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The effect of propofol-based anesthesia versus low dose propofol with less than half MAC sevoflurane on intraoperative trans-cranial motor evoked potential during spine surgeries: Ratios rather than values

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ABSTRACT

Background: Transcranial motor evoked potentials (TcMEP) were proved to be useful during complicated spinal surgeries to prevent iatrogenic complications. The effect of anesthetic agents was comprehensively discussed in literature. We investigated a new balanced anesthetic protocol using propofol and sevoflurane in addition to continuous fentanyl infusion in which we compared values and ratios of amplitudes and latencies of TcMEP waves at different time point.

Materials and Methods: A total of 60 patients underwent spinal surgeries were randomly allocated into two groups who received either 75–100 µg/kg/min propofol (***P*** group) or 25 ug/kg/min propofol and 0.2% below corrected-to-age- half MAC of sevoflurane (***BA*** group). TcMEP was recorded before positioning (R1), after positioning (R2), and after skin incision (R3). R2/R1 and R3/R2 ratios were calculated. Modified Aldrete Score was recorded on discharge from PACU.

Results: Fluids infused and urine output were significantly increased in ***P*** group ($p<0.001$). HR and MAP were significantly lower in ***P*** group ($p<0.001$), but CVP was lower in **P** group at R1 and R2 ($p = 0.019, 0.037$). TcMEP was recorded from Vastus lateralis (VL) and Deltoid(D) muscles, which showed a significant lower amplitude in ***P*** group at different time points ($p<0.05$) without significance in latencies. While when ratios were compared (L2/L1 and L3/L2), it showed significant differences ($P<0.001$ and 0.041, respectively). Aldrete score was significantly higher in ***BA*** group.

Conclusion: Balanced regimen using propofol and sevoflurane resulted in a comparable TcMEP recording, hemodynamic stability and a better recovery from anesthesia during spinal surgeries.

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1. Introduction

During spinal surgeries – especially with the new advanced techniques in complicated spinal deformities and minimally invasive spinal surgeries – several important structures as spinal cord, nerve roots, and even vascular supply can be put in a potential risk of injury. Neurophysiological Intraoperative Monitoring (NIOM) modalities have been introduced aiming to monitor the neural integrity during these surgeries; the term was defined in 1970s. The most frequently used modalities are somatosensory-evoked potentials (SSEP), motor-evoked potentials (MEP), free run or spontaneous myography (SEMG), and triggered electrical myography (TEMG). [1]

Previously, *Stagnara's wake-up test* was widely used to monitor intraoperative iatrogenic spinal injuries, which involved waking the patient during surgery to ask him/her to move the suspected limb. In fact, this test was not appropriate to many patients either due to personal variations (cognitive), anesthetic environment (depth of anesthesia needed to accommodate surgery) or the long time elapsed from the injury that made ultimate correction unachievable. [2] Choosing the appropriate modality to monitor a specific surgery is challenging; SSEP, monitoring the dorsal column-medial lemniscus pathway may not detect anterior cord injuries which is the main nightmare during surgeries. On the other hand, MEP is monitoring the corticospinal pathway (which is not covered by SSEP). Hence, MEP monitoring was introduced as a faster (but not continuous) intraoperative monitoring modality with a great success rate, especially Transcranial approach (TcMEP), which was introduced by *Merton and Morton in 1980*. [3]

In the standard TcMEP, stimulation electrodes are placed at C1 and C2 *(10–10 international system)* for lower extremities muscle group, producing a train of

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six pulses with 50 ms pulse width in an interval of 2 *milliseconds* (*ms*). Recording electrodes are placed subdermal in the target group of muscles as adductor pollicis brevis and tibialis anterior muscle. [4] Of course, many protocols have been described and must be tailored for every patient. Decrease of more than 50% in stimulus amplitude or more than 2 ms delay in latency is an alarm criterion. [5] Records from TcMEP currently interpret in many ways, most commonly: all-or-nothing, the amplitude, threshold, and morphology criterions. To optimize signal detection, anesthetic agent must be finely tuned to the desired effect with minimal influence on the stimulus. Propofol with its fast metabolic clearance rate and sevoflurane, which has a low Ostwald coefficient for blood gas, are the most popular agents used beside narcotics during TcMEP. [6]

Unfortunately, commonly used clinical concentrations of inhalant anesthetics like sevoflurane may interfere through the inhibition of interneuron generators of I-waves in cerebral cortex and anterior horn cells through pre and post synaptic NMDA receptor. Also, intravenous agents, most commonly used is propofol, may suppress α-motoneurons through $GABA_a$ receptors. These effects came always in a dose–dependent manner. [1] Induction doses of propofol (2–5 mg/kg) cause amplitude depression of MEP responses, as does high-dose continuous infusion (80–100 µg/kg/min). MEPs are greatly affected by the use of halogenated agents and can be ablated even with doses of 0.5–1 MAC. [6] It is documented that generous application of opioids can improve MEP monitoring due to the reduction of spontaneous muscle contraction and lowering of the needed MAC of volatile anesthetic agents and intravenous infusion rate of anesthetics. [7,8] Unfortunately, other factors may contribute in fallacies of readings as usage of neuromuscular blockade, hypothermia, variations in mean blood pressure and blood carbon dioxide content. [1]

Aim of our work is to study the effect of minimal doses of both propofol and sevoflurane with medium dose fentanyl to achieve a satisfactory depth of anesthesia, hemodynamic stability, minimal interference with TcMEP recording and better recovery from anesthesia.

2. Patients and methods

2.1. Subjects

After approval by the Ethical Committee (EC) at the National Cancer Institute (Cairo University) and ElSahel Teaching Hospital (GOTHI, Cairo) and after written informed consents from all patients; 60 patients out of 69 assessed patients with American Society of anesthesiologists (ASA) grades I–II who were scheduled for spinal surgeries (intraspinal tumors resection, spondylolisthesis correction, traumatic spinal fractures fixation …. etc.) were included in this prospective double-blind randomized study *(NCT04997707)*. Patients aged less than 18 years, or with history of drug abuse, any pulmonary disease, preoperative motor deficit, history of epilepsy, pacemakers and cochlear implants, previous intracranial surgeries, or needed to deepen anesthetic plane during surgery; were excluded from this study.

2.2. Randomization and blindness

Using computer-generated randomization; patients were allocated into two groups; *Propofol (**P**)* group and *balanced anesthesia (**BA**)* group, each is 30 patients. All data from patients were presented anonymously for confidentiality. Surgeons and neurophysiologists were the same throughout the study and were *blind* to the anesthetic technique. Anesthesia was delivered by more than one anesthetist who were *not* blind for the technique but all were *blind* for the measured outcomes and aim of the study.

2.3. Anesthesia technique

On arrival to OR, patients were checked for any exclusion criteria and all routine preoperative evaluations were done. Patients received 0.1 mg/kg midazolam IV. After connecting basic monitoring cables (NIBP, pulse oximetry and ECG); radial artery was cannulated under local infiltration. Anesthesia was conducted using 4 µg/kg fentanyl, 2–3 mg/kg propofol IV, and 0.5 mg/kg atracurium to facilitate endotracheal intubation. After intubation, central venous catheter, nasopharyngeal temperature probe and urinary catheter were inserted. Fentanyl infusion was delivered to all patients using a syringe pump in a rate of 2 µg /kg/h and was discontinued 60 min before the end of surgery. *From that time*, patients were allocated into the study groups: ***P** group* who received propofol infusion at a rate of 75–100 ug/kg/min (maximum rate of infusion was administered when muscle relaxant was ceased before TcMEP recording) or ***BA** group* who received propofol infusion at a rate of 25 µg /kg/min and sevoflurane in 0.2% below calculated half MAC. 1 MAC was calculated to age as follows: age of 18–25 years, 26–40 years, and ≥40 years MAC will be 2.6%, 2.2%, and 1.8%, respectively, then final concentration to be delivered will be 0.2% lower than calculated half MAC. [9,10] Patients were mechanically ventilated with O_2/air mixture (FiO_2 50%) in a rate of 10–12/minand tidal volume of 6–8 ml/kg to insure SpO2 around 99% and end-tidal CO_2 between 28 and 35 mmHg. Body temperature was kept between 35 and 37°C using warm fluids and warming blankets. Sudden increase in pulse rate and systolic blood pressure were considered light depth of anesthesia and were overcome by rescue doses of fentanyl (1 µg/kg), increase of propofol infusion rate to the preset rate or both.

Intraoperative fluids were given guided by central venous pressure and urine output. Episodes of hypotension (MAP <60 mmHg in normotensive patients or <70 mmHg in hypertensive patients) were treated with Norepinephrine (Levophed®) in an infusion of 0.05–1.0 µg /kg/min.

2.4. TcMEP monitoring

After anesthesia induction, transcranial stimulation electrodes were connected at C1- C2, Cz, and C3–C4 (*10–10 international system*) and subdermal needles were inserted in the appropriate muscles, according to the protocol selected. Shared muscles in all the protocols were deltoid(D) muscle in cervical surgeries and Vastus lateralis (VL) in lumbar spine operations. So, we chose these two muscles to monitor both right and left then mean of both readings was calculated. Processing was done using NIM-SPINE™ SYSTEM (2005 Medtronic Sofamor Danek USA, Inc.). The stimulation used is a train-of-five square wave stimulation, 2 *ms* interstimulus interval, 500 microsecond (*µs*) width and 40–220 milliampere (*mA*) intensity, which can be increased with 10 *mA* steps till muscle action potential is recorded. The first TcMEP ***(R1)*** was taken before positioning and surgical incision, at least 20–25 min after induction, fading of the neuromuscular blockade was checked by train-of-four and double-burst stimulation using peripheral nerve stimulator connected to the ulnar nerve. A second reading ***(R2)***, which is the surgical baseline reading, was taken 20 min later; after positioning of the patient, again muscle relaxant fading was confirmed before the reading as above. A third reading ***(R3)*** was taken after the surgical incision. With every TcMEP reading, MAP, pulse rate, oximetry, end-tidal CO_2, nasopharyngeal temperature, ulnar *train-of-four* response, sevoflurane percentage concentration/propofol infusion rate and CVP were recorded. R2/ R1 ratio was calculated which was dedicated to the effect of anesthetic regimen, while subsequent readings indicated both the effect of anesthetic regimen and any surgical insult (if any). Any decrease in wave amplitude by more than 50% in relation to previous reading and increase in latency more than *2 ms* were recorded as an alarming criterion.

2.5. Recovery from anesthesia

Motor activity, respiration, circulation, consciousness, and O_2 saturation were scored as 0, 1, or 2 using Modified Aldrete Recovery Score for a maximal score of 10 [11]. After fulfilling adequate recovery with a score > 8, patients were discharged from Post Anesthesia Care Unit (PACU) to the intermediate care unit. All patients were checked by neurosurgeons for any motor deficit.

2.6. Outcome measures

Primary outcomes included: R1 and R2 (latency and amplitude), R2/R1 ratio as calculated by TcMEP software and revised manually and postanesthesia recovery score using Modified Aldrete scoring system. Secondary outcomes included: MAP, pulse rate (HR), SpO_2, temperature (T), propofol infusion rate (ml/hour), end-tidal sevoflurane % ($Sevo_{et}$ %), CVP, and end-tidal CO_2 ($CO2_{et}$), which were recorded every 15 min, PaO_2 and $PaCO_2$ and pH_a, which were measured every 1 h, R3/R2 ratio and TOF and /or double burst stimulation which were measured before every TcMEP reading.

2.7. Statistical calculations

2.7.1. Sample size estimation

Sample size was calculated considering all primary outcomes, but we chose *the largest* sample size calculated which was for the *latency* of TcMEP wave. Meanwhile, *latency* was the most sensitive outcome regarding the effect of both regimens. Based on the previous article published by **Palazon et al**. [12] in which difference in latency between their groups was 3 with an average variability of 3 and using *G* power program; a total sample size of 46 (23 per group) was found to be sufficient to detect that effect size, with power of 90% and 5% significance level, but we increased sample size to 60 patients to increase power of the study.

2.7.2. Statistical analysis

Recorded data were analyzed using the statistical package for social sciences, version 21.0 (SPSS Inc., Chicago, Illinois, USA). Quantitative data were expressed as mean± standard deviation (SD) while qualitative data were expressed as frequency and percentage. Independent samples *t*-test of significance was used when comparing between two means. Mann-Whitney U test was used when two-group compared for nonparametric data. Chi-square (x_2) test of significance was used in order to compare proportions between qualitative parameters. The confidence interval was set to 95% and the margin of error accepted was set to 5%. So, the *p* value was considered significant as the following: *p* value <0.05 was considered significant, *p* value <0.001 was considered as highly significant while *p* value ≥ 0.05 was considered insignificant.

Table 1. Demographic data, associated diseases and habits of patients in both groups.

	Group P *(n = 30)*	Group BA *(n = 30)*	*p value*
Age *(yrs.)*	50.07 ± 10.37	51.13 ± 8.6	0.669
Weight *(kg)*	62.93 ± 14.12	63.17 ± 12.97	0.842
Gender *(male/female, n. (%))*	14(46.7%)/16 (53.3%)	16(53.3%)/14 (64.7%)	0.605
Hypertensive *(yes/no, n. (%).)*	25(83.3%)/5 (16.7)	23(76.7%)/7 (23.3%)	0.519
Diabetic *(yes/no, n.(%))*	24(80%)/6(20%)	25(83.3%)/5 (16.7%)	0.739
Smoker *(yes/no, n.(%))*	22(73.3%)/8 (26.7%)	20(66.7%)/10 (33.3%)	0.573

P group: 75–100 µg/kg/min propofol, *BA group*: 25 ug/kg/min propofol and 0.2 below corrected-to-age-half MAC of sevoflurane.
Values expressed in mean ± standard deviation or numbers (n) and percentage (%).

Table 2. Operative data of patients in both groups.

	Group P *(n = 30)*	Group BA *(n = 30)*	*p value*
Anesthesia time *(min.)*	242.5 ± 36.05	251.17 ± 42.56	0.665
Estimated blood loss *(ml)*	788.33 ± 170.54	776.67 ± 151.28	0.780
Infusion volume *(ml)*	3706.67 ± 729.16	2688.33 ± 490.90	0.001***
Urine output *(ml)*	1153.33 ± 299.98	893.33 ± 181.34	0.001***
Needed noradrenaline *(yes/no, n.(%))*	27(90%)/3((10%)	8(26.7%)/22 (73.3%)	0.001***
Fentanyl rescue doses *(yes/no,n. (%))*	27(90%)/3((10%)	24(80%)/6(20%)	0.156

P group: 75–100 µg/kg/min propofol, *BA* group: 25 ug/kg/min propofol and 0.2 below corrected-to-age-half MAC of sevoflurane. Values expressed in mean ± standard deviation or numbers (n) and percentage (%). *$p < 0.05$, **$p < 0.01$, ***$p < 0.001$.

3. Results

3.1. Patients' characteristics

Among 69 patients who were assessed preoperatively; 60 patients were eligible and completed this study with a safe intraoperative TcEMP monitoring without any postoperative neurological complications (Figure 1). No significant difference was detected between groups regarding age ($p = 0.314$), sex ($p = 0.436$), or BMI ($p = 0.108$). Meanwhile, our data showed no significant difference between both groups related to any associated disease or habits as hypertension, DM, or smoking (Table 1).

3.2. Operative data

Mean total anesthesia time and estimated blood loss showed no significant difference between groups ($p = 0.665$ and 0.780, respectively). Total infused

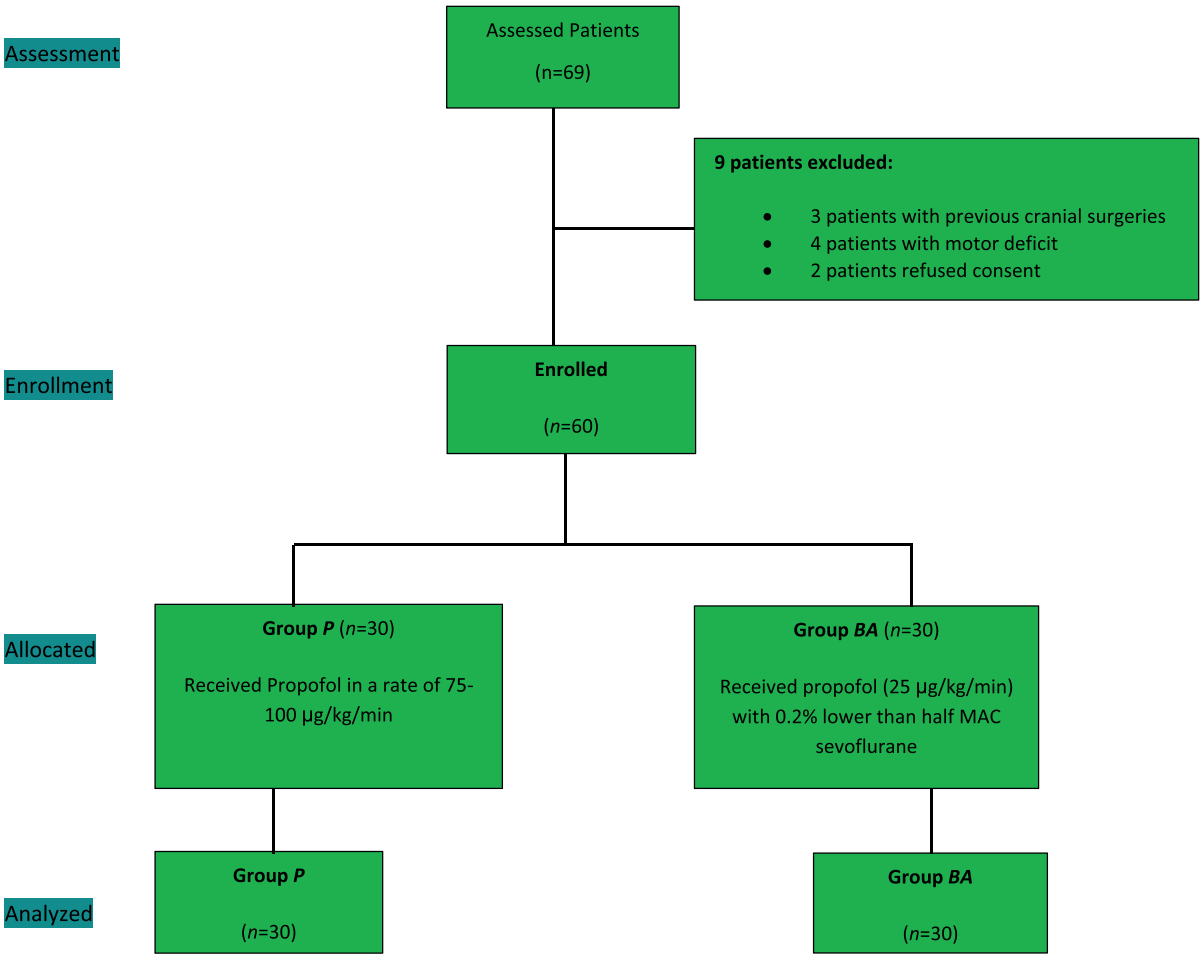

Figure 1. Consort flow diagram of patients.

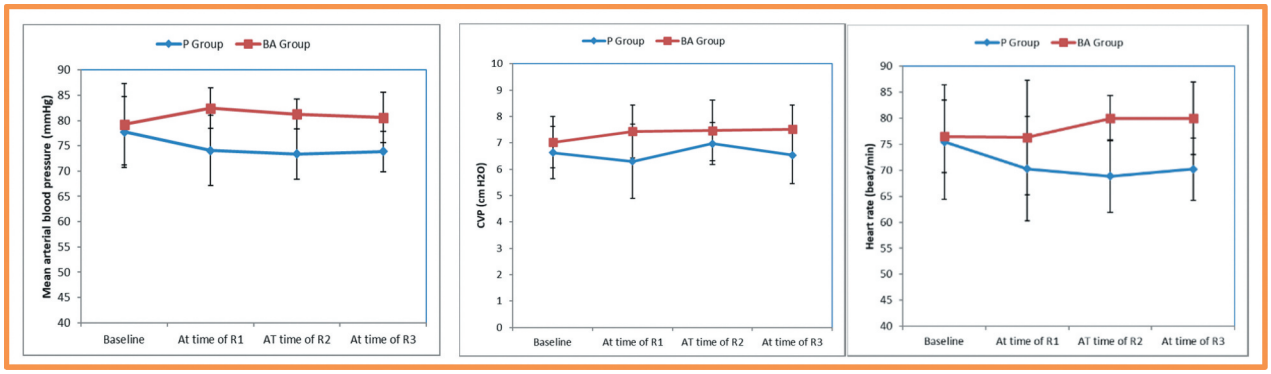

Figure 2. Comparison of both groups showing mean arterial pressure, heart rate, and central venous pressure (CVP). ***P*** group: 75–100 µg/kg/min propofol, ***BA*** group: 25 ug/kg/min propofol and 0.2 below corrected-to-age-half MAC of sevoflurane. (**R1**) TcMEP was recorded before positioning, (**R2**) after positioning, and (**R3)** after skin incision.

Table 3. Comparison of Temperature, SpO_2, $EtCO_2$, PaO_2, $PaCO_2$, and pHa between groups.

Checkpoint parameter	Baseline		R1		R2		R3	
	P group	*BA group*	*P group*	*BA group*	*P group*	*BA group*	*P group*	*BA group*
Temperature °C	36.98 ± 0.18	36.84 ± 0.22	36.81 ± 0.17	36.63 ± 0.20	36.63 ± 0.14	36.44 ± 0.21	36.56 ± 0.21	36.31 ± 0.24
	p value = 0.131		***p value = 0.589***		***p value = 0.104***		***p value = 0.281***	
SpO_2 (%)	99.40 ± 0.62	99.50 ± 0.63	97.27 ± 1.23	98.20 ± 1.06	97.13 ± 1.14	97.90 ± 0.88	97.17 ± 1.37	97.97 ± 0.96
	p value = 0.538		***p value = 0.263***		***p value = 0.504***		***p value = 0.112***	
$EtCO_2$ (*mmHg*)	31.43 ± 1.65	31.57 ± 1.55	31.20 ± 1.37	31.57 ± 1.48	31.80 ± 0.92	31.50 ± 1.28	31.63 ± 1.25	31.30 ± 1.02
	p value = 0.748		***p value = 0.324***		***p value = 0.302***		***p value = 0.262***	
PaO_2 (*mmHg*)	118.57 ± 10.54	119.33 ± 11.15	96.43 ± 1.61	100.07 ± 2.97	95.20 ± 1.45	97.97 ± 2.25	97.77 ± 4.64	97.23 ± 1.99
	p value = 0.785		***p value = 0.805***		***p value = 0.213***		***p value = 0.565***	
$PaCO_2$ (*mmHg*)	35.97 ± 2.03	35.90 ± 1.71	36.87 ± 1.22	35.80 ± 1.56	36.60 ± 1.54	35.43 ± 1.38	37.57 ± 1.45	36.00 ± 1.68
	p value = 0.891		***p value = 0.466***		***p value = 0.313***		***p value = 0.288***	
pHa (mmHg)	7.41 ± 0.01	7.44 ± 0.13	7.12 ± 1.16	7.13 ± 1.01	7.20 ± 0.76	6.87 ± 1.38	7.39 ± 0.01	6.99 ± 1.21
	p value = 0.291		***p value = 0.769***		***p value = 0.256***		***p value = 0.179***	

P group: 75–100 µg/kg/min propofol, ***BA*** group: 25 ug/kg/min propofol and 0.2 below corrected-to-age-half MAC of sevoflurane. (R1) TcMEP was recorded before positioning, (R2) after positioning and (R3) after skin incision. **A**: amplitude of TcMEP wave and **L**: latency of TcMEP wave. Values expressed in mean ± standard deviation. $p > 0.05$ is insignificant.

volume of fluids throughout operations was significantly higher in ***P*** group ($p< 0.001$) compared to ***BA*** group, which was correlated to the significantly higher total urine output in ***P*** group ($p<0.001$). Significant difference was detected regarding number of patients who received noradrenaline intraoperatively ($p<0.001$), while rescue doses of fentanyl were not significant between groups ($p = 0.156$) (Table 2).

3.3. Intraoperative hemodynamic data

At baseline, both groups showed no significant difference regarding HR ($p = 0.66$), MAP ($p = 0.44$), and CVP ($p = 0.272$), but *at subsequent timepoints* HR and MAP showed significant lower values in ***P*** group compared to ***BA*** group ($p <0.001$). CVP showed significant lower readings at R1 and R3 timepoints in ***P*** group ($p = 0.019$ and *0.037* respectively), but at R2 no significant difference was detected ($P = 0.505$) (Figure 2). Temperature, Spo_2, $Etco_2$, Po_2, Pco_2, and pH_a showed no significant difference between both groups either at baseline or at other checkpoints (Table 3).

3.4. TcMEP monitoring

Tc MEP was done to all patients in both groups successfully without any postoperative neurological complications. As we used preset computerized scenarios;

Table 4. Absolute values of amplitudes and latencies.

		R1		R2		R3	
Target muscle	**Group**	A1	L1	A2	L2	A3	L3
Vastus lateralis (VL)	*P group*	85.60 ± 36.31	31.79 ± 9.82	72.47 ± 37.58	32.41 ± 10.04	63.67 ± 34.10	33.66 ± 10.25
	BA group	95.89 ± 38.09	29.44 ± 9.12	90.11 ± 31.09	29.04 ± 9.93	87.67 ± 29.42	29.66 ± 9.48
	t-test	2.436	0.339	3.401	0.639	3.071	0.906
	p-value	0.026*	0.566	0.013*	0.433	0.019*	0.351
Deltoid (D)	*P group*	74.20 ± 25.60	28.72 ± 8.87	56.40 ± 21.41	29.89 ± 8.89	64.33 ± 16.91	31.42 ± 9.35
	BA group	92.29 ± 35.76	29.51 ± 6.44	85.00 ± 32.05	28.64 ± 5.91	85.29 ± 32.77	28.86 ± 5.93
	t-test	3.853	0.045	6.206	0.113	13.866	0.437
	p value	0.029*	0.835	0.022*	0.74	0.001**	0.516

P group: 75–100 µg/kg/min propofol, ***BA*** group: 25 ug/kg/min propofol and 0.2 below corrected-to-age-half MAC of sevoflurane. **(R1)** TcMEP was recorded before positioning, **(R2)** after positioning and **(R3)** after skin incision. **A**: amplitude of TcMEP wave and **L**: latency of TcMEP wave. Values expressed in mean ± standard deviation, *$p< 0.05$, **$p<0.001$.

Table 5. Amplitude and latency' ratios at deltoid muscle in both groups.

Amplitude ratio	Group P *(n = 30)*	Group BA *(n = 30)*	*p value*
A2: A1 ratio	0.76 ± 0.13	0.94 ± 0.09	0.001***
A3: A2 ratio	0.81 ± 0.09	0.99 ± 0.07	0.023*
p value	0.386	0.019*	
Latency ratio			
L2: L1 ratio	1.06 ± 0.02	0.97 ± 0.05	0.001***
L3: L2 ratio	1.05 ± 0.02	1.02 ± 0.05	0.041*
p value	0.084	0.013*	

P group: 75–100 µg/kg/min propofol, ***BA*** group 25 ug/kg/min propofol and 0.2 below corrected-to-age-half MAC of sevoflurane. **A**: amplitude of TcMEP wave and **L**: latency of TcMEP wave. Values expressed in mean ± standard deviation. *$p < 0.05$, **$p < 0.001$, and ***$p < 0.001$.

appropriate target muscles were suggested by the NIOM system were monitored, but we fixed both Deltoid (D) muscle for cervical spine surgeries and Vastus Lateralis (VL) muscle for lumbar. Our data showed that amplitude of TcMEP was significantly lower in ***P*** group when compared to ***BA*** group regarding VL at R1 ($p = 0.026$), R2 ($p = 0.013$), and R3 ($p = 0.019$), while latency recorded from the same muscle showed no significant difference when both groups were compared at different timepoints. For deltoid muscle, amplitude was significantly lower in ***P*** group at different time points ($P = 0.029, 0.022,$ and $<0.001,$ respectively), while latency showed no significant difference between groups all throughout (Table 4).

To confirm the effect of anesthetic regimen *by time* on TcMEP waves, we used *ratios of means* in deltoid muscle. Regarding amplitude A2:A1 ratio, it was significantly lower in ***P*** group ($p<0.001$) and A3:A2 was also significant between groups ($p = 0.023$) with lesser p value. Latency showed no significant difference when we compared means in both groups but when we used ratios, L2:L1 was highly significant ($p< 0.001$) and L3:L2 showed a significant difference ($p = 0.041$) between groups. Inside groups comparisons showed no significant difference in ***P*** group while significant difference was detected in ***BA*** group ($p = 0.013$) (Table 5).

3.5. Recovery from anesthesia

Using modified Aldrete score, ***BA*** group showed a significantly higher median and interquartile range (IQR) than ***P*** group [9 [9,10] *vs*. 8 [7–9], *respectively*] with a $p <0.001$ (Figure 3).

4. Discussion

Since 7th decade of the last century – when the term NIOM was defined – many modalities had been used to monitor iatrogenic neurological injuries during complicated spinal surgeries, one of these modalities was TcMEP, which necessitates the use of tailored anesthetic regimen with a negligible effect on the recorded MEP waves during such surgeries. MEPs allow a satisfactory monitoring of the motor pathway, from cortex to corticospinal pathway then nerve root distally to peripheral nerve, but unfortunately their waves are very sensitive to either inhalational or intravenous anesthetic agents in varying degrees. [12] Many anesthetic protocols had been introduced to minimize the effect of anesthetics on the recorded wave during

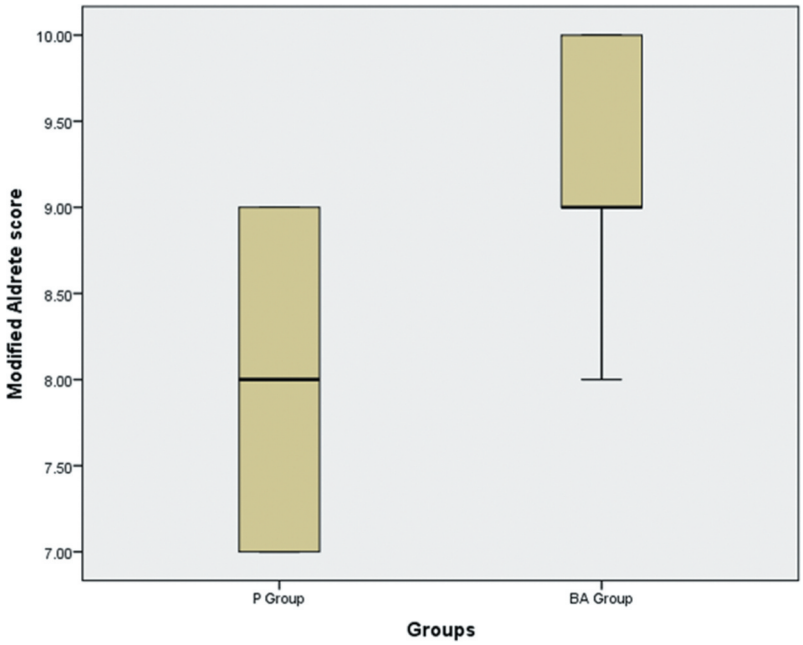

Figure 3. Box plot of Aldrete Score comparison between both groups at PACU. **P** group: 75–100 µg/kg/min propofol, ***BA*** group: 25 ug/kg/min propofol and 0.2 below corrected-to-age-half MAC of sevoflurane. **(R1)** TcMEP was recorded before positioning, ***(R2)*** after positioning and ***(R3)*** after skin incision. Group P: 75–100 µg/kg/min propofol, BA group 25 ug/kg/min propofol and 0.2 below corrected-to-age-half MAC of sevoflurane.

TcMEP. Propofol and sevoflurane were evidenced to be the most suitable agents. Propofol was claimed to reduce cerebral blood volume, which may alter MEP signaling at cortical level and to its unwanted effects on hemodynamic status and delayed recovery from anesthesia due to its context half-life if used in a dose more than 150 µg/kg/min. [13] Sevoflurane which has a superior recovery criterion due to its low Ostwald coefficient to blood-gas; also, was proved to have a dose dependent suppression on MEPs. [14] Although a wide range of MAC was studied ranging from 0.5 to 1.5 MAC; results showed a higher possibility of false-positive wave changes when compared to TIVA due to its inhibitory effect on the pyramidal activation of motor neurons located at the anterior grey column or its depressant effect on the synapses in the cerebral cortex [5]' [13], these findings pushed many of neuroanesthetists to rely mainly on propofol during TcMEP despite of its undesired hemodynamic effects.

Hence came the hypothesis of this work to study the clinical implications of a balanced anesthetic protocol in which sevoflurane was administered in a percentage lower than calculated half MAC and propofol in a rate of 25 µg/kg/min – *which we used in our center ten years ago*- compared to the traditional TIVA regimen using propofol in a dose of 75–100 µg/kg/min used in many centers worldwide.

Five findings had been demonstrated in this study: (1) despite of detecting no significant difference regarding operative time and total blood loss, total infused fluids and total urine output was significantly higher with propofol regimen. (2) HR, MAP, and CVP were significantly lower with propofol based regimen. (3) TcMEP recordings were elicited successfully and were above the preset alarming criteria in both groups, but the amplitude showed significantly lower values with propofol regimen in all target muscles when compared to *balanced anesthesia* regimen, while latency values showed no significant difference between both groups. (4) When latencies ' ratios were compared instead of absolute values; a significant difference between both groups and inside ***BA*** group was observed. (5) Balanced regimen achieved a faster recovery with higher Aldrete recovery score values than propofol-based regimen.

In 2002, *Kammer et al.* [13] compared both sevoflurane and propofol in subanesthetic doses during MEP monitoring using transcranial magnetic stimulation (TMS) in nine volunteers and they concluded that both agents are not suitable for TMS monitoring which was surprising and encouraged the researchers to reevaluate the efficacy of both agents especially with the modern NIOM machines.

Propofol is the preferred agent in most specialized centers with cutoff doses ranging from 50 to 200 µg/kg/min, in the Delphi Consensus study done by *Walker et al.* [5] more than 50% of expert teams asked about the preferred dose during TCMEP who preferred 100 µg/kg/min to ensure a good depth of anesthesia with the help of anesthesia depth monitoring because most of anesthetists use bolus doses of propofol to overcome light plane of anesthesia which may interfere with MEP recording. *Palazon et al.* [12] compared the effect of both 0.5 MAC sevoflurane and propofol at effect site concentration of 2.5 µg/ml and they demonstrated larger amplitude with shorter latency of waveforms with propofol in both upper and lower limbs with differences higher than 50% in amplitude and greater than 10% in latencies between groups. *Park et al.* [15] compared two concentrations of sevoflurane in four case reports – 0.5 and 1 MAC- and concluded that with 1 MAC, MEPs could not be recognized but with 0.5 MAC, it was possible. Same results were showed by *Wang et al* [16] who compared increasing end-tidal concentration of sevoflurane – 0.0%, 0.5%, 1.0%, and 1.5%- while increasing stimulation voltage from 300 V to 600 V and concluded that MEPs was inhibited by sevoflurane when administered in a dose-dependent manner but increasing the stimulation voltage can be used to elicit a successful MEP monitoring. Afterwards; *Yang et al.* [17] compared propofol with various combined inhalational and intravenous regimens, one of these was sevoflurane – 0.5–1% – with propofol as an intermittent IV infusion (37.5–65 µg/kg/min) and stated that MEPs were successfully performed in all patients, but the lack of comparisons between groups and small sample sizes (five patients each) were considerable limitations.

In our present study we used 0.2% below *adjusted-to -age* half MAC values of sevoflurane and less than 100 ug/kg/min propofol infusion, which were still below most agreed-upon in the Delphi Consensus Study conducted by *Walker et al*. [5]

Many other factors were evidenced to affect recording during TcMEP including body temperature, hypoxia, altered PH_a, PO_2, and hyper or hypocapnia [17], which were similar in both groups and were kept within normal range during our study. Hypotension can affect MEP recordings as confirmed by *Lieberman et al.* [18] who observed that hypotension was associated with a decrease in TcMEP output, meanwhile *Lotto et al.* [6] obtained reliable spinal MEPs during deliberate hypotension – which is no more used during recent neuroanesthesia – with MAP 60–70 mmHg. During our current study, *Propofol Based Regimen* showed significant lower MAP and HR values than *Balanced Anesthesia Regimen,* which resulted in more hemodynamic stability. To alleviate any effect on TcMEP recording; MAPs were kept above 70 mmHg in both groups with a significantly more frequent use of noradrenaline in *Propofol* group. Meanwhile, CVP readings were significantly lower in *Propofol* group with a range from 6.3 to 7.5 cmH_2O in both groups. A higher urine output was detected in *Propofol* group, which can be explained by the proved protective

mechanisms of propofol at the renal cells. Inhibiting oxidative stress by decreasing the expression of nuclear factor kB, lowering formation of F (2)-isoprostane and induction of hemeoxygease-1 expression which protects from ischemic renal injuries, were among these mechanisms. On the other hand, sevoflurane was evidenced to impair kidney function due to its defluorination and production of *compound A* which has been associated with nephropathy with renal tubular injury which can explain the decreased urine output compared to propofol specially in prolonged surgeries. [19] Surely, lowered CVP values and increased urine output necessitate the higher infused volumes of intravenous fluids during surgeries to maintain hemodynamics, which were significantly higher in *Propofol* group.

This study also compared both amplitude and latency ratios of TcMEP' waves rather than absolute values used in previous studies; comparing changes from baseline. Ratios gave us a more accurate scale over time which was directly attributed to the effect of selected anesthesia regimen provided that other influencers as MAP, temperature, PH_a, PO_2, etc. are kept within normal. R2 was recorded after positioning and before surgical incision, so was considered surgical baseline value and subsequent recordings were compared to R2. We noticed that, although absolute latency values were not significantly different when both groups were compared at any timepoint for deltoid muscle, L2:L1 and L3:L2 ratios were significantly different between both groups with more prolonged latency wave in propofol group. On the other hand, comparison of both ratios within every group revealed no significance in *Propofol* group while in *Balanced Anesthesia Regimen* group a significant increase of latency was elicited by time which was still significantly lesser when compared with *Propofol* group. Amplitude ratios behaved in the same way when compared either between or within groups.

When both groups were compared for Modified Aldrete Score as a discharge criterion at PACU; it was significantly higher in *Balanced Anesthesia Regimen* group which indicated a better and faster recovery for patients receiving this regimen.

Limitations of this study included: *firstly*; the difficulty to have a baseline TcMEP recording before anesthesia due to its intractable pain. *Secondly*; we did not use Bispectral Index (BIS) due to the different mechanisms of actions of used drugs on its readings and hence it could not be an independent variable.

4. Conclusion

Although both regimens elicited successful TcMEP recordings in all patients; our tailored balanced regimen showed higher amplitude values and latencies' ratios at all target muscles. More stable hemodynamic status was observed with the balanced regimen with a faster recovery at PACU.

Disclosure statement

No potential conflict of interest was reported by the author(s).

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