Fast or Slow? A Comparison Between Two Transcranial Electrical Stimulation Techniques for Eliciting Motor-Evoked Potentials During Supratentorial Surgery

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Purpose: During intraoperative neurophysiological monitoring of motor pathways, two types of transcranial electrical stimulation are available, i.e., constant-current and constant-voltage stimulation. Few previous studies, performed only during spinal surgery, analyzed and compared them during intraoperative neurophysiological monitoring. The aim of our study was to compare these two stimulation techniques for eliciting motor-evoked potentials during intraoperative neurophysiological monitoring in a group of patients affected by supratentorial lesions.

Methods: Supratentorial lesions from 16 patients were retrospectively collected and analyzed. Motor-evoked potentials were performed only from transcranial electrical stimulation because the inability to place the subdural strip electrodes correctly did not permit to perform direct cortical stimulation. At the beginning of surgery, in each patient, motor-evoked potentials were monitored by using both "fast-charge" constant-voltage and "slow-charge" constant-current stimulation. Several neurophysiological parameters were collected and compared between the two stimulation techniques by means of statistical analysis.

Results: "Fast-charge" constant-voltage stimulation allowed statistically higher efficiency rates for eliciting motor-evoked potentials compared with "slow-charge" constant-current stimulation, both for upper and lower limbs. We also found that threshold and maximal charge as well as charge density were significantly lower during constant-voltage stimulation, thus lowering the potential tissue damage.

Conclusions: "Fast-charge" constant-voltage transcranial electrical stimulation is feasible and safe during intraoperative neurophysiological monitoring for supratentorial surgery and may be preferable to "slow-charge" constant-current stimulation.

Key Words: "Fast-charge", "Slow-charge", Transcranial electrical motor–evoked potentials, Intraoperative monitoring.

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Motor-evoked potentials (MEPs) represent bioelectrical signals derived from skeletal muscles by means of stimulation of the pyramidal tract. Although in the outpatient setting they are achieved by transcranial magnetic stimulation, during intraoperative neurophysiological monitoring (IONM), they can be elicited by transcranial or direct cortical electrical stimulation (TES/DCS). The motor responses (compound muscular action potential [cMAP]) are recorded from different muscles of the cranial, cervicobrachial, or lumbosacral area, thus allowing the continuous functional assessment of motor pathway.[1,2]

DCS is the gold standard technique for MEP monitoring and mapping during supratentorial surgery, especially in awake patients in whom TES is not feasible due to painful electrical stimulation through the scalp.[3,4]

Two different stimulation paradigms are available for TES/DCS, i.e., constant-voltage stimulation and constant-current stimulation. During voltage-controlled stimulation, the amount of current delivered to the tissue depends on tissue impedance according to Ohm equation ($I = \Delta V/Z$), where I stand for intensity (measured in mA), ΔV stands for voltage difference (measured in Volts), and Z stands for impedance (measured in kΩ). In case of constant-current paradigm, the stimulator delivers a constant current independently of the tissue and electrode impedance variations by adjusting the voltage across the stimulating electrodes.[5–7] Constant-voltage stimulators contain a capacitor that delivers high voltage pulses with a duration range of 50 to 100 μs ("fast-charge"), with an output current range of 0 to 1,000 mA from a source voltage as high as 400 V. During constant-current stimulation, high current pulses are usually delivered with a pulse width range of 300 to 500 μs ("slow-charge") and an output current range of 0 to 200 mA.[7,8]

To date, few studies, performed only during spinal surgery, compared the two techniques by assessing their ability to elicit MEPs during IONM, showing a higher success rate for "fast-charge" constant-voltage stimulation.[9,10]

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To the best of our knowledge, these two methods have not been compared during IONM for supratentorial surgery, yet. The aim of this retrospective study was to compare “fast-charge” and “slow-charge” TES for eliciting MEPs during IONM in a group of patients affected by supratentorial lesions.

MATERIALS AND METHODS

We performed a retrospective analysis of adult patients affected by supratentorial lesions who underwent surgery with IONM between January 2020 and September 2020 at our university hospital. Considering the retrospective, noninterventional nature of this study, according to local regulations, no approval of the ethics committee or other institutional board was required. Written informed consent was obtained for surgery and for the anonymous use of clinical data in all the patients.

At our hospital, multimodal IONM consisting of EEG-electocorticogram, somatosensory evoked potentials, and MEPs, according to a standardized international approach,[3] is routinely performed by using either the Axon NIM Eclipse workstation (Medtronic) or the ISIS IOM Xpert Plus System workstation (Inomed). As explained by users’ manuals, Axon NIM Eclipse can deliver two types of stimulation: a constant-voltage stimulation with a narrow range of possible pulse widths (25–75 μs) and high maximal output values (400 V/400 mA) - defined as “fast-charge” stimulation - or a constant-current stimulation with a wider range of pulse widths (25–1.000 μs) and lower maximal output values (100 mA)- defined as “slow-charge” stimulation-. Conversely, ISIS IOM System can deliver only a constant-current stimulation paradigm with a maximal output of 200 mA and a wide range of pulse widths. When using Axon NIM Eclipse workstation, at the beginning of surgery, TES is usually performed from both the aforementioned techniques to check the best charge delivery paradigm that can elicit reliable motor responses avoiding muscular twitches that could interfere with surgical maneuvers.

Hence, for the purpose of this study, we selected the patients according to the following criteria:

1. Patients operated under general anesthesia in whom MEP monitoring was performed only from TES because DCS was not feasible due to one of the following reasons: excessive distance of the neoplastic lesion from the rolandic cortex, presence of previous surgical adherent scars that prevented the proper subdural electrode placement, or presence of different intraoperative technical problems such as the dislocation or malfunctioning of the subdural strip electrode.
2. Patients who underwent intraoperative motor monitoring from TES delivered only by the Axon NIM Eclipse workstation.

MEP monitoring was performed from 2 pairs of scalp corkscrew electrodes (Friendship Medical) placed on the C3/C4 (for upper limb) and C1/C2 (for lower limb) locations of the international 10–20 system, with the anode as the active electrode.

cMAPs were recorded from needle electrodes (Spes Medica) inserted in four target muscles controlateral to the lesion site: *extensor communis digitorum*, first dorsal interosseus, *tibialis anterior,* and *abductor hallucis*. The low frequency filter was set at 30 Hz, and the high frequency filter was set at 10 kHz.

In each selected patient, at the beginning of surgery, TES was delivered with a multipulse technique both from a “fast-charge” constant-voltage paradigm and a “slow-charge” constant-current paradigm. Surgery was then performed by using either the “fast-charge” or “slow-charge” stimulation, depending on physician’s choice based on the evocability of MEPs in the absence of muscle twitches potentially interfering with surgical maneuvers.

Stimulation parameters adopted are summarized in Table 1.

All the patients were anesthetized with a total intravenous anesthesia protocol by using propofol and remifentanil continuous infusion. Neuromuscular blockers were allowed only at the beginning of surgery. Neither halogenated gas nor nitrous oxide (N_2O) was allowed.

At baseline (before surgeon started excision), we collected the following stimulation parameters: threshold and maximal intensity of stimulation, threshold and maximal cMAP amplitude, threshold and maximal total charge and efficiency, and, finally, charge density and total energy delivered. According to international standards, threshold intensity was calculated as the intensity required to obtain a cMAP with an amplitude $\geq$ 50 μV in at least 5 of 10 trials.[11]

Maximal intensity was calculated as the intensity above which no further increase of cMAP amplitude occurred. During constant-voltage stimulation, for each stimulus, Axon NIM Eclipse workstation gave us the intensity value, expressed in mA, corresponding to the voltage delivered (expressed in Volts). Total charge was calculated as follows: $\Delta Q = I \times PW \times$ number of pulses, where ΔQ stands for charge (in μC), I for intensity (in mA), and PW for pulse width (in μs).

Efficiency was calculated as the ratio between the cMAP amplitude and the ΔQ. Finally, the charge density and the energy delivered per pulse were calculated according to the following equations: charge density $= \Delta Q$/electrode area and $E = I^2 \times PW \times Z$, where Z stands for the anode impedance. To obtain the result in mJ, it is necessary to multiply it by the conversion factor “0.001,” when I is expressed in mA, PW in μs, and Z in kΩ.[4,10,12]

The stimulating area of the corkscrew electrode was calculated approximately taking into account the following factors: length and diameter of the needle, diameter of the helices, and pitch between the two helices. We also considered that, usually, the corkscrew penetrates the subcutaneous tissue only with one helix. In this way, we obtained a value of 1.7 cm^2.

For each variable collected, we performed a *post hoc* analysis to compare the two stimulation techniques.

We also estimated the successful rate at the baseline: TES was considered successful when the cMAP amplitude of each muscle monitored was greater than 50 μV.[13]

As warning criteria, we adopted the disappearance/irreversible deterioration of the cMAP at least in one muscle either in upper or lower limb. In line with international guidelines, we considered as deteriorated a cMAP amplitude reduction $>$50% compared with baseline or a reduction clearly below earlier amplitudes when preceding trial-to-trial variability was more than 50%.[4]

TABLE 1. Stimulation Patterns Adopted in Our Patients

TES "Fast-Charge" Constant-Voltage Stimulation		TES "Slow-Charge" Constant-Current Stimulation	
Pulses	4	Pulses	4
PW (μs)	75	PW (μs)	500
ISI (ms)	2	ISI (ms)	2
Maximal output current (mA)	400	Maximal output current (mA)	100
Anode impedance (kΩ)	0.39 ± 0.17	Anode impedance (kΩ)	0.39 ± 0.17

ISI, interstimulus interval; PW, pulse width; TES, transcranial electrical stimulation.

Statistical Analysis

Descriptive analysis of the main features of the study population was performed by using mean ± SD or median and percentile for continuous/ordinal variables.

The Wilcoxon signed-rank test was used to compare neurophysiological parameters. All analyses were conducted using Stata/SE (version 14.0 Stata Corp.) for Windows. Statistical significance levels were set at $P < 0.05$. All data are available on request.

TABLE 2. Demographic and Clinical Characteristics of the Population Studied

Parameters	Value (N or %, Mean ± SD)
Number of patients	16
Age	61.63 ± 14.30
Sex	
Male	7 (43.75%)
Female	9 (56.25%)
Lesion type	
Low-grade glioma	9 (56.25%)
High-grade glioma	3 (18.75%)
Meningioma	1 (6.25%)
Metastasis	3 (18.75%)
Tumor site	
Frontal	8 (50%)
Parieto-occipital	2 (12.5%)
Temporal	6 (37.5%)
Tumor side	
Right	10 (62.5%)
Left	6 (37.5%)
Anesthetic protocol	
Remifentanil ($\mu g \cdot kg^{-1} \cdot minute^{-1}$)	0.17 ± 0.10
Propofol ($\mu g \cdot kg^{-1} \cdot hour^{-1}$)	6.27 ± 1.93
TcMEPs successful rate	
"fast-charge" constant-voltage stimulation	14/16 (87.5%)
"slow-charge" constant-current stimulation	13/16 (81.25%)

RESULTS

A total of sixteen adult patients affected by supratentorial lesions were retrospectively analyzed.

Demographic and clinical characteristics of the population studied are summarized in Table 2. Most of the patients (56.25%) were affected by low-grade gliomas, and the frontal lobe was the most represented site (50%). TES success rate was very high with both the stimulation paradigms without any significant differences (87.5%, 14/16 with "fast-charge" stimulation; 81.25%, 13/16 with "slow-charge" stimulation). In all the patients with unsuccessful TES (3/16), i.e., with lack of cMAP recordings at baseline, only lower limb MEPs were not evocable probably because of a motor deficit already present before surgery. In two of them, MEPs were not elicitable with both the techniques while in one patient only "slow-charge" stimulation was unsuccessful. This result may be explained by the suboptimal motor pathway stimulation due to the lower maximal output current values delivered from a constant-current paradigm. In these patients, motor monitoring was performed only from upper limb muscle recordings.

Despite the aforementioned limitations, in all the patients (16/16), intraoperative motor monitoring was performed without any problems during surgery which means that no deterioration of cMAPs occurred during surgery.

No seizures occurred during surgery.

Statistical analysis is summarized in Table 3: as shown, we found statistically significant differences between "fast-charge" and "slow-charge" stimulation with respect to stimulation intensity, charge, charge density, and efficiency both for upper and lower limbs. Constant-voltage stimulation was associated with higher values of intensity and efficiency and lower values of charge and charge density. Regarding the energy, we found significant differences only for threshold values with constant-voltage stimulation being associated to higher energetic pulses.

No difference was found regarding threshold and maximal cMAP amplitudes for upper limbs. For lower limbs, only maximal cMAP amplitudes were different between the two techniques, with higher values after "fast-charge" stimulation.

In most patients (12/16, 75%), the neurophysiologist chose to perform the motor monitoring by using constant-voltage TES; despite the high-intensity stimulation delivered, no muscle twitch capable of interfering with the surgical maneuvers occurred.

DISCUSSION

IONM is recommended during resection of supratentorial lesions located near the rolandic or language-related regions, during surgery for infratentorial lesions within the brainstem and the cerebellopontine angle, and for intramedullary spinal cord tumors.[14]

In spinal cord tumors, Sala et al.[15] demonstrated that MEP could improve long-term motor outcome significantly.

During supratentorial surgery, it was demonstrated that IONM, in particular language mapping and motor mapping/monitoring, increases surgical indications for lesions localized within eloquent areas, thus improving the extent of resection and

TABLE 3. Neurophysiological Variables Collected During IONM

	"Slow-Charge" Constant-Current Stimulation						"Fast-Charge" Constant-Voltage Stimulation							
	Upper Limb						**Upper Limb**							
	ECD			**FDI**			**ECD**			**FDI**				
Variable	**Median**	**25°**	**75°**	**Median**	**25°**	**75°**	**Median**	**25°**	**75°**	**Median**	**25°**	**75°**	***P* ECD**	***P* FDI**
Threshold intensity (mA)	35.50	26.75	48.25	35.00	25.50	47.50	112.00	83.75	144	113	85	148	**0.0004**	**0.0006**
Threshold cMAP amplitude (μV)	63.90	55.73	82.18	93.90	61.90	219.50	71.05	64.78	109.50	205	93.50	353.50	0.0784	0.0614
Threshold total ΔQ (μC)	71	53.50	96.50	70	51	95	33.60	25.13	43.20	33.90	25.50	44.40	**0.0004**	**0.0006**
Threshold ΔQ density/pulse (μC/cm^2)	10.44	7.86	14.19	10.29	7.5	13.96	4.93	3.69	6.35	4.98	3.74	6.53	**0.0004**	**0.0045**
Threshold efficiency (μV/μC)	1.04	0.73	1.47	1.22	1.11	3.77	2.52	1.63	3.47	4.38	3.17	11.15	**0.0009**	**0.0006**
Threshold energy/pulse (mJ)	0.18	0.13	0.37	0.18	0.14	0.37	0.27	0.18	0.42	0.26	0.21	0.44	**0.0278**	**0.0193**
Max intensity (mA)	77.5	60	100	80	65	97.5	226.5	159.5	318	237	153	300.5	**0.0003**	**0.0014**
Max cMAP amplitude (μV)	1.051	710.75	2.141	2.695	957.5	3476.5	1.613	725.05	2.735	2.542	1.532	3622.5	0.0784	0.1738
Max total ΔQ (μC)	155	120	200	160	130	195	67.95	47.85	95.4	71.10	45.9	90.15	**0.0061**	**0.0075**
Max ΔQ density/pulse (μC/cm^2)	22.79	17.64	29.4	23.79	19.11	28.67	9.99	7.03	14.03	10.45	6.75	13.25	**0.001**	**0.0018**
Max efficiency (μV/μC)	7.08	3.62	12.12	13.48	7.47	21.33	18.06	9.69	36.16	36.58	26.59	56.27	**0.0041**	**0.0400**
Max energy/pulse (mJ)	0.96	0.61	1.47	0.82	0.61	1.46	1.19	0.6	2.72	1.25	0.64	2.11	0.0643	0.1096
	Lower Limb						**Lower Limb**							
	TA			**AH**			**TA**			**AH**				
	Median	**25°**	**75°**	**Median**	**25°**	**75°**	**Median**	**25°**	**75°**	**Median**	**25°**	**75°**	***P* TA**	***P* AH**
Threshold intensity (mA)	72.50	51.25	77.50	65	55	82	222	150	254	217	145.25	233	**0.0009**	**0.0014**
Threshold cMAP amplitude (μV)	82.85	66.08	113	70	60	128	216	58	119	79	63.38	86	0.7565	0.8103
Threshold total ΔQ (μC)	145	102.50	155	130	110	164	67	44.85	76.2	65.10	43.58	69.90	**0.0009**	**0.0014**
Threshold ΔQ density/pulse (μC/cm^2)	21.33	15.07	22.79	19.15	16.17	24.11	9.26	5.96	11.2	8.51	5.66	10.23	**0.0009**	**0.0014**
Threshold efficiency (μV/μC)	0.71	0.55	0.86	0.58	0.37	0.87	1.42	0.91	2.50	1.28	1.06	2.16	**0.0009**	**0.0192**
Threshold energy/pulse (mJ)	0.61	0.48	1.21	0.7	0.47	0.82	0.91	0.67	1.76	0.8	0.61	1.34	**0.03**	**0.025**
Max intensity (mA)	77.50	60	100	80	65	98	252	174	385	255.5	220.5	371.5	**0.0006**	**0.0009**
Max cMAP amplitude (μV)	1.051	710.75	2.141	733	313	1.670	970	522	1.321	1.296	905.25	3.174	0.0536	**0.0257**
Max total ΔQ (μC)	180	155	200	190	162.5	200	75.60	52.2	115.35	76.65	66.15	111.45	**0.0104**	**0.0131**
Max ΔQ density/pulse (μC/cm^2)	26.47	22.79	29.41	27.94	23.89	29.41	11.78	7.63	17.41	11.51	9.39	16.5	**0.0104**	**0.0131**
Max efficiency (μV/μC)	2.80	1.73	3.49	3.91	1.57	8.65	11.47	6.45	15.81	17	7.98	41.04	**0.0194**	**0.0063**
Max energy/pulse (mJ)	1.11	0.77	1.52	1	0.98	1.5	1.64	1.11	2.98	1.99	1.05	2.79	0.1527	0.0989

Statistical analysis between constant-current and constant-voltage stimulation is reported. Total ΔQ was calculated as follows: $\Delta Q\ (\mu C) = I \times PW \times$ number of pulses, where I stands for intensity and PW for pulse width. Energy was calculated as follows: $E\ (mJ) = I^2 \times PW \times Z$, where Z stands for the anode impedance.

In bold, statistical significant values are reported.

ΔQ, charge; AH, abductor hallucis; cMAP, compound muscular action potential; ECD, extensor communis digitorum; FDI, first dorsal interosseus; TA, tibialis anterior.

decreasing postoperative neurological symptoms. These features have a positive impact on the overall survival and the quality of life.[16]

Among the various authors, a clear agreement on which are the optimal stimulation parameters during TES is still lacking because some focus the attention on the different charge delivery paradigm, whereas others on the total amount of charge delivered during IONM.[2,17–19]

By optimizing the stimulation parameters, it is possible to achieve reliable MEPs with the lowest intensity and duration, thus lowering the potential stimulation-related injuries. In fact, charge, which is directly proportional to the intensity and to the pulse width, represents the amount of delivered electricity and it has been proven to be an excitotoxic factor in experimental animals. Moreover, energy, which is directly proportional to the square of the intensity, the pulse width, and the electrode–tissue interface impedance, can induce a potential thermal injury as well.[12]

Charge density is another factor related to possible stimulation-induced injuries. In previous studies, an injury charge density threshold of 40 μC/cm^2/phase was identified when biphasic pulse trains of 50 Hz were applied for 15 hours. Although this threshold value was used during chronic direct stimulation studies in animal experiments, it was extended by analogy to TES as well.[8]

However, the relevance of these experiments for intraoperative motor monitoring is not clear; maximal reported charge values delivered from multipulse or Penfield cortical stimulation exceeded the experimental injury threshold, but no clinical or histological injury was described. Conversely, maximal published TES parameters were shown to induce intracranial charge and charge density values below the experimental injury threshold. TES is considered a safe technique considering that, below the aforementioned threshold, the cortex was shown to tolerate stimulation indefinitely.[4,8,20,21] Regarding the potential thermal injury, it has been shown that, to avoid scalp burns, TES should not exceed a safety limit of 50 mJ.[4]

Either constant-current stimulation or constant-voltage stimulation can be used during TES: constant-voltage stimulators contain a capacitor that delivers high voltage pulses of brief duration while during constant-current stimulation, high current pulses are usually delivered with a higher pulse width range. However, reported parameters vary considerably, and none have been proven optimal.[2,7,8,22,23]

Recently, it has been shown that, during DCS, optimal stimulation parameters are the interstimulus interval with the lowest threshold energy (i.e., rheobase^2 × chronaxie) and the PW at its chronaxie. Based on a study on 20 patients, an interstimulus interval of 4 ms and a PW of 0.2 ms have been shown as optimal or near-optimal stimulation parameters.[12]

Haussman et al.[19] evaluated the effects of different modalities of charge application by monitoring and comparing MEPs after slow (500 μs) versus fast (50 μs) charge delivery, during IONM of spine surgery using multipulse TES. They concluded that both the stimulation techniques are comparable with respect to feasibility, intraindividual variability, and mean parameters of MEPs. Nevertheless, fast-charge stimulation provided higher stimulation efficiency and required about 35% less total charge for MEP monitoring.

Recently, Shigematsu et al. and Masuda et al. showed higher success rate of the TES-MEP using constant-voltage stimulation during spinal surgery. Moreover, the cMAP amplitudes elicited with constant-voltage stimulation were consistently higher than those elicited with constant-current stimulation. Maximal voltage was 500 V while maximal current was 200 mA.[9,10]

Even if the sample is small, our study is worthy of attention mainly for the rigorous methodology adopted. In fact, each patient acted as a control of him/herself and the neurophysiological parameters were collected without potential bias such as difference in anesthetic protocols, types of lesion, disease durations, or ages. Moreover, to the best of our knowledge, this is the first report that compares the two stimulation techniques for supratentorial lesions.

"Fast-charge" constant-voltage stimulation allowed statistically higher efficiency rates compared with "slow-charge" constant-current stimulation both for upper and lower limbs. Both techniques proved to be safe considering values of charge density and energy below the recommended injury threshold. Indeed, no injury from TES occurred in our patients, based on a careful clinical examination.

The higher maximal cMAP amplitudes obtained from constant-voltage TES could be explained by the suboptimal stimulation achieved with constant-current TES because the maximal stimulation output is 100 mA instead of 400 mA, which can be achieved with the former technique.

Threshold and maximal intensity were higher during a "fast-charge" paradigm. The higher intensity values delivered from a "fast-charge" technique could be a potential bias because extremely high intensities might activate the corticospinal tract distally and may therefore produce false-negative results.[14,24] Nevertheless, most of our patients (75%) completed IONM by means of constant-voltage TES. Despite the high stimulation intensity delivered, we did not observe any false-negative results, that is, no new neurological deficit occurred at the end of surgery.

LIMITATIONS

We acknowledge that the retrospective nature of this study has inherent limitations and potential bias, such as selection and observation bias. Moreover, we are aware that the distinction between "fast-charge" constant-voltage stimulation and "slow-charge" constant-current stimulation is somewhat artificial because it is due to stimulator design characteristics. Another limitation is that our findings from TES cannot be applied to DCS because no comparison could be made between these two stimulation techniques.

CONCLUSIONS

"Fast-charge" constant-voltage stimulation is feasible and safe during TES for supratentorial surgery and may be preferable to "slow-charge" constant-current stimulation. Further studies with larger patient samples will be necessary to confirm our results and to address the aforementioned critical issues.

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