Short thesis for the degree of doctor of philosophy (PhD)

Application of intraoperative electrophysiological examinations during neurosurgical operations

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by

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The examination takes place at the library of the Department of Neurosurgery, University of Debrecen, 29th August, 2019 11:00

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1. Background and aims

The lesion of the involved structures during neurosurgical interventions can lead to neurological deficit. In eloquent regions it may result in the significant worsening of life quality, and at the same time it can also limit certain oncological treatments.

Preoperative imaging still has fundamental role in the planning of neurosurgical operations, including special modalities like functional MRI, tractography, fiber tracking, etc. These examinations can be used with neuronavigation systems, thus we can control coninuously the site of approach and resection related to eloquent territories.

However, imaging has mostly structural information, according to the preoperative intracranial conditions. During surgery the craniotomy, loss of cerebrospinal fluid, and the process of resection may alter the basline conditions, and it may lead to inaccurate navigation. We need continuous feedback from the function of the ivolved structures to maximize safe resection. This can be achieved by the application of intraoperative electrophysiological examinations.

Electrophysiology can be used in pediatric population as well, however, the use of certain modalities can be limited. Incomplete maturation and developmental process can restrict the use of certain types of examinations. These modalities can be applied among adults reliably, however in childhood due to the immature nervous system, or technical difficulties, the application can be challenging.

Our aim is to provide a technical background for the different intraoperative electrophysiological examinations, and to use it routinely, furthermore to set a tailored monitoring scenario for the different neurosurgical operations. With the stable electrophysiological background we introduce a new surgical method in Hungary, the selective dorsal rhizotomy for the treatment of spasticity.

Considering the high number of pediatric neurosurgical interventions we paid special attention to the application of these modalities in childhood, particularly to the detection of dwaves. This examination has the most reliable predictive value in terms of expectable postoperative motor deficit after intramedullar spine surgeries.

We also aim to analyze the effect of the introduction of intraoperative electrophysiology during the surgical treatment of tethered cord syndrome by comparing the outcomes of surgeries with and without electrophysiological control.

2. Methods and patients

2.1 Hardware

We have used Inomed ISIS IOM Portable (Inomed, Germany) device. This instrument can record 16 bipolar channels (free run EMG, compound muscle action potentials) and 8 monopolar channels (SSEP, VEP, BAEP). We can stimulate with direct nerve stimulator, bipolar cortical stimulator, 2 transcortical electric stimulator and 4 bipolar preripherial nerve stimulator.

The registration channels and stimulators can be tailored in practically any combination for the actual surgery, and can be saved as preset scenarios. During the awake surgeries before 2011 we used Ojemann cortical stimulator and Nihon Kohden Neuropack MEB 9200 device.

2.2 Cortical and subcortical white matter stimulation

Direct cortical stimulation can help to localize the motor cortex during the operation. It has mapping value, so by analyzing the responses we can define the situation of the motor cortex related to the operated pathology. We use bipolar stimulator with the following parameters: biphasic stimulation, 1000 µs pulse width, frequency at 50 Hz, amplitude between 4 and 12 mA, gradually increased until response is elicited. During the stimulation we recorded muscle

responses on the contralateral side with needle electrodes. We can also detect the responses with visual observation of the muscle contractions, however, we found the latter less reliable. At the same time, in awake conditions the patients could indicate subtle motor responses, but considering that needle electrode detection is also reliable, to avoid the discomfort caused by awake surgeries we usually did not operated on awake patients in these cases.

Pathologies in the deep white matter can involve the corticospinal tract. We can stimulate the white matter fibers directly, similar to motor cortex stimulation. We applied high frequency stimulation (50 Hz) with 1000 μ s pulse width. The applied amplitude is similar to motor cortex stimulation, the stimulator probe had smaller, 2 mm tip distance.

2.3 Awake surgeries

Checking the integrity of verbal functions is possible only in awake condition. Before surgery we apply total scalp block, then we stimulate the exposed cortical areas. Stimulation leads to cortical depolarization, and in the meanwhile changes in verbal functions have to be assessed. We apply similar stimulation parameters as for motor cortex mapping. Before the awake operations, the patients have to go through detailed examinations, including funtional MRI, tractography, routine anaesthesiological evaluation, and neuropsyhological examination. The latter includes the patient's preparation for the awake surgery, evaluation of verbal functions, cognitive functions and IQ. Considering the complex evaluation of verbal functions the presence of the neuropsychologist in the operation room is indispensable.

2.4 Cranial nerve monitoring

This modality is usually applied during the resection of cranial base tumors. These pathologies are often meningiomas, or neurinomas. With the examination we can control the integrity of the motor fibers of the cranial nerves. We place needle electrodes into the

innervated muscles, and observe the response after stimulation. Paralel free run-EMG can also be applied, which is very sensitive for mechanic irritation of the nerve. The stimulator probe is a concentric bipolar instrument. We use 200 µs pulse width at 3 Hz. Amplitude varies between 0,1 and 5 mA. Higher amplitude is better to exclude false negative, lower amplitudes can exclude false positive responses. With this modality we can reliably map and monitor the motor parts of cranial nerves.

2.5 Motor evoked potentials (MEP)

This modality includes trascranial electric cortical stimulation (TES), and the detection of compound muscle action potentials in the relevant muscle groups. To detect the response intact cortical functions, corticospinal tract, peripherial nerves and neuromuscular junctions are necessary. The electrical stimulation is applied via scalp electrodes at the C1, C2, C3 and C4 positions according to the 10-20 EEG electrode setup. For the stimulation either C1-C2, or C3-C4 positions are used. A train of 5 alternating stimuli is applied with 1000 µs pulse width and 4 ms interstimuli interval. Amplitude can be as high as 220 mA. Facilitation is also possible with 2-3 series of stimulation at a maximum frequency of 3 Hz. Sustained MEP responses indicate intact postoperative motor functions. Vanishing MEP waves imply postoperative paresis, either transient, or permanent. MEP alone can not predict whether the deficit reversible or not.

2.6 D-wave registration

D-wave detection has the best predictive value in terms of long term motor outcomes. This modality is similar to MEP, as transcortical electric stimulation is applied at the sites of C1-C2, or C3-C4. However, in this case we apply only one single stimulus with 500 µs pulse width, and the response is detected on the dorsal surface of the myelon, epidurally. For better

results we can average 4-5 responses. Detecting electrodes are placed in the midline, one proximal, and one distal from the pathology. Changes have to be observed at the distal position, the proximal electrode is for control to exclude technical failure. If the amplitude of d-wave decreases below 50% of the baseline, permanent paresis can be expected. If it stays above 50% of the baseline, only transient paresis can be expected, even with vanishing MEP responses. These changes usually appear as a trend, so in the case of decreasing amplitude suspending the operation temporarily, irrigation with saline, or papaverin can reverse the tendency. Considering the strong predictive value of d-wave, whenever it is possible to elicit, this should be used to define the extent of safe resection.

2.7 Somatosensory evoked potentials (SSEP)

This modality is used to monitor the integrity of the sensory system. In our practice it is the part of the scenario used during intramedullar resections. However, the usual posterior midline myelotomy causes significant changes in the registration and thus it is not useable in the later phase of the operation. SSEP can also give indirect information about cerebral blood flow, thus it can be useful for example during aneurysm surgeries. The SSEP waves are detected at C3', C4' (upper extremities), or at Cz', Fz positions (lower extremities) after stimulating peripherial nerves (tibial or median nerve). The stimulation is applied at 4,7 Hz frequency, pulse width is 200 µs, amplitude is increased until motor response is detected at the muscles innervated by the stimulated peripherial neve. We usually average 100-150 responses. Changes in the amplitude or latency refers to impairment of the sensory system. SSEP can be also used to localize the central sulcus, as the polarity of the waves are opposite in front of, and behind the central sulcus. This phenomenon is known as phase reversal.

2.8. Peripherial nerve/nerve root stimulation

Monitoring and mapping the peripherial nerves and nerve roots is similar to the method used in the case of cranial nerves. This examination is applied during the surgeries of peripherial nerve pathologies (neurinomas, malignant peripherial nerve seath tumors), or more often during the resection of intraspinal tumors involving the roots of the cauda equina.

2.9 Control of the vegetative functions

This modality is useful during the surgeries at the site of the conus medullaris, or during the resection of pathologies involving the cauda equina. Mapping the peripherial fibers is possible with direct stimulation, and detecting the response in the external anal sphincter. Anal MEP can also be applied by transcortical electric stimulation. In this case responses are also detected from the external anal sphincter. Registering the bulbocavernosus reflex is a more complex method. It includes the stimulation of the pudendal nerve, and recording the responses in the external anal sphincter. The stimulation of the afferent fibers of the reflex is possible at the sites of the exposed cauda roots, and this way this modality has not only monitoring, but mapping function as well.

2.10. Setup for selective dorsal rhizotomy

This special operation needs unique electrophisiological setup. Examinations have 2 aims. First, to safely identify motor fibers and spare them. Second, to choose the most active fibers to be transsected. Free-run EMG can help to distinguish motor and sensory fibers. To test the sensory fibers we apply 12 channel registration including the following muscles: m. quadriceps, m. biceps femoris, m. adductor femoris, m. tibialis anterior, m. peroneus longus and m. triceps surae. The separeted sensory fibers are stimulated at 1 Hz and 100 µs pulse width with increasing amplitude until motor response threshold is reached. The maximal

amplitude is 30 mA due to hardware limits. At the threshold amplitude a 1 second tetanic 50 Hz train of stimuli is applied. Responses are evaluated, and the most active 2/3 of the sensory fibers are transsected at every level between L.I. and S.I. In the case of L.I. segment due to anatomical specialities often the more active 50% of sensory fibers are transsected.

2.11. Other modalities

Visual evoked potentials (VEP) are used to evaluate the integrity of the visual pathway. The system is activated by a light source, responses are detected occipitally above the primary visual cortex at Oz, O1 and O2 positions.

Brainstem auditory evoked potentials (BAEP) can be used during the surgeries of vestibular schwannomas. We detect the responses after the application of a voice stimulus. Recording electrodes are placed at A1 and A2 sites according to the 10-20 EEG system, reference electrode is placed to the vertex. Our experience was that reproducible responses could not be detected during these surgeries, thus we did not use it routinely.

The above mentioned modalities are usually applied in combination, tailored to the actual surgical plan and pathology.

2.12 Statistical analysis

We evaluated the results collected during the surgical treatment of tethered cord syndrome with statistical analysis. We compared the data of the surgeries done with, and without electrophysiological monitoring. We applied Pearsons' chi square test with Yates continuity correction where it was necessary. P value below 0,05 was considered statististically significant difference.

2.13 Anaesthesiological aspects

During the monitored surgeries we used routinely total intravenous anaesthesia with the combination of propofol and fentanyl, recording bispectral index to determine the depth of anaesthesia. We applied scalp block for awake surgeries, combined with propofol sedation during the opening phase of the surgery. The effect of propofol can be sustained in a couple of minutes, and afterwards the patient is able to cooperate.

2.14. Patients' data

We analyzed the results of our first 60 operations with electrophysiological examinations. We applied cranial nerve monitoring in 22 cases, cauda equina monitoring in 10 cases, checking the motor pathway in 16 cases, multimodal monitoring during intramedullar tumor resection in 6 cases, monitoring of 3 degenerative spine correction surgeries and 3 awake surgeries. The results of awake surgeries were independently analyzed with further cases of awake surgeries from different institutes. Altogether the results of 16 cases were collected. These operations were indicated by either epileptological or oncological basis, and the resection was in close proximity to the speech areas. We conducted selective dorsal rhizotomy on 30 selected patients with cerebal palsy. We also checked the feasability of the different modalities in pediatric population, during 96 pediatric neurosurgical interventions. The results of tethered cord surgeries were analyzed based on the data collected from 102 surgeries, 32 with, 70 without electrophysiological control.

3. Results

3.1 Intraoperative electrophysiological monitoring during surgeries involving eloquent neurological structures

We analyzed the results of our 60 first cases. We applied cranial nerve monitoring (facial

nerve) in 22 ponto-cerebellar tumor rsection. We used 2 channel detection in the first 7 cases, but after a false positive response from the masseter muscle (trigeminal nerve) resulting in facial nerve palsy we added a third channel to exclude the false positive results. We also applied free-run EMG to detect mechanical traction on the nerve. In 15 cases there was no deterioration in facial nerve functions, in 3 cases mild, in further 3 cases middle grade facial palsy occurred. The latter 6 cases also showed good recovery in long term.

We monitored the cauda equina in 10 cases, including the surgery of tethered cord, intradural tumor resection in the lumbar region and one Tarlov cyst resection. In one case transient deterioration was detected, which recovered after rehabilitation, in 2 cases mild improvement occurred, and in the rest of the cases no changes were observed.

Motor pathway was examined in 16 cases. We applied cortical stimulation in 9 cases. Besides the motor responses we observed the clinical activation of the muscles, but we found the detection with needle electrodes more sensitive. In the cases of 7 deep white matter and brainstem pathology we used TES-MEP examination, and in 6 cases we also used direct stimulation technic as well. We could also detect response by stimulating the nucleus of the facial nerve during the resection of a brainstem cavernoma. In the cases of the tumors located in the central region postoperatively we detected no change in 3 cases, mild improvement in 2 cases, and transient hemiparesis in 4 cases. In the cases of deep white matter and brainstem pathologies we observed improvement of motor functions in 2 cases (one with new facial nerve palsy), no change in 3 cases, transient hemiparesis in one case, and severe hemiparesis in one case.

During the resection of intramedullar tumors we applied the combination of the above mentioned modalities, including SSEP, TES-MEP, d-wave detection. The most important examinations are TES-MEP combined with d-wave detection, as the results of these two modalities can predict the early and long term motor outcomes of the surgery. In the analyzed

time period we operated on 6 patients with intramedullar tumor. The outcomes included improvement in 2 cases, transient mild paraparesis in one case, deep sensory deficit in 2 cases, and mild trunk ataxia in one case.

In the cases of degenerative spine diseases we used SSEP and TES-MEP examinations. In the analyzed time frame 3 scoliotic spine diseases were corrected. The evoked potentials were elicitable reliably, and no postoperative deterioration occured in any of the cases.

We combined our experiences about awake surgeries with the results of 2 other neurosurgery centre (MÁV Hospital and National Institute of Neurosciences). Altogether 16 cases were included based on oncological or epileptological indication. In one case the manipulation in the proximity of the cranial base elicited high level of pain which led to the need of deeper sedation, and thus cooperation was no longer possible. In this case after surgery we detected hemiparesis and speech impairment, CT scan showed ischaemic lesion in the region of the internal capsule and caudate nucleus. In 2 cases the involvement of motor cortex made the speech control more difficult, as stimulation induced contralateral muscle contraction involving the face and tongue, thus the evaluation of speech functions was limeted. In 2 cases due to the flow artifacts around cavernomas fMRI results were not reliable. In both cases the stimulation of the cortex above the cavernomas elicited speech impairment, and as a result the resection was not possible based on the intraoperative findings in one case.

3.2 Experiences related to selective dorsal rhizotomy

We conducted 30 surgeries in the analyzed time period. In 5 cases we operated on adult patients, who were able to walk. Among the patients there were 23 premature born patient, 7 born in gemini and 2 in trigemini pregnancy. All the surgeries were done with single level approach, and in all cases we applied electrophysiological examinations. There were no motor or vegetative deficit postoperatively, and we did not observe any cerebrospinal fluid

leakege, wound healing problem, infection or bleeding.

3.3 Intraoperative electrophysiological examinations in childhood

We conducted 96 neurosurgical operations on 95 pediatric patients (under 14 years) with electrophysiological control. Based on our data, all of the modalities can be applied in pediatric patients. Certain modalities, especially those analyzing the functions of the peripherial nerves, can be applied with the same success rate as in adults, even in very young age. However, more complex examinations have lower success rate due to the incomplete maturation processes of the nervous system.

Special attention is paid for the detection of d-wave. We tried to elicit d-wave in 4 cases during the surgeries of thoracal or cervical intramedullar pathologies. The average age of the patients was 6 years (0,8-11,2 years), and we succeeded once, in the case of the youngest, 10 month old child. Though the detection was feasible only proximally from the pathology, its relevance is based on the fact, that previously no one published d-wave detection in such young age.

3.4 The role of intraoperative electrophysiological examinations during the surgical treatment of tethered cord

We processed the data collected from 102 surgeries. The interventions were done with electrophysiological control in 70 cases (IOM group), and without monitoring in 32 cases (no IOM group). We operated on 13 adult and 89 pediatric patients.

The average risk of postroperative worsening was 7,8%. Electrophysiology decreased the value from 12,5% to 5,7% (p=0,2369). In 7 cases worsening involved vegetative functions, and in one case occurres as gait impairment. In 3 cases the deficit recovered completely, with this corrections the permanent surgical risk was 2,9% with electrophysiology and 9,4%

without electrophysiology (p<0.001). Improvement occurred in 13 cases, all in the IOM group (p=0,02203).

Long term results were available after 79 operations. The average follow-up period was 45,72 months (1,5-150 months). Neurological progression occurred in 11,3% of the IOM patients, and in 30,8% of the no IOM patients (p=0,03341).

We operated on 44 patients without symptoms. Early postoperative deficit occured only in the no IOM cases (8,7%, p = 0.5101). Long term follow up was available in 38 cases in this group. The ratio of progression free follow up was 90% versus 61,1% in the favour of the IOM group (p=0.03649).

Neurological impairment was present in 58 cases. Deterioration occured in 4,1% versus 11,1% (IOM versus no IOM cases), but the difference was not significant (p=0,955). Improvement was detected only in the IOM group (22,4%), but the difference was statistically not significant (p=0,2642). Among these patients we did not observed significant difference in long term improvement, or in the ratio of progression free follow up (p=0,8074, and p=0,7135).

Our data showed that with the introduction of intraoperative electrophysiological monitoring the permanent surgical risk can be reduced significantly, the progression can be avoided in significantly greater ratio, including patients without neurological symptoms. However, the underlying pathology or the complexity of the surgery does not have significant effect on the outcomes.

4. Discussion

The use of developing imaging methods alone is often not enough for safe neurosurgical operations. During surgeries the results of preoperative imaging and intraoperative electrophysiological findings together can help to maximize the extent of safe resection and

minimize postoperative deterioration.

The aim of intraoperative electrophysiological examinations can be mapping of the eloquent region by stimulation methods, or continuous monitoring of certain functions. In the latter case the changes in the responses can refer to the impairment of the monitorred structures. The advantage of mapping is that we can identify the localization of different functions, however, examinations have to be repeated. Monitoring means continuous examination of certain functions, but these modalities have no mapping functions, and sometimes changes appear only after the lesion.

As among adults, in pediatric neurosurgical cases, the safety of the procedures and the prevention of postoperative deficits is very important. Preoperative examinations with a few exceptions can be done in childhood. However, certain intraoperative electrophysiological examinations have special difficulties in childhood due to the immature nervous system.

As conclusion, we can state that neurosurgical treatment has changed significantly due to the developing technical background. Numerous interventions can now be safely done that were not possible, or only with very high risk. Modern imaging can visualize structural and functional units, and these territories can be controlled in real time during surgery with the use of neuronavigation. Intraoperative imaging is more and more available, and we also have to mention the evolution of surgical microscopes, ultrasonic aspirators, drills, etc. However, even with these tools the protection of complex neurological structures can still be difficult. To identify the structural and funtional units we have to use intraoperative electrophysiological examinations. Almost any neurological function can be assessed, and thus protected during surgery, either in awake, or in sedated condition.

As the result of our work we introduced multimodal intraoperative electrophysiological examinations, and we made our interventions safer. Creating a stable electrophysiological background we introduced selective dorsal rhizotomy in Hungary for the treatment of

spasticity. We paid special attention to the application of these modalities in childhood. Our data showed that with certain restrictions these examinations can be applied in pediatric neurosurgical cases. Particularly important result, that we could apply d-wave recording, the modality with the best predictive value in terms of postoperative motor outcome, in a 10 month old patient with success.

We proved that intraoperative electrophysiological examinations can decrease the risk of permanent postoperative deterioration after the surgical treatment of tethered cord, and long term results are also significantly better. This means that more aggressive surgery can be done more safely. The long term outcome was significantly favourable with electrophysiology in the group of patient operated on with preventive aim.

Also partially as the result of our work intraoperative electrophysiological examinations are used in more and more neurosurgical and orthopaedic centres in Hungary.

5. New scientific results

- with the use of intraoperative electrophysiological examinations the permanent surgical risk can be significantly lowerd during the surgical treatment of tethered cord
- with the use of intraoperative electrophysiological examinations the long term prognosis of patients operated on for tethered cord can be significantly improved
- with the use of intraoperative electrophysiological examinations the the long term prognosis of tethered cord patients operated on with preventive aim can be significantly improved
- we proved that d-wave detection can be successfully applied even in very young age (10 months of age)

6. Appendix: Publication list certified by the Kenézy Life Sciences Library of the University of Debrecen



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DEENK/155/2019.PL PhD Publikációs Lista

Candidate: Gábor Fekete Neptun ID: GM5HE5

Doctoral School: Doctoral School of Neurosciences

List of publications related to the dissertation

1. Fekete, G., Bognár, L., Novák, L.: Surgical treatment of tethered cord syndrome - comparing the results of surgeries with and without electrophysiological monitoring.

Child Nerv. Syst. "Accepted by Publisher", 1-17, 2019.

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 Fekete, G., Valálik, I., Fogarasi, A., Bognár, L.: Új lehetőségek a neurológiai betegségek kezelésében: Parkinson sebészet, fájdalom sebészet, epilepszia sebészet, őssejtkezelés. Háziorv. Továbbk. Szle. 14 (2), 82-87, 2009.

Total IF of journals (all publications): 4,086
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The Candidate's publication data submitted to the iDEa Tudóstér have been validated by DEENK on the basis of the Journal Citation Report (Impact Factor) database.

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