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Optimum interpulse interval for transcranial electrical train stimulation to elicit motor evoked potentials of maximal amplitude in both upper and lower extremity target muscles

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Objective: The aim of this study was to determine the optimum interpulse interval (OPII) for transcranial electrical train stimulation to elicit muscle motor evoked potentials (TES-MEP) with maximal amplitude in upper and lower extremities during intra-operative spinal cord monitoring.

Methods: Intraoperative spinal cord monitoring with TES-MEP was performed in 26 patients who had (corrective) spine surgery. Optimum interpulse interval (OPII) were determined for the abductor pollicis brevis muscle (APB) representing the upper extremity and the anterior tibialis muscle (TA) representing the lower extremity. The IPI was varied between 0.5 and 4.0 ms, where the OPII was defined as the IPI with the highest muscle MEP amplitude for each muscle group. Differences between upper and lower extremity OPIIs were analyzed. Furthermore, the MEP amplitudes difference between the upper and lower extremity OPIIs and between the OPII and IPI 2 ms was determined.

Results: The mean OPII APB representing the upper extremity was 1.78 ± 1.09 ms on the left side and 1.82 ± 0.93 ms on the right side. The lower extremity showed a mean OPII TA of 2.26 ± 1.16 ms on the left and 2.73 ± 0.88 ms on the right side. The mean differences between the OPII APB and OPII TA were significant for p = 0.019 (Student’s T-test). No within patient differences in OPIIs between the left and the right side were found.

Results: The mean MEP amplitude reduction, the APB amplitude at OPII TA compared to the APB at OPII APB, was 32.5 ± 27.9%. For the TA a mean amplitude reduction of 33.4 ± 27.4% was found. The mean amplitude reduction for the OPII amplitudes compared to the amplitudes at IPI 2 ms was 53.6 ± 25.5% for the APB and 45.8 ± 28.3% for the TA.

Conclusion: Large intra- and interindividual differences were found between the mean OPIIs of the TA and APB muscles (range 1.78–2.73 ms) representing the upper and lower extremity. Significance: Based on the results of this study, it is advisable to perform a set-up procedure for each individual patient undergoing TES-MEP to determine the optimal parameter settings when using supramaximal intensity of TES.

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1. Introduction

Recently, transcranial electrical stimulation to elicit motor evoked potentials (TES-MEP) has increasingly been used to monitor intraoperative spinal cord functioning during (corrective) surgery of the spine. During TES-MEP the muscles in the upper and lower extremity are measured by administered transcranial electrical pulses. A small number of high frequency successive transcranial electrical pulses with a predefined pulse width and interpulse interval time (IPI) are given as pulse trains. Several studies have already shown TES-MEP to be a reliable, sensitive and valid method to monitor the intra-operative neurological status of a patient (Peleoni et al., 2002; Langeloo et al., 2003; Macdonald et al., 2007; Liebermann et al., 2008; Tanaka et al., 2011). A decrease of less than 80% in MEP amplitudes for a certain muscle group was found to be a good criterion for excluding possible neurological damage (Langeloo et al., 2003). However, many other amplitude criteria for events exist and are still being considered.

Despite the more frequent use of TES-MEP, questions still remain concerning the different set up parameters used in this spinal cord monitoring technique. There is, for example, still some controversy about the optimum interpulse interval time (OIP), defined as the IPI with which the highest muscle amplitude is found. Factors that might influence the optimum interpulse interval are anesthetic depth, stimulus intensity, pulse width and the choice of muscle(s) to be targeted. Furthermore there are intra- and interindividual differences of unknown origin.

To date, no agreement on the optimal parameters for the train of stimuli has been found (Macdonald, 2006; Deletis and Sala, 2008). The (O)IPI, as well as other set-up parameters, seem to depend on whether current or voltage stimulation is used. With current stimulation, most often performed with slow charge delivery (pulse width 0.5 ms), the OIP is found to be 4.0 ms (Kothbauer et al., 1998; Deletis et al., 2001a;b; Novak et al., 2004; Szelenyi et al., 2007). Fewer intraoperative neuromonitoring studies have been performed using voltage stimulation. However, when voltage stimulation has been used, the IPI seemed to be lower than the IPI used in current stimulation (Calancie et al., 1998; Pelosi et al., 2002). These studies, almost without exception, were performed for lower extremity muscle groups with a fast charge delivery (pulse width 0.05–0.1 ms). To record MEPs of the thenar and hypothenar, the OIP appeared to be 1 ms for voltage stimulation when stimulus intensities over 150 V and pulse width 0.05 ms had been used (Macdonald and Stigbs, 2003; Scheufler et al., 2005). A 1–2 ms IPI can also be advantageous for facial MEPs because it helps to distinguish stimulus artifacts from the short latency responses (Dong et al., 2005; MacDonald, 2006). For lower extremity muscle groups, IPI of 2–4 ms are frequently used by many practitioners when monitoring the integrity of the spinal cord. The OIPI for leg muscles is still underexplored.

Since 1996 TES-MEP neuromonitoring in our institution (Sint Maartenskliniek Nijmegen, The Netherlands) has been performing using a train of pulses with an interpulse interval of 2 ms and a pulse width of 0.1 ms. In subsequent years, a process to optimize different set-up parameters, e.g. the number of pulses in a train and the stimulus intensity, has been introduced. Despite the optimization of number of pulses in a train (5 ppt) and stimulus intensity, some patients have still shown only small MEP amplitudes. Factors that might influence the optimum interpulse interval time (IPI) are given as pulse trains. Several studies have already shown TES-MEP to be a reliable, sensitive and valid method to monitor the intra-operative neurological status of a patient (Peleoni et al., 2002; Langeloo et al., 2003; Macdonald et al., 2007; Deletis et al., 2008; Tanaka et al., 2011). A decrease of less than 80% in MEP amplitudes for a certain muscle group was found to be a good criterion for excluding possible neurological damage (Langeloo et al., 2003). However, many other amplitude criteria for events exist and are still being considered.

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The objective of this preliminary study was threefold. The first goal was to determine the optimum interpulse interval (OIP) times for TES elicited MEP amplitudes during intraoperative spinal cord monitoring using the tibialis anterior muscle to represent the lower extremity and the abductor pollicis brevis muscle to represent the upper extremity. The second one was to determine the mutual MEP reductions, that is the amplitude reductions for the upper extremity muscle when choosing the lower extremity OIPI and vice versa. Thirdly, the differences in muscle amplitudes between the amplitudes elicited by using IPI 2 ms and the maximal amplitudes at the OIPs, called the 2 ms MEP reductions, were analyzed.

2. Methods

2.1. Patients

In this study data from 26 consecutive patients undergoing (corrective) surgery of the cervical or thoraco-lumbar spine with TES-MEP monitoring were included. The group of 8 male and 18 female patients had a mean age of 31.3 years ± 21.7 (range 10–80 years). Surgeries were performed between January 2007 and May 2008 in the Sint Maartenskliniek Nijmegen (The Netherlands). Twenty-four patients underwent surgery at thoraco-lumbar level: 21 spinal fusions for idiopathic and degenerative scoliosis, two colurnnotomies with spinal fusion for M. Bechterew, and one fusion because of metastatic activity in the thoracic spine. The remaining two had surgery at the cervical spine: a colurnnotomy for M. Bechterew and a cervical spinal fusion occiput-Th1 for rheumatoid arthritis instability. No patient had any neurological deficits preoperatively.

2.2. TES-MEP

Intraoperative neuromonitoring was performed by transcranial electrical motor evoked potential (TES-MEP) in all patients, using the Neuro-guard stimulator (JS-center, Bedum, The Netherlands). For the stimulation two uncoated needle electrodes were inserted subcutaneously at Cz (Anode; Rochester ref 016393, length 3.7 cm, diameter 26GA). The cathode, a modified single cautery ground plate (3 M ref 9160F), was placed on the forehead. The TES elicited MEP amplitudes were recorded with two bipolar Ag/AgCl muscle surface electrodes (3 M™). Before the pre-operative set-up procedure, the patient was anesthetized. For the TES-MEP, a pulse width of 0.1 ms was used. To adapt the settings of the TES-MEP for each patient, first the voltage inducing the supramaximal MEP was defined. The stimulus voltage intensities that induced the supramaximal MEP were typically 1.25–3 times that of the threshold voltage. Next the OIPI was defined by varying the IPI between 0.5 and
4.0 ms while recording MEP amplitudes. IPI (ms) vs MEP amplitude curves were made for each muscle involved (Fig. 1). The curves were constructed in 0.1 ms steps between 0.5 and 2.0 ms IPI; about half of the patients also had 0.1 ms steps between 2.0 and 4.0 ms IPI; for the others the steps were in 0.2 ms steps between 2.0 and 4.0 ms IPI. Based on these curves, the OIPI was defined as the IPI with the highest MEP amplitude; an OIPI was determined for each muscle recorded.

The MEP amplitudes were recorded for four muscles bilaterally, thus for a total of eight muscles. In all protocols the abductor pollicis brevis muscle (APB) and the tibialis anterior muscle (TA) were used. If the surgery was performed for cervical spine pathology, three upper extremity and one lower extremity muscle were chosen, whereas for thoraco-lumbar surgeries, one upper extremity and three lower extremity muscles were chosen. The APB was chosen to represent the upper extremities; the TA was used for the lower extremities. For both the APB and the TA, the OIPI was defined as the IPI (range 0.5–4.0 ms) for which the highest MEP amplitude was found. The amplitudes for both the APB and the TA were determined (OIPI_{APB} and OIPI_{TA}). In addition, the APB and the TA amplitudes at the 2 ms IPI were also determined (Fig. 2).

2.3. Anesthesia regime

As premedication, patients received midazolam (7.5 mg) and meloxicam (7.5–15 mg) 1 h before the general anesthesia. Intravenous anesthesia peroperatively used remifentanyl (0.2–0.5 μg/kg/min), propofol (induction 2 mg/kg, continuous infusion 4–6 mg/kg/hr) and S-ketamine (2.5 μg/kg/min). About half an hour before the end of the surgical procedure, morphine was started; it was continued for the first post-operative hours or days.

2.4. Statistics

First, for each individual patient, the OIPI (ms) was determined, as well the APB as the TA, called the OIPI_{APB} and OIPI_{TA}. Mean and standard deviation (SD) were calculated for the OIPI_{APB} and the OIPI_{TA} separately. A two-tailed, paired Student’s T-test was used to analyze whether there was a significant difference between the mean OIPI_{APB} and mean OIPI_{TA} (p < 0.05). Both left and right muscle amplitudes were determined to be able to analyze the intra-individual difference for a specific muscle.

Secondly, the individual’s MEP amplitude of the APB at OIPI_{TA} was compared to the MEP amplitude at OIPI_{APB}, and vice versa. These differences were expressed as percentage amplitude difference.
reduction compared to the reference muscle’s maximum OIPI amplitude. Mean and standard deviations of the APB and TA reductions were determined as well as the number of individual TA and APB reductions above 80%. A two-tailed paired Student’s T-test determined whether there was a significant difference between mean APB reduction and mean TA reduction ($p < 0.05$).

Finally, the amplitude reductions were determined for the APB and TA amplitudes at the 2 ms IPI compared to each of the respective OIPI maximal amplitudes. Thus, for each individual patient, these calculations were performed.

If significant differences were found between patients left and right side data, the amplitude reductions were analyzed for each side; otherwise only the left side data was used in further analyses.

### 3. Results

#### 3.1. Optimum interpulse interval times

The mean OIPI$^{APB}$ for the left upper extremity side was $1.78 \pm 1.09$ ms (range 0.7–4.0 ms). For the lower extremity, the OIPI$^{TA}$ was $2.26 \pm 1.16$ ms (range 0.7–4.0 ms) for the left side (Table 1). Seventeen patients showed an OIPI$^{TA}$ exceeding the OIPI$^{APB}$, five patients showed a higher OIPI$^{APB}$ than OIPI$^{TA}$ while in three patients the OIPI$^{APB}$ and the OIPI$^{TA}$ were equal. The mean difference between the OIPI$^{APB}$ and OIPI$^{TA}$ was $0.48 \pm 0.97$ ms (range 0–2.5 ms) ($p = 0.019$).

The mean of the OIPIs on the right was $1.82 \pm 0.93$ ms for the APB and $2.73 \pm 0.88$ ms for the TA muscle: a significant difference ($p = 0.00$). On the left side, the difference between the means for these two muscles was not significant. Furthermore, no significant differences were found between the means on the right or left side for either TA or APB. Therefore, the amplitude reductions were analyzed using data from the left side.

Histograms of the IPIs per ms were constructed; the distribution had a bimodal character (Fig. 3A). This was most pronounced for the individual OIPIs of the APB. A first APB peak was seen at $1.09 \pm 0.28$ ms and a second one at $2.89 \pm 0.67$ ms. For the TA, the first peak was found at $1.15 \pm 0.32$ ms and the second peak at $3.01 \pm 0.78$ ms (Fig. 3B). To more clearly show the bimodal nature of the OIPIs, a histogram of the sum of all the IPIs for all four muscles was constructed (Fig. 3C).

#### 3.2. Mutual MEP reductions

The mean mutual reduction in the left-sided MEP amplitudes was $32.5 \pm 27.9\%$ for the APB (range 0–83.7) and $33.4 \pm 27.4\%$ for the TA (range 0–95.4) (Table 1). The difference between these two mean amplitude reductions was not significant ($p = 0.89$). For both the TA and APB muscle, one patient showed an amplitude reduction greater than 80%.

#### 3.3. MEP reductions at IPI 2 ms

The APB MEP-amplitudes at IPI 2 ms showed a mean reduction of $53.6 \pm 25.5\%$ (range 0.0–95.6) compared to their maximum amplitudes at the OIPI$^{APB}$ (Table 1). For the TA muscle, the mean amplitude reduction was $45.8 \pm 28.3\%$ (range 0.0–92.4). For the TA muscle, three individual patients showed an amplitude reduction greater than 80% while for the APB this was four patients.

### 4. Discussion

In daily practice, using TES in spinal cord monitoring, large intra- and interindividual differences were found in MEP amplitudes. In this study, a significant difference was found between the mean OIPI for the left tibialis anterior muscles (2.26 ms), and the mean OIPI for the left abductor pollicis brevis muscles (1.78 ms). Right-sided OIPIs were $0.73$ ms for the TA and $1.82$ ms for the APB which is a statistically significant difference. These data correspond with previously published literature in which short optimum IPIs were found with voltage stimulation for the thenar and hypothenar muscles (Scheufler et al., 2005). Within individual patients, no significant differences were found between the right- and the left-side amplitudes for the TA and the APB. However, there is a tendency toward shorter OIPIs on the left compared to the right side. Large intra-individual differences found in MEP amplitudes might therefore be caused by the muscles of upper extremity having shorter OIPIs compared to the lower extremity muscles. Inter-individual differences are shown by the wide range of OIPIs for both the TA and the APB muscle (0.7–4.0 ms). Right- and left-side muscle data within the individual patients might be considered as paired data. For the reason only left-side data were used for the statistical analyses of amplitude reduction.

The TES-MEP neuromonitoring in this study was performed with fast charge delivery voltage stimulation (pulse width 0.1 ms). This type of neuromonitoring has been used in our institution since 1997 and has shown its great suitability over the years (Langelo et al., 2001, 2003). Because this study was performed as a retrospective study, no other data is available with which to compare it. Therefore the OIPIs found in this study might be different from those found in slow charge delivery studies (pulse width 500 μs) which are usually applied with current stimulation (Kothbauer et al., 1998; Szélényi et al., 2007). Furthermore, it should again be emphasized that all other factors that might influence the OIPI and the MEP motor thresholds were kept constant in...
of subjects in this study, it however resulted in making it even more difficult to choose the optimum IPI. The question remains what causes this phenomenon. The difference between the first and second peak was about 1.8 ms for both muscles. This corresponds with the value of the refractory period for an action potential. It has been hypothesized that the maximum of EPSP summation of motor neurons results from the combined effects of the IPI in monosynaptic connected corticospinal axons and from di- or multisynaptic connections via interneurons that introduce one or more synaptic delays. However, the presence of a bimodality might be a premature conclusion and more data will be necessary to verify and characterize the bimodality of the OIPI distribution.

In literature, neuromonitoring studies using voltage stimulation were often performed with a 2 ms IPI as a standard IPI for all patients (Jones et al., 1996; Calancie et al., 1998; Pelosi et al., 2002; Tamkus and Rice, 2012). This study however showed that the mutual amplitude reductions were less compared to the 2 ms amplitude reductions. Our pre-operative TES parameter set-up procedure now includes optimizing the IPI. Choosing one of the OIPIs (the upper or the lower extremity OIPI) might result in better optimization compared to using 2 ms as a standard IPI.

The large differences in OIPI between the intra- and inter-extremity as well as those between patients reflect the complexity of neural circuits involved in the generation of the muscle MEP. Each patient might have slightly different segmental neural connectivities and interneurons with their synaptic delays. Besides this neuronal complex system, part of the inter-individual differences in this study might also be caused by the patients’ diversity, especially concerning their age (range 10–80 years). It is well known that younger patients’ neuronal systems may have a different neural connectivity resulting in different action potential generations (Sala et al., 2010).

In conclusion, the results of this retrospective preliminary study confirmed large inter- and intraindividual differences in OIPIs for the upper and lower extremity muscles. As no optimum IPI could be found that applied to all muscle groups in the upper and lower extremities, choosing a single IPI will always be a compromise. Furthermore, a bimodal distribution appeared to apply to the muscle OIPIs. Based on the results of this study, most of the spinal cord monitoring measurements should therefore be performed with IPIs between 0.8 and 1.4 ms or between 2.5 and 3.5 ms. It is advisable to include a pre-operative spinal cord monitoring set-up procedure to find the optimum IPI for each specific patient. Future studies with more data to explore the neurophysiological background may be useful to further optimize the set-up procedure for the IPI in TES-MEP.

5. Conflict of interest

For this study, there is no conflict of interest.

References


