Motor and Somatosensory Evoked Potentials Are Well Maintained in Patients Given Dexmedetomidine during Spine Surgery

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Background: Many commonly used anesthetic agents produce a dose-dependent amplitude reduction and latency prolongation of evoked responses, which may impair diagnosis of intraoperative spinal cord injury. Dexmedetomidine is increasingly used as an adjunct for general anesthesia. Therefore, the authors tested the hypothesis that dexmedetomidine does not have a clinically important effect on somatosensory and transcranial motor evoked responses.

Methods: Thirty-seven patients were enrolled and underwent spinal surgery with instrumentation during desflurane and remifentanil anesthesia with dexmedetomidine as an anesthetic adjunct. Upper- and lower-extremity transcranial motor evoked potentials and somatosensory evoked potentials 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.

Results: Of the total, data from 30 patients were evaluated. Use of dexmedetomidine, as an anesthetic adjunct, did not have an effect on the latency or amplitude of sensory evoked potentials greater than was prespecified as clinically relevant, and though the authors were unable to claim equivalence on the amplitude of transcranial motor evoked responses due to variability, recordings were made throughout the study in all patients.

Conclusion: Use of dexmedetomidine as an anesthetic adjunct at target plasma concentrations up to 0.6 ng/ml does not change somatosensory or motor evoked potential responses during complex spine surgery by any clinically significant amount.

SPINAL surgery with instrumentation is associated with the risk of iatrogenic injuries to the spinal cord. The combination of somatosensory evoked potential (SSEP) and transcranial electric motor evoked potential (TceMEP) monitoring has resulted in a high degree of sensitivity in predicting postoperative neurologic outcomes.[1,2] By detecting intraoperative spinal cord compromise early, neurologic monitoring can allow surgical interventions to decrease the incidence of new-onset postoperative neurologic deficits.[3–6] Corrective action taken promptly as indicated by evoked potential changes is effective at preserving neurologic function.[7]

Anesthetic agents have a dose-dependent adverse effect on the ability to record evoked potential responses.[8–14] Anesthetics may thus reduce the ability of evoked responses to detect compromised spinal function. Reduced efficacy of neurologic monitoring might in turn reduce the ability of surgeons to take corrective action. Preserving the quality of SSEP and motor evoked potential (MEP) and minimizing the effects of anesthetic agents on neurologic monitoring are thus priorities.

Dexmedetomidine, an α_2-receptor agonist, is routinely used to provide analgesia and sedation without respiratory depression in critically ill patients.[15] Hemodynamic stability, negligible respiratory depression, and reduction of other anesthetic and analgesic requirements[16–19] make it an interesting option for intraoperative use as an adjunctive agent for general anesthesia. Dexmedetomidine seems to have minimal effects on the ability to record evoked potential in animals.[20] However, there is limited and conflicting evidence in human subjects.[21–24] We therefore tested the hypothesis that dexmedetomidine does not significantly alter the neuromonitoring parameters in patients undergoing complex spinal surgery with instrumentation during desflurane and remifentanil anesthesia. The parameters tested were amplitude and latency of P37 and N20 waves of SSEP as primary outcome, and voltage threshold, which is necessary for transcranial TceMEP stimulation, and area under the curve of TceMEP as secondary outcomes.

Materials and Methods

With institutional review board (Cleveland Clinic, Cleveland, Ohio) approval and written informed patient consent, we enrolled 37 patients undergoing spinal instrumentation surgery between May 23, 2006, and July 12, 2007. Patients were aged 18 to 70 yr and had American Society of Anesthesiologists physical status I, II, or III. Exclusion criteria included any contraindication to

dexmedetomidine or TceMEP monitoring (such as implanted intracranial device, history of seizures, and previous neurosurgical procedure), concurrent use of α_2 agonists, history of heart block, congestive heart failure, severe left ventricular dysfunction, existing sensory or motor deficits, or serum creatinine concentration greater than 2.0 mg/dl. After enrollment, additional exclusion criteria were inability to obtain TceMEP baseline or postinduction use of neuromuscular relaxant or propofol. The surgical procedures were extensive lumbar or thoracic spine procedures with instrumentation mainly with posterior approach, although some patients had combined anterior and posterior approach. Because of the invasiveness of these procedures, evoked potentials were crucial to detect neural injury.

Protocol

Patients were premedicated with 0.5–1.0 mg midazolam. After preoxygenation, anesthesia was induced with 1–2 mg/kg propofol and 0.2 μg · kg^{-1} · min^{-1} remifentanil. Rocuronium at 0.6 mg/kg or succinylcholine at 1 mg/kg was used to facilitate intubation. End-tidal desflurane, 4%, in 50% oxygen was used to maintain anesthesia, and the concentration was not modified during the study period. A radial artery catheter was inserted, and a BIS® sensor (Aspect Medical Systems, Inc., Norwood, MA) was positioned. Bispectral Index was maintained from 40 to 60 by titrating remifentanil as necessary. Blood pressure, as required by protocol, was tightly controlled; it was within 20% of baseline for preinduction and within 10% of baseline for subsequent recordings, and no deliberate hypotension was used. End-tidal carbon dioxide was maintained within normal limits. The average temperature during the study was 35.5°C.

In this single-blind, randomized, crossover study, evoked responses were evaluated under four conditions: initial baseline (before dexmedetomidine infusion), during random-ordered infusion of dexmedetomidine (0.3 and 0.6 ng/ml), and a final baseline 1 h after discontinuation of the dexmedetomidine infusion. The order of the dexmedetomidine infusion was based on computer-generated randomizations; sequences were concealed in opaque envelopes.

Neuromonitoring needle electrodes were positioned and secured on the skin. (Evoked potential monitoring is routine for major spinal surgery in our institution.) Baseline evoked responses were measured approximately 1 h after induction. When a good signal-to-noise ratio was documented, the randomization envelope was opened. Mean arterial pressure was subsequently maintained nearly constant throughout the measurement period with remifentanil and vasoactive agents as necessary. Dexmedetomidine (Precedex®; Hospira, Lake Forest, IL) was administered to the designated target plasma con-

centration (0.3 or 0.6 ng/ml) by STANPUMP software** *via* a Harvard Apparatus Model 22 syringe pump.[25]

After a 10-min baseline recording period (before surgical stimulation), the first dexmedetomidine infusion was started at the target of 0.3 or 0.6 ng/ml as defined by the randomization. Ten minutes after the start of the infusion, a second set of evoked potential recordings was obtained over an additional 10 min. At the end of this second recording period, the dexmedetomidine infusion was paused for a washout period of 20 min to allow the plasma dexmedetomidine concentration to decrease to 0.3 ng/ml or less. The dexmedetomidine infusion was then restarted at the alternate target concentration. Ten minutes after the start of this second infusion, a third set of evoked potential recordings were obtained, again for 10 min. At the end of this third recording period, the dexmedetomidine infusion was terminated. Sixty minutes of drug washout was permitted to allow plasma dexmedetomidine concentration to decrease to negligible levels before the fourth and final set of evoked responses was obtained.

Measurements

Heart rate, blood pressure, and oxygen saturation were monitored by electrocardiogram leads II and V, a noninvasive blood pressure monitor (*via* intraarterial line or blood pressure cuff), and a pulse oximeter, respectively. Core temperature (*via* esophageal thermistor) and the remifentanil infusion rate were also recorded.

The spinal cord was monitored by recording both upper- and lower-extremity TceMEPs and right and left median and posterior tibial nerve SSEPs. After induction of anesthesia, but before draping or incision, sterile stimulating and recording needle electrodes were placed in accordance with the international 10–20 system of electrode placement as described in American Electroencephalographic Society Guidelines 9, 12, 13, and 14.[26-29] The band-pass filter for SSEP and myogenic responses recorded for TceMEP was 30–2,000 Hz, with a sampling rate of 10,000 Hz.

The cortical response for the lower extremity is called the P37, and the cortical response for the upper extremity is called the N20. With posterior tibial nerve stimulation, cortical response of the P37 potential from Cz or CPi (ipsilateral to the side of stimulation) was recorded depending on which site provided the maximum response. For right posterior tibial nerve stimulation, we recorded from CP4 or CPz again depending on which provided the optimal signal. Similarly, we used CP4 or CP3 for the active electrode for median or ulnar nerve stimulation to record the N20 potential. The reference electrode was placed at Fpz. A stimulation rate for both median nerve and posterior tibial nerve stimulation was 3.1 Hz, with an artifact rejection level of 50 μV.

** STANpump program is available at: http://anesthesia.stanford.edu/pkpd. Accessed October 1, 2007.

The stimulating electrodes were placed at C3 and C4. The multipulse technique was used to record TceMEP.[30] Recordings were made by measuring myogenic responses as a result of transcranial stimulation from the first dorsal interosseous and adductor hallucis. These muscles were chosen because they provided easily obtainable MEP measurements at the lowest stimulation intensity. The stimulus parameters for TceMEP were constant current stimulatory with a stimulus pulse width of 500 μs with 7 pulses and an interstimulus interval of 2 ms. In obtaining MEP threshold measures, constant current stimulation began at 100 mA. The stimulating intensity was then increased in steps of 25 mA until reproducible MEPs were obtained contralateral to the stimulating anodal electrode. This procedure was then repeated for the other side. These currents were considered threshold MEP intensities.

If no baseline MEP response was seen at 500 mA, monitoring TceMEP for that side was discontinued. If no baseline TceMEP was seen on either side at 500 mA, the study was terminated. The SSEP and MEP response was displayed on a computer screen in real time and stored on hard disk. The MEP amplitude was calculated as peak-to-trough amplitude, as well as the area under the curve. Latency was measured for P37 from the onset of the stimulus to the trough of the P37 potential. The latency of the N20 response was recorded from the onset of the stimulus to the peak of the N20 potential. The amplitudes were measured from trough to peak of the P37–N45 complex and peak to trough of the N20–P25 complex. Evoked potentials were monitored with an Epoch XP Neuromonitor (Axon Systems, Hauppauge, NY).

Five milliliters arterial blood was sampled in the middle of each 10-min recording period and stored on ice until the end of each individual study period. Blood samples were then centrifuged at 3,000 times gravity for 10 min, and the plasma from each sample was divided into aliquots in 1.5-ml Eppendorf tubes (Eppendorf North America, Westbury, NY), frozen in liquid nitrogen, and then stored in a monitored −80°C freezer until further analysis. A reverse-phase, high-performance liquid chromatographic method with tandem mass spectrometric detection was validated for the quantitative analysis of dexmedetomidine in human plasma. The quantitation limit was 0.020 ng/ml, and the assay showed linear responses in the concentration range of 0.020–10.0 ng/ml. The average within-run precisions (coefficients of variation) were 4.9% and 4.5%. The average between-run precision was 1.8%. The average accuracy at different quality control sample concentrations was between 89.1% and 104.0% for the determination of dexmedetomidine in human plasma.

Analysis

While evoked responses were monitored for clinical purposes throughout surgery, study-related analysis was restricted to the four 10-min-long periods described above: initial baseline, 0.3 and 0.6 ng/ml target dexmedetomidine concentrations in random order, and a final baseline 1 h after discontinuing dexmedetomidine. Evoked potential measurements were analyzed by one author who is a board-certified clinical neurophysiologist (D.R.N.) and was blinded to the randomization and plasma dexmedetomidine concentrations. Evoked potential measurements included

1. SSEP P37 amplitude (peak to trough, in microvolts)
2. SSEP N20 amplitude (peak to trough, in microvolts)
3. SSEP P37 peak latency (in milliseconds)
4. SSEP N20 peak latency (in milliseconds)
5. Area under the curve amplitude from first dorsal interossei and adductor hallucis muscles
6. Lowest threshold constant current stimulus intensity sufficient to elicit a consistent MEP

Heart rate, mean arterial pressure, and Bispectral Index values were also averaged over each 10-min recording period.

Equivalency of the evoked potential's parameters at each dose concentration compared with the initial baseline evoked potential responses was assessed using the "two one-sided tests procedure" of Schuirmann,[31] which claims equivalency if two simultaneous individual null hypotheses are rejected: first, that the difference is less than the lower bound of a predetermined equivalency interval, and second, that the difference is greater than the upper bound of the equivalency interval. The significance level was 0.025 for testing each of the two doses to baseline. Using the methods of Schuirmann, this amounted to accepting the alternative hypothesis of equivalence if each individual one-sided test was significant at the 0.0125 criterion. An algebraically equivalent and perhaps more straightforward method for assessing equivalence is to compare the 97.5% confidence interval for the difference to the *a priori* equivalency region—if the confidence interval for the difference lies entirely within the equivalency interval, the null hypothesis of nonequivalence is rejected.

SD estimates for SSEP amplitude observed by Samra *et al.*[32] ranged from 50% to 100% of the mean, with means ranging from 1 to 1.4, and the SD for latency was observed to be approximately 10% of the mean, with a mean of 44 in 20 elective surgery patients receiving remifentanil. Thornton *et al.*[24] observed the SD of Pa amplitude to be approximately 50% of the mean (between 49% and 52% of the mean for placebo and two doses of dexmedetomidine) in nine healthy volunteers. Therefore, we defined equivalency to be a mean change of less than 50% of the initial baseline median for SSEP amplitude (P37 and N20 amplitudes were averaged for

Table 1. Summary of Several Intraoperative Parameters at Baseline and at Two Doses of Dexmedetomidine for n = 30 Patients Undergoing Complex Spine Surgery

	Baseline	0.3 ng/ml	0.6 ng/ml	Final
Mean arterial pressure, mmHg	77 (73, 83)	80 (72, 83)	79 (72, 85)	75 (71, 82)
Temperature, °C	35.6 (35.3, 35.9)	35.7 (35.2, 36.0)	35.6 (35.4, 36.1)	36.4 (35.8, 36.7)
Bispectral Index	48 (41, 57)	45 (43, 58)	45 (41, 51)	50 (45, 58)
Remifentanil dose, ng/kg	0.10 (0.10, 0.15)	0.11 (0.10, 0.15)	0.10 (0.10, 0.20)	0.10 (0.08, 0.15)
SSEP amplitude, μV	0.7 (0.5, 1.1)	0.7 (0.4, 1.0)	0.6 (0.4, 1.0)	0.6 (0.4, 1.0)
SSEP N20 latency, ms	21.2 (20.1, 22.3)	21.0 (19.9, 22.3)	21.0 (19.9, 22.1)	20.3 (19.2, 22.3)
SSEP P37 latency, ms	41.8 (39.2, 43.7)	41.8 (40.2, 43.1)	41.7 (40.0, 43.8)	40.7 (38.9, 42.7)
MEP voltage	159 (120, 230)	155 (115, 230)	165 (120, 260)	170 (118, 240)
MEP amplitude AUC, thousands	4 (1, 12)	4 (2, 9)	2 (1, 10)	5 (2, 11)

Results are shown as median (quartiles). End-tidal desflurane was maintained at 4% throughout the study period.

AUC = area under the curve; MEP = motor evoked potential; SSEP = somatosensory evoked potential.

the purposes of our study), a mean change of less than 10% of the initial baseline median for SSEP latency, a mean change within 100 V of the initial baseline median for MEP voltage stimulus, and a mean change of less than 50% of the initial baseline median for MEP area under the curve amplitude.

Sample size was based on both amplitude and latency of the SSEP, the primary outcomes. We assumed an SD of approximately 75% of the mean for amplitude based on the literature above; for latency, we assumed a SD of approximately 20% of the mean. For both outcomes we assumed a within-subject correlation (baseline to each dexmedetomidine concentration) of approximately 0.70. To have 80% power to find equivalence or "no effect" from baseline for both comparisons at the 0.025 significance level, given that the true difference is within the specified region, the required sample size was 26 for amplitude and 28 for latency. We therefore recruited 30 patients for the study. All statistical analysis was performed using SAS version 9.1 (SAS Institute Inc., Cary, NC) statistical software.

Results

We enrolled 37 patients, but only 30 completed the study. Data were not used from 7 patients who did not complete the study, because analysis was based on treatment received and not intention to treat. Among those excluded, 3 were excluded because neuromuscular relaxation was requested by the surgeon; 2 were excluded because reliable baseline TceMEP recordings proved impossible; and 1 was excluded because a bolus of propofol was inadvertently given during one of the measurement periods. Finally, 1 patient was excluded when TceMEPs recordings from the legs disappeared during surgery; prompt removal of traction by the surgeon restored TceMEPs to baseline levels. No data from these 7 patients were included in subsequent analysis.

Of the remaining 30 participants, 16 were female and 14 were male. The mean (SD) age, height, and weight were 45 (14) years, 171 (10) cm, and 82 (20) kg, respectively. The average plasma dexmedetomidine concentra-

tion during the 0.3-ng/ml target infusion was 0.29 (SD 0.6) ng/ml, and the plasma concentration during the 0.6-ng/ml target infusion was 0.63 (SD 0.16) ng/ml. Medians and quartiles for several intraoperative parameters, including the five response measurements, are reported for both baseline phases and each dexmedetomidine dose in table 1. Figures 1–5 display side-by-side box plots of each response variable *versus* experimental phase (initial baseline, 0.3 ng/ml dexmedetomidine, 0.6 ng/ml dexmedetomidine, and the final baseline). Figure 6 displays the SSEPs and TceMEPs recordings at different study recording periods.

An assumption required for using the two one-sided tests procedure is normality of the baseline-to-dose differences. SSEP amplitudes and latencies for median and posterior tibial nerves met this normality assumption, whereas MEP amplitude and MEP voltage were transformed to the log (base 2) scale to satisfy the assump-
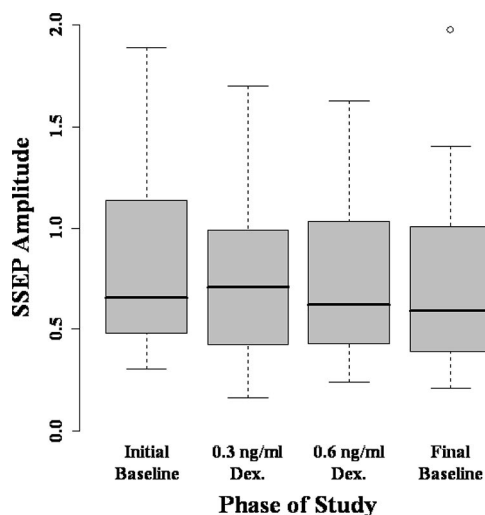

Fig. 1. Somatosensory evoked potential (SSEP) amplitude *versus* experimental phase for n = 30 patients undergoing complex spine surgery. The *shaded box* links the 25th and 75th quartiles, and the *horizontal line* inside of the shaded region is the sample median. *Whiskers* are drawn out from the (25th, 75th) quartiles to the points with (smallest, largest) values within 1.5 times the length of the box; *points* outside these thresholds are plotted individually. Dex = dexmedetomidine.
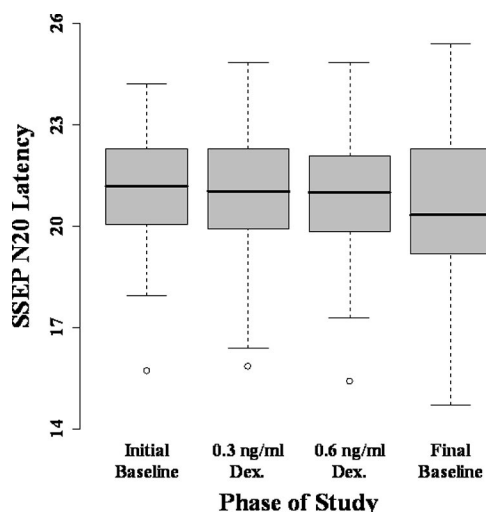
Fig. 2. Somatosensory evoked potential (SSEP) N20 latency *versus* experimental phase for n = 30 patients undergoing complex spine surgery. The *shaded box* links the 25th and 75th quartiles, and the *horizontal line* inside of the shaded region is the sample median. *Whiskers* are drawn out from the (25th, 75th) quartiles to the points with (smallest, largest) values within 1.5 times the length of the box; *points* outside these thresholds are plotted individually. Dex = dexmedetomidine.

tion; this transformation had the effect of making the equivalency region for both MEP outcomes asymmetric about zero. Specifically, the equivalency region limits used for testing MEP amplitude were -1.00 and 0.59 (*e.g.*, $\log_2(1 - 50\%) = -1.00$ and $\log_2(1 + 50\%) = 0.59$), and for MEP voltage these limits were -1.43 and 0.70, as the prespecification of 100 V corresponded to 63% of the baseline median. A summary of the transformations and the equivalency intervals used for testing is given in table 2.
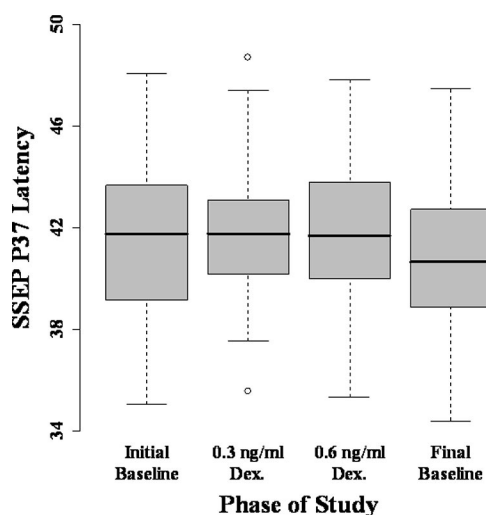

Fig. 3. Somatosensory evoked potential (SSEP) P37 latency *versus* experimental phase for n = 30 patients undergoing complex spine surgery. The *shaded box* links the 25th and 75th quartiles, and the *horizontal line* inside of the shaded region is the sample median. *Whiskers* are drawn out from the (25th, 75th) quartiles to the points with (smallest, largest) values within 1.5 times the length of the box; *points* outside these thresholds are plotted individually. Dex = dexmedetomidine.

Fig. 4. Motor evoked potential (MEP) voltage *versus* experimental phase for n = 30 patients undergoing complex spine surgery. The *shaded box* links the 25th and 75th quartiles, and the *horizontal line* inside of the shaded region is the sample median. *Whiskers* are drawn out from the (25th, 75th) quartiles to the points with (smallest, largest) values within 1.5 times the length of the box; *points* outside these thresholds are plotted individually. Dex = dexmedetomidine.
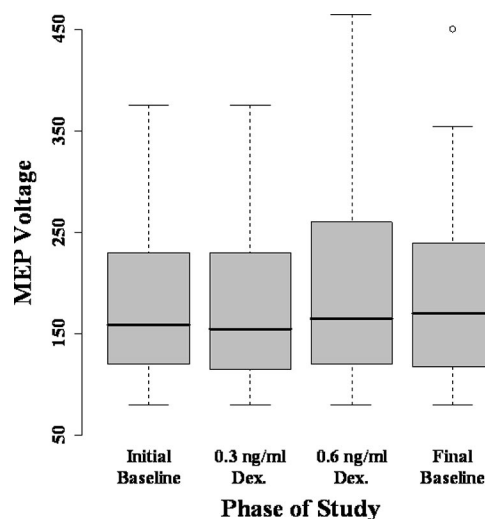
Results of the tests comparing dexmedetomidine doses of 0.3 and 0.6 ng/ml with initial baseline are displayed in tables 3 and 4, respectively, for each of the five outcomes of interest. It is observed that for both doses, SSEP amplitude, SSEP latency, and MEP voltage were significantly equivalent, as the respective 97.5% confidence intervals for the mean difference lay entirely within the equivalency intervals; the 97.5% confidence interval gives our best assessment of the
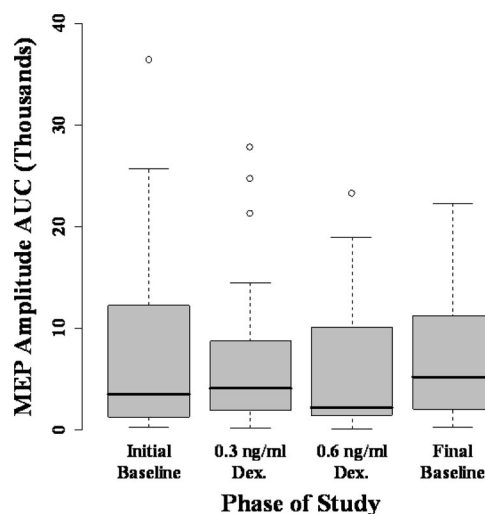
Fig. 5. Motor evoked potential (MEP) amplitude area under the curve (AUC) *versus* experimental phase for n = 30 patients undergoing complex spine surgery. The *shaded box* links the 25th and 75th quartiles, and the *horizontal line* inside of the shaded region is the sample median. *Whiskers* are drawn out from the (25th, 75th) quartiles to the points with (smallest, largest) values within 1.5 times the length of the box; *points* outside these thresholds are plotted individually. Dex = dexmedetomidine.
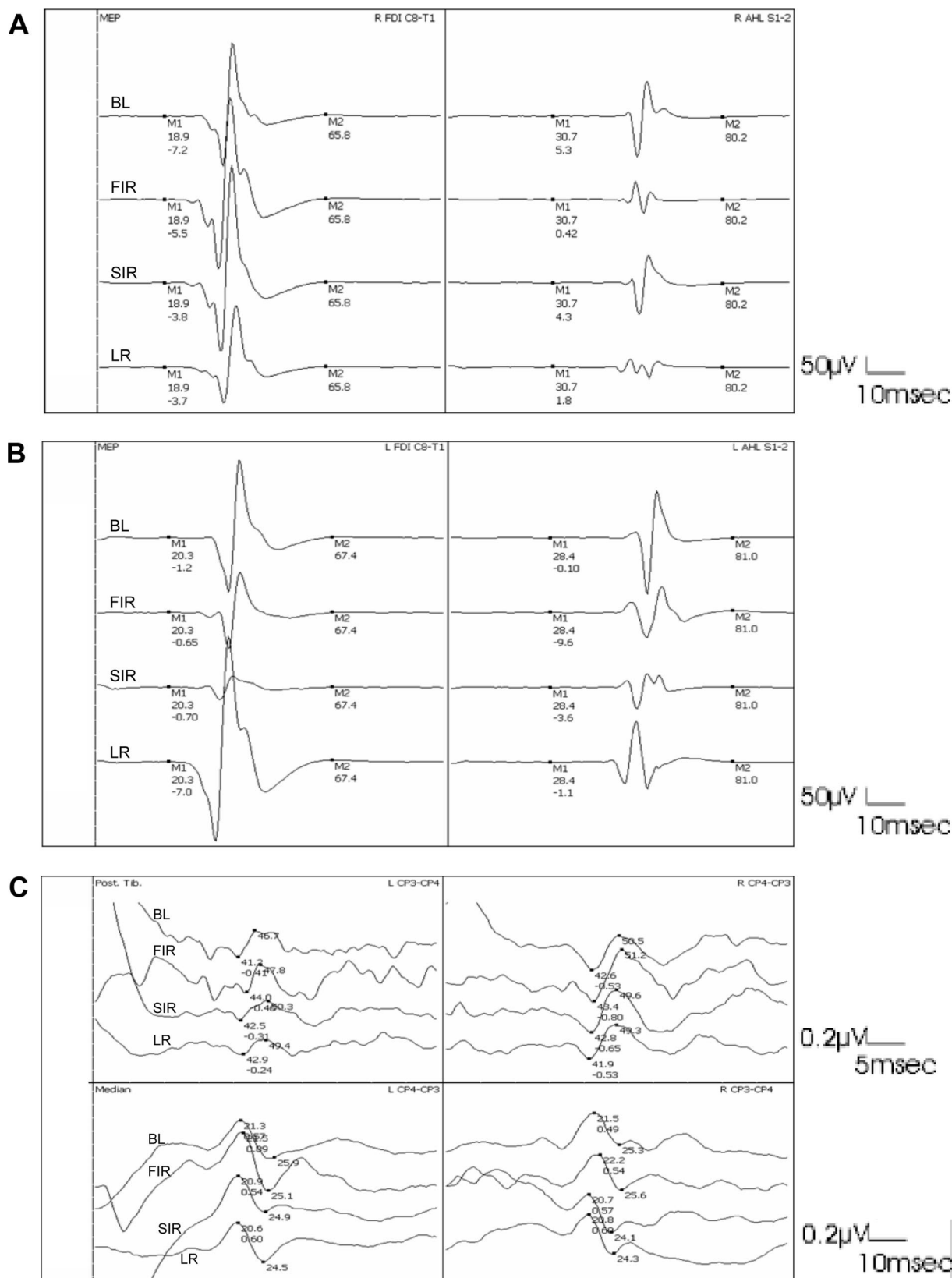
BL = Baseline Recording; FIR = First Infusion Recording; SIR = Second Infusion Recording; LR = Last Recording

Fig. 6. Transcranial motor evoked potentials (TceMEPs) and somatosensory evoked potentials (SSEPs) at different study recording periods. (*A*) Right first dorsal interossei (R FD1 C8-T1) and abductor hallucis longus (R AHL S1-2) TceMEP. (*B*) Left first dorsal interossei (L FD1 C8-T1) and abductor hallucis longus (L AHL S1-2) TceMEP. (*C*) Left (L) and right (R) posterior tibial nerve (Post Tib) and median nerve (Median) SSEP.

Table 2. Summary of Prespecified Equivalency Criteria for Each of the Five Outcome Variables, and the Resulting Equivalency Intervals Used for the Two One-sided Tests Procedure*

Outcome Variable	Baseline Median	Prespecification of Equivalency	Equivalency Interval
SSEP amplitude, μV	0.66	50%†	[−0.33, 0.33]
SSEP latency: N20/hand, ms	21.2	10%†	[−2.12, 2.12]
SSEP latency: P37/leg, ms	41.8	10%†	[−4.18, 4.18]
MEP voltage	159	63%†‡	[−1.43, 0.70]§
MEP amplitude AUC	3,513	50%†	[−1.00, 0.59]§

* The two one-sided tests procedure rejects the null hypothesis that the mean difference D (from initial baseline to dexmedetomidine dose) is outside the equivalency interval if two simultaneous one-sided null hypotheses are rejected: that D is less than the lower limit of the interval and that D is greater than the interval's upper limit, or alternatively, if the confidence interval for the difference lies entirely within the equivalency interval. † Percent of initial baseline median. ‡ Equivalency prespecified as 100 V (63% of the baseline median). § Outcome analyzed on the log (base 2) scale to meet the small-sample normality assumption required or testing, thus making the equivalency interval asymmetric about zero; *e.g.*, the equivalency specification of 50% of the baseline median for motor evoked potential (MEP) amplitude area under the curve (AUC) corresponded to equivalency limits of $\log_2(1 - 50\%) = -1.00$ and $\log_2(1 + 50\%) = 0.59$ on the log scale.

SSEP = somatosensory evoked potential.

true treatment effect for each outcome. However, we were unable to conclude that MEP area under the curve amplitude was significantly equivalent between the doses, because the confidence intervals corresponding to this outcome each overlapped one of the equivalency interval bounds. Though not tested statistically because it was not a primary aim of the study, similar results for each outcome were observed when comparing the final baseline (washout phase 1 h after second dexmedetomidine infusion dose) with the initial baseline (table 5).

Discussion

Anesthetic agents have a dose-dependent negative effect on evoked potential responses. Dexmedetomidine has a hypnotic effect through action on α_2 receptors in the locus ceruleus and analgesic properties through receptor stimulation in the spinal dorsal horn.[33,34] Dexmedetomidine may prove especially helpful during major spinal and intracranial surgery because it is not associated with respiratory depression and reduces anesthetic and analgesic requirements.[16–19] Furthermore, in these studies, it seems that dexmedetomidine provides protection in animals against hypoxic and excitotoxic injuries, especially when given before the injury.[20] This neuroprotective effect is mediated by α_{2A}-receptor subtypes.[35–39]

In an animal study (rats), Bol *et al.*[40] described a site effect half-life of dexmedetomidine of 8.6 min. Dexmedetomidine onset of action as measured by sedation has been reported in the range of 11–25 min,[18,41] where the shortest onset times were described in children. In another study, the authors found dexmedetomidine to suppress postanesthesia shivering in pediatric patients on average within 5 min. In all of these studies, the delivery method consisted of a bolus dose of 1 μg/kg over 10 min. In their study, Hsu *et al.*[42] allowed 5 min for an equilibration between plasma and effect site. Their measurements were performed at 10 min after the start of the target infusion. We therefore decided to allow a 10-min onset of effect time after the start of the target infusion assuming a fast equilibration between plasma and central concentrations of dexmedetomidine. Pharmacokinetic models indicate that this is plenty of time in the context of a computer-controlled infusion of this rapidly acting drug.[25] And, consistent with this modeling, actual plasma concentrations were close to targeted values.

We are aware of two pediatric cases in which Tce-MEPs deteriorated during spine surgery with dexmedetomidine.[23] In the first case, a 13-yr-old patient with kyphoscoliosis who presented for posterior spinal fusion received $0.5 \ \mu g \cdot kg^{-1} \cdot min^{-1}$ remifentanil with $0.5 \ \mu g \cdot kg^{-1} \cdot h^{-1}$ dexmedetomidine. The remifentanil dose is high compared with our dose; further-

Table 3. Results of the Two One-sided Tests Comparing 0.3 ng/ml Dexmedetomidine with Initial Baseline for Each of the Five Outcomes of Interest (n = 30)

Outcome Variable	Mean (SD)			Prespecified Equivalency Region for Mean Difference*	97.5% CI† for Mean Difference*
	Initial Baseline	0.3 ng/ml Dexmedetomidine	Difference*		
SSEP amplitude, μV	0.8 (0.5)	0.8 (0.4)	−0.08 (0.24)	[−0.33, 0.33]	(−0.18, 0.03)‡
SSEP latency: N20/hand, ms	21.1 (1.9)	21.0 (2.1)	−0.04 (0.87)	[−2.12, 2.12]	(−0.42, 0.35)‡
SSEP latency: P37/leg, ms	41.6 (2.9)	42.1 (3.1)	0.51 (1.16)	[−4.18, 4.18]	(−0.00, 1.00)‡
$\log_2$ MEP voltage§	7.4 (0.6)	7.3 (0.7)	−0.02 (0.20)	[−1.43, 0.70]	(−0.11, 0.06)‡
$\log_2$ MEP amplitude AUC§	11.9 (1.9)	11.7 (2.0)	−0.11 (1.78)	[−1.00, 0.59]	(−0.88, 0.65)

* 0.3 ng/ml minus initial baseline. † Bonferroni-adjusted confidence interval (CI) for two comparisons (one at each dexmedetomidine dose). ‡ The null hypothesis of nonequivalence was rejected for this outcome using the two one-sided tests procedure; this is seen by observing that the 97.5% CI lies entirely within the equivalency interval (the 97.5% CI is our best assessment of the mean of the patient-specific differences). § Outcome analyzed on the log (base 2) scale to meet the small-sample normality assumption required for testing.

AUC = area under the curve; MEP = motor evoked potential; SSEP = somatosensory evoked potential.

Table 4. Results of the Two One-sided Tests Comparing 0.6 ng/ml Dexmedetomidine with Initial Baseline for Each of the Five Outcomes of Interest (n = 30)

Outcome Variable	Mean (SD)			Prespecified Equivalency Region for Mean Difference*	97.5% CI† for Mean Difference*
	Initial Baseline	0.6 ng/ml Dexmedetomidine	Difference*		
SSEP amplitude, μV	0.8 (0.5)	0.8 (0.4)	−0.06 (0.22)	[−0.33, 0.33]	(−0.16, 0.03)‡
SSEP latency: N20/hand, ms	21.1 (1.9)	21.0 (2.0)	−0.07 (0.97)	[−2.12, 2.12]	(−0.50, 0.36)‡
SSEP latency: P37/leg, ms	41.6 (2.9)	42.1 (3.1)	0.42 (1.49)	[−4.18, 4.18]	(−0.23, 1.10)‡
Log$_2$ MEP voltage§	7.4 (0.6)	7.4 (0.7)	0.01 (0.24)	[−1.43, 0.70]	(−0.10, 0.11)‡
Log$_2$ MEP amplitude AUC§	11.9 (1.9)	11.4 (2.2)	−0.45 (1.68)	[−1.00, 0.59]	(−1.20, 0.29)

* 0.6 ng/ml minus initial baseline. † Bonferroni-adjusted confidence interval (CI) for two comparisons (one at each dexmedetomidine dose). ‡ The null hypothesis of nonequivalence was rejected for this outcome using the two one-sided tests procedure; this is seen by observing that the 97.5% CI lies entirely within the equivalency interval (the 97.5% CI is our best assessment of the mean of the patient-specific differences). § Outcome analyzed on the log (base 2) scale to meet the small-sample normality assumption required for testing.

AUC = area under the curve; MEP = motor evoked potential; SSEP = somatosensory evoked potential.

more, experience with dexmedetomidine in pediatric patients remains limited. The second case was in a 19-yr-old patient who presented for kyphoscoliosis correction and received a dexmedetomidine infusion of 0.5 μg · kg^{-1} · h^{-1} with 0.6 μg · kg^{-1} · h^{-1} sufentanil and 100 μg · kg^{-1} · min^{-1} propofol. MEPs deteriorated when a bolus of 1 μg/kg dexmedetomidine was given over 10 min to deepen the level of anesthesia; the dose was high enough to induce increased blood pressure due to stimulation of peripheral α_2 receptors. In our study, the 0.6-ng/ml target infusion corresponds to an infusion rate of approximately 0.3 μg · kg^{-1} · h^{-1}, which is in the lower range of recommended infusion doses for dexmedetomidine (0.2–0.7 μg · kg^{-1} · h^{-1}). Furthermore, in one of our patients excluded from the study for inadvertently being given a propofol bolus, motor evoked responses were also abolished. We cannot exclude that dexmedetomidine alone at bolus doses or when used with bolus doses of propofol might obliterate the evoked motor response. In our study, we restricted the dose of remifentanil to 0.2 μg · kg^{-1} · min^{-1} and maintained anesthesia with desflurane, not propofol. It remains possible that much higher infusion rates and plasma concentrations produce substantial impairment of evoked potential responses.

Our results indicate that dexmedetomidine—up to 6 ng/ml—has no effect on SSEPs, but the area under the curve of the motor evoked responses was too variable for us to claim equivalence as per our definition of 50% of the initial baseline median. However, in all the study subjects, MEP recordings were possible throughout the study phase with no change in the stimulating current.

In our study, patients served as their own control group; therefore, it was crucial that the only factor to change between recording periods was dexmedetomidine concentration in plasma. Therefore, desflurane was always maintained at 4% and only remifentanil was titrated because any change in desflurane concentration would be reflected in evoked potential responses, thus making it impossible to observe the real effect of dexmedetomidine. Remifentanil was titrated because it has little if any effect on evoked responses.

We conclude that dexmedetomidine might be used as an adjunct to volatile anesthetics, but it should be taken into account that we were unable to reject the hypothesis that it attenuates the motor evoked responses by an amount greater than 50%, whereas the somatosensory evoked responses were demonstrated beyond statistical uncertainty to be equivalent. Further studies are needed to investigate the effect of higher doses of dexmedetomidine on MEPs.

Table 5. Summaries of the Five Outcomes of Interest for Initial and Final (1 Hour after the Second Dexmedetomidine Infusion) Baseline Phases, as Well as the Difference between the Baseline Phases

Outcome Variable	Initial Baseline Mean (SD)	Final Baseline Mean (SD)	Difference: (Final − Initial) Baselines	
			Mean (SD)	95% CI
SSEP amplitude, μV	0.8 (0.5)	0.7 (0.4)	−0.12 (0.28)	(−0.23, −0.01)
SSEP latency: N20/hand, ms	21.1 (1.9)	20.5 (2.2)	−0.50 (1.35)	(−1.00, 0.02)
SSEP latency: P37/leg, ms	41.6 (2.9)	41.1 (3.1)	−0.68 (1.56)	(−1.30, −0.08)
Log$_2$ MEP voltage*	7.4 (0.6)	7.4 (0.7)	−0.01 (0.37)	(−0.15, 0.14)
Log$_2$ MEP amplitude AUC*	11.9 (1.9)	12.1 (1.6)	0.25 (1.62)	(−0.37, 0.88)

* Outcome analyzed on the log (base 2) scale to meet the small-sample normality assumption required for testing the primary hypotheses of equivalency between 0.3 ng/ml dexmedetomidine and baseline and between 0.6 ng/ml dexmedetomidine and baseline.

AUC = area under the curve; CI = confidence interval; MEP = motor evoked potential; SSEP = somatosensory evoked potential.

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