels of dexmedetomidine and propofol reflected the interaction of both drugs on healthy subjects with a history of idiopathic scoliosis. Similar targeted blood levels of dexmedetomidine and propofol in patients with a history of neuromuscular scoliosis or other spinal disorders, for example, myelopathy, may have greater impact on the tceMEPs. This assumption needs to be confirmed in patients with compromised baseline spinal cord function or an appropriate animal model.

We conclude that dexmedetomidine may be used as an anesthetic adjunct to remifentanyl–propofol TIVA in procedures requiring tceMEP and SSEP monitoring. Target plasma concentrations of 0.4 ng/ml dexmedetomidine and 2.5 μ g/ml propofol seem to have minimal effect on tceMEP amplitude. The increasing dose of dexmedetomidine above this target level, with or without increasing doses of propofol, may attenuate the amplitude of tceMEP in an unacceptable percentage of patients, reducing the reliability of spinal cord monitoring. Potential risks and benefits of adding dexmedetomidine should be assessed before its addition as an adjunct to TIVA in these procedures.

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Appendix: Methods for Classification and Analysis of the Dichotomous Outcome

Baseline measurements for the transcranial electric motor-evoked potentials (tceMEP) response to the transcranial electrical stimulation were obtained for each muscle within a subject. The physiologic system that generates the tceMEP response is a nonlinear time-bound dynamical system. The state of the system and, thus, its output in response to stimulus changes with time and is influenced by multiple factors.³⁰ As a consequence, there is a significant variability in the amplitude of the tceMEP from trial to trial. The trials are sufficiently separated in time so that the effects of the previous pulse train (refractory period, hyperexcitability period) have dissipated before another pulse train is presented. The data analysis must account for this variability. The same consideration applies to the measurements taken after a loading dose of dexmedetomidine (and propofol when given). The ratio of the two measurements represents the joint probability of observing baseline value x and postinfusion value y . There are 16 possible ratios of equal probability from the data. The highest and lowest ratios were discarded. The result-

ing set of ratios is the best estimate of the distribution of the possible ratios for a muscle group within a subject. To determine whether the tceMEP amplitude was attenuated, the ratio sets were examined on a subject by subject basis for each muscle group. A muscle was considered affected if the 95% CI of the natural log (loge) of the ratio contained the value -1.386 . This would indicate a reduction of the tceMEP amplitude from a baseline of 75%. To calculate the 95% CI, all ratios were loge transformed. The Anderson–Darling test³¹ for small sample sizes was used to test normality. The critical value for the Anderson–Darling test, at a significance level of 0.05, is 0.751; any value less than the critical value indicates normality. Results indicated that 77.5% (124 of 160) of the distributions were normal. If the transformed ratio set was normally distributed, the normal approximation was used to calculate the geometric mean, standard deviation, and 95% CI. Ratio sets that were not normally distributed were analyzed using Monte Carlo simulation. The ratio set was sampled 1,000 times, if the sampled value was less than -1.386 , 50 or more times the probability of accepting the null hypothesis was at least 0.05; consequently the muscle under analysis was considered to be affected.

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