„LUCIAN BLAGA” UNIVERSITY SIBIU

FACULTY OF MEDICINE

DOCTORAL SCHOOL

THE CONTRIBUTION OF INTRAOPERATIVE NEUROPHYSIOLOGICAL MONITORING IN NEUROSURGERY

PhD THESIS SUMMARY

Academic supervisor: PhD candidate:

Prof. Univ. Dr. PEREANU MARCEL FILIP DAN

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LIST OF ABBREVIATIONS

AEP – auditory evoked potentials

AH – abductor halucis

APB – abductor policis brevis

BAEP – brain stream auditory evoked potential

C-arm – radiographic device with fluorescence

CAP – compound action potential

CBT – corticobulbar tract

CD – cervico-dorsal

CMAP – compound muscle action potential

CoMEPs – corticobulbar motor evoked potentials

CST – corticospinal tract

CUSA – Cavitational Ultrasonic Surgical Aspirator

DCS – direct cortical stimulation

DTI – diffusion tensor imaging

EEG - electroencephalogram

EMG - electromyography

EP – evoked potential

ISI – interstimulus interval

ITI – inter-train interval

IONM –intraoperative neurophysiological monitoring

IT - infra-tentorial

LED – light emission diode

LS – lumbo-sacral

LL – lower limbs

MAC – minimum alveolar concentration

MEP – motor evoked potentials

MRI – magnetic resonance imaging

MUP – motor unit potential

MVD –microvascular decompression

ND – neuro-tonic discharges

NMB – neuromuscular blockade

ORL - otorhinolaryngology

PCA – pontocerebellar angle

SEP – sensory evoked potentials

ST - supra-tentorial

TA – anterior tibialis

tES – transcranial electrical stimulation

TIP – time – irrigation - pressure

TIVA – total intravenous anesthesia

TOF – train-of-four

UL – upper limbs

VEP – visual evoked potentials

Key words: Intraoperative neurophysiological monitoring, sensory evoked potentials, motor evoked potentials, auditory evoked potentials, visual evoked potentials, electromyography, direct cortical stimulation, direct nerve stimulation

N.B. The PhD thesis comprises of 37 figures and 6 tables, out of which 7 figures and 2 tables were selected for the summary; the bibliography of the summary also represents a selection, as the entire bibliography of the PhD thesis consists of 186 titles.

LIST OF PUBLICATIONS

1. **Filip D**, Pereanu M. Multimodal intraoperative neurophysiological monitoring during spinal surgery. Acta Medica Transilvanica. 2016;21(1):89-90. CNCSIS B+
2. **Filip D**, Pereanu M. Pedicle screw stimulation in lumbosacral surgery. Acta Medica Transilvanica. 2016;21(4):27-29. CNCSIS B+
3. **Filip D**, Pereanu M, Matei C. Usefulness of intraoperative neurophysiological monitoring in supra-tentorial brain tumor resection. Acta Medica Transilvanica. 2017;22(2):71-74. CNCSIS B+
4. **Filip D**, Pereanu M, Matei C. The importance of intraoperative neurophysiological monitoring in the surgery of sub-tentorial pathology. Acta Medica Transilvanica. 2017;22(3):41-44. CNCSIS B+

Contributions at sessions and conferences:

1. **Filip D**, Matei C. Intraoperative neurophysiological monitoring in brain tumors. National ASNER Conference. 2015; Abstract book:18.
2. **Filip D**, Matei C, Nistor S, Flore P, Pereanu M. Intraoperative neurophysiological monitoring in lumbosacral surgery – case presentation. National ASNER Conference. 2016; Abstract book:20.
3. **Filip D**, Matei C, Pereanu M, Talău M. The contribution of neurophysiological intraoperative monitoring in microvascular decompression for trigeminal neuralgia. 3rd Congress of Southeast Europe Neurosurgical Society. 2017; Abstract book:225.
4. **Filip D**, Matei C, Pereanu M, Talău M. Neurophysiological intraoperative monitoring in cauda equina tumor surgery – two case reports. 3rd Congress of Southeast Europe Neurosurgical Society. 2017; Abstract book:227.
5. Matei C, **Filip D**, Dancu I, Calvun E, Nistor S, Flore P. Subcortical mapping of language pathways in low grade glioma surgery. 3rd Congress of Southeast Europe Neurosurgical Society. 2017; Abstract book:10.
6. **Filip D**, Matei C, Dancu I, Calvun E, Nistor S. Neurophysiological intraoperative monitoring in cerebral awake surgery. National ASNER Conference 2017;Abstract book:14.

INTRODUCTION

The aim of this paper is to evaluate the efficiency, utility and security of intraoperative neurophysiological multimodal monitoring during neurosurgical procedures, given that in our country these techniques are not practiced on a regular basis.

The main objectives of the intraoperative neurophysiological monitoring (IONM) are to optimize the results of surgical interventions and to preserve the neurophysiological functions. These objectives are met by providing real time information on the functional role and the integrity of important neurological structures during the surgery using mapping and monitoring.

Mapping is used especially in neurosurgery and some ENT interventions. The mapping technique is applied in order to identify certain structures such as the motor cortex, cranial nerves or the corticospinal tract. It is especially important in cases when the pathologic process is near or invades function nervous tissue and produces a distortion of the local anatomy. The mapping results help define security margins of the pathologic process, which allows a complete resection, while providing the certainty that no neurologic deficit is caused. Negative mapping results are as important as the positive ones, as they prove the absence of functional nervous structures in the resected tissue. Most often the mapping is intermittent, being performed at an early stage and then at a later stage in different critical phases. Nonetheless, sometimes there is a need of continuous mapping, as in the case of the dissection of the acoustic nerve neuroma or brain tumors, where an early warning is needed in case of approaching a cranial nerve or the corticospinal tract.

The monitoring consists of the constant recording of the functional integrity of neurological, ENT, orthopedic or vascular structures and pathways. Generally a multimodal monitoring is used, combining more IONM techniques, such as motor evoked potentials (MEPs), sensory evoked potentials (SEPs), auditory evoked potentials (AEPs) and electromyography (EMG), strategically selected on the basis of the pathological circumstances. Stable IONM results provide assurance for continuing with the intervention; if the signals obtained deteriorate prompt intervention in order to restore them is required and in order to avoid a nervous injury or even that the surgery is stopped.

IONM interpretation is done by qualified personnel, which underwent training and gained experience. It is not sufficient to detect a warning, as most surgeons do not know the cause and which measures to take in such a case. Based on his experience the neurophysiologist suggests the cause of the modification in IONM parameters and which measures need to be taken in order to correct them. This way the neurophysiologist takes and shares responsibility for the diagnosis and the intraoperative management. For the optimization of the surgical result, while avoiding a neurological deficit the scope of the neurophysiologist is to minimize falsely positive results, which are to interfere with the surgical act, but also the falsely negative ones, which are to avoid neurological injuries.

Intraoperative neurophysiologic monitoring aims at reducing complications and postoperative neurological morbidity, providing real time information on the integrity of nervous structures, thus becoming one of the most valuable patient protection means during surgery. IONM timely warns the surgeon with respect to possible injuries of nervous structures, so that corrective measures can be taken in order not to cause irreversible neurological damage. At the same time, IONM allows more radical resections to be conducted.

Future efforts in the field of IONM will include the development and spreading of training courses and certifications of medical staff. In addition to this, it is necessary that a data basis is created in order to augment the value of the IONM technique. IONM's capacity will be broadened with the help of progress in methodology and devices. In the following decades, I expect that guidelines are developed and professional associations in this field are created.

With this study and with the scientific activity performed in parallel I tried to promote the intraoperative neurophysiological monitoring techniques in our country and I will continue to do so by means of articles and scientific presentations at conferences and communication sessions, organized by the societies for neurophysiology, neurosurgery and neurology.

I want to express my gratitude to Prof. Dr. Pereanu Marcel, the scientific coordinator of the PhD thesis for the constant support and guidelines for performing this study. Also I would like to thank the team of neurosurgeons led by Dr. Matei Claudiu, comprising of Dr. Nistor Sofia and Dr. Flore Paul, alongside the anesthesiologist Dancu Iulia and the medium qualified staff, without whom the present study could not have been conducted.

I express my gratitude to the management of the "Lucian Blaga" University and the Faculty of Medicine from Sibiu, as well as the management of the Polisano Clinic from Sibiu, where I conducted my research.

Last but not least, I would like to thank my family.

1. Intraoperative neurophysiological monitoring

1.1. General aspects

Evoked potentials have first been described in 1875. They are electrical responses of the nervous system to a peripheral stimulus. Within the intraoperative neurophysiological monitoring (IONM) evoked potentials (EP) represent a nervous response to a repetitive stimulus, recorded at a distance from the place of stimulation. The recording is done with the help of electrodes, which are applied in predefined areas on the skin or the scalp in order to obtain the clearest potentials.

Generally speaking, sensory evoked potentials (SEP) analyze the sensory pathway, which starts from a sensory nerve, continues through the dorsal medullary columns and the medial lemniscus, projecting itself on the primary post rolandic somatosensory cortex. The motor evoked potentials (MEP) evaluate the descending pathways from the pre-rolandic motor cortex through the radial coronary, posterior limb of the internal capsule, cerebral peduncle, pons, bulbar pyramids, the medullar corticospinal tract to the peripheral nerves. The brain stem auditory evoked potentials (BAEP) analyze the auditory pathway from the vestibulocochlear nuclei through the cerebral trunk to the mesencephalon (1, 2).

IONM can detect cerebral ischemia quite early in order to allow a rapid intervention and in order to avoid the irreversible deterioration of the brain tissue. The electrical activity of the brain tissue is closely connected to the blood stream. During cerebral ischemia the collapse of the electrical activity precedes the deterioration of the homeostasis and the irreversible neuronal damage. This relationship underlines the utility of IONM in brain surgery, as a means of identifying ischemia at an early stage, before irreversible brain damage is caused, thus allowing a time frame necessary for corrective measures (3).

1.2. IONM in supra-tentorial procedures

The scope of mapping and monitoring of the eloquent cortical areas and of the subcortical pathways is to perform a excision as complete as possible, radical, while also maintaining the neurological functions unaltered. At supra-tentorial level, patients with brain aneurysms, arteriovenous cerebral malformations, central or insular tumors, cerebral injuries of other types or patients with refractory epilepsy can benefit from IONM. The methods used for monitoring are sensory evoked potentials (SEP), the phase-reversal technique, motor evoked potentials (MEP), mapping of the motor, sensory or language areas. IONM of the functional integrity of motor and sensory areas and tracts is not invasive and it does not interfere with the surgical procedures. It gives immediate feedback regarding the functional harming of the structure being monitored, and in certain cases it ensures the possibility to intervene in order to correct this event. The intraoperative EP monitoring, at the beginning using SEP, then also MEP has become an accepted technique for estimating the integrity of medullar, bulbar, troncular and cerebral sensory and motor pathways.

1.3. IONM in infra-tentorial procedures – posterior cerebral fossa

Due to the dense concentration of nervous structures and neurophysiological functions in the brain stem, surgical morbidity is high as compared to other structures of the central nervous system. IONM aims at reducing complications and postoperative neurological morbidity by delivering real time information about the integrity of nervous structures, thus becoming one of the most valuable means of protection for patients during surgical interventions. IONM warns the surgeon in due time in order for them to take corrective measures so that irreversible neurological injuries do not occur. At the same time, IONM allows that a more radical resection is performed. In order to ensure the functional integrity of the nervous structures, the monitoring of evoked potentials and electromyography of the cranial nerves need to be used (4).

1.4. IONM in spinal cord pathology

IONM utilization was introduced in traumatic spinal pathology, spinal deformities, neurosurgical diseases or neurovascular spinal diseases, spinal arthroplasty. Most spinal patients already have a neurological deficiency, the scope of the surgery being that the function is preserved and maybe even clinically improved. From an anatomical point of view, at spinal medullar level the monitoring addresses the descending lateral corticospinal pathways, motor pathways and ascending sensory pathways from the posterior cord. Peripheral nerves and limb musculature can also be monitored.

1.5. IONM in lumbosacral surgery

Spinal lumbosacral pathology is a common problem with adult patients, as the rate of surgical lumbosacral interventions is of approx. 136/100000/ year. Neurological complications in spinal surgery occur in approx. 6 % of the cases depending on the ampleness and complexity of the intervention (5).

The scope of the intraoperative neurophysiological monitoring in lumbosacral surgical procedures is to detect radicular irritation at an early and potentially reversible stage. Electromyography is the most frequently used electrophysiological method in order to monitor the function of nervous roots during spinal surgery.

2. Aims, material and method

2.1. General hypothesis

Certain types of neurosurgical interventions can put different important nervous structures at risk – motor, sensory or language, central or peripheral – the function of which can be monitored intraoperatively with the help of multimodal neurophysiological methods. The intraoperative neurophysiological monitoring methods IONM are the motor evoked potentials through transcranial or direct cortical electrical stimulation, the sensory evoked potentials, mapping and cortical and subcortical monitoring of the corticospinal tract, mapping of cortical and subcortical language areas, auditory evoked potentials of the brainstem and visual evoked potentials, spontaneous electromyography or stimulated electromyography of cranial or spinal nerves.

As this type of multimodal intraoperative neurophysiological monitoring is not done on a regular basis in our country, through my study I tried to contribute regarding the necessity of using this technique in neurosurgical practice.

2.2. Aims of the study

The study represents a prospective and observational study on a series of consecutive cases with the aim of establishing the efficiency, utility and security of intraoperative neurophysiological monitoring methods during several different neurosurgical interventions.

The aim of this study was to pursue the efficiency of acquiring and the monitorability respectively of the motor evoked potentials, sensory evoked potentials, auditory evoked potentials of the brainstem, of the spontaneous electromyographic potentials or through stimulation, and of other neurophysiological intraoperative monitoring modalities.

Also the modifications of these evoked potentials were studied intraoperatively, while correlations with the possible causes of their appearance are made. The restoring of these parameters after applying specific measures, as well as the postoperative evolution of the patients was observed. On the basis of these data the utility of intraoperative neurophysiological monitoring in preserving the function of nervous structures and for ensuring a favorable evolution of the patients considering optimal resections was established.

Both the security of the patient and the avoidance of complications during performing IONM techniques were a constant concern.

2.3. Material and method

76 consecutive patients were included in this study, whom needed neurosurgical interventions on different segments of the central or peripheral nervous system. The patients underwent surgery in the Polisano Clinic in Sibiu within the time frame May 2014 - September 2017.

2.3.1. Monitoring of motor evoked potentials through transcranial electrical stimulation

2.3.1.1. Application of the electrodes for the transcranial electrical stimulation

The standard application for obtaining MEP through transcranial stimulation is C3/C4 for the upper limbs and C1/C2 for the lower limbs, 2 cm anterior to the standard EEG positions. The stimulation of C1/C3 will lead to a response in the right limbs, while C2/C4 one in the left limbs.

2.3.1.2. Transcranial electrical stimulation

The multi-puls transcranial electrical stimulation technique consists in applying a train of five to seven transcranial or direct cortical electrical impulses, while the responses are acquired at the level of the limb muscles as compound motor action potential CAP. The stimulation frequency is of approx. 2 Hz with an inter-stimulus interval within the impulse train of 4 ms.

2.3.1.3. Selection of the musculature for MEP recording

The most frequently utilized muscles are abductor pollicis brevis APB for the upper limbs, but also the antebrachial flexors or extensors can be added. For the lower limb the most frequently used muscle is the abductor hallucis brevis, which has dominant corticospinal innervation. An alternative would be the anterior tibialis muscle. I used a practical set up with APB for the upper limbs and AH and TA for the lower limbs.

2.3.2. Monitoring of sensory evoked potential

2.3.2.1. The stimulation technique

The stimulation place of the medial nerve is located at the wrist of the hand between the tendons of the long palmar muscle and radial carpal flexor muscle 2 cm proximal. The tibial nerve is stimulated adjacently and posterior of the internal malleolus. The stimulation is performed simultaneously for all limbs.

2.3.2.2. Application of the SEP recording electrodes

According to the international appliance system EEG 10-20 the scalp recording electrodes will be in positions Cz'-Fz' for the lower limbs and C3'- C4' for the upper limbs; the points Cz',C3' and C4' are located 2 cm posterior from the points Cz, C3, C4 of the classic EEG positioning.

2.3.3. IONM in supra-tentorial brain injuries

I monitored cases from a neurophysiological point of view operated for primary or metastatic brain tumors, malignant and benign, MAV, intra-axial or extra-axial, supra-tentorial.

2.3.3.1. Motor evoked potentials through transcranial electrical stimulation

For MEP monitoring I used the application for transcranial stimulation with corkscrew type electrodes in the points C1/C2 for the lower limbs and C3/C4 respectively for the upper limbs, 2 cm anterior to the classic EEG position, where the craniectomy allowed such an approach.

The MEP recording was performed with the help of the needle electrodes applied intramuscularly in the abductor policis brevis APB muscle for the upper limbs, anterior tibial and TA and abductor halucis AH for the lower limbs. The stimulation parameters were:

- Stimulus intensity between 50-100 mA for upper limbs and 100-150 mA for lower limbs;
- Impulse duration=0.5 ms;
- Train of 5 impulses with a frequency of 250 Hz corresponding to an ISI of 4 ms;
- Stimulation rate of 0,2-2 Hz.

2.3.3.2. Monitoring of sensory evoked potential

SEPs are acquired by stimulation of a peripheral nerve with a bipolar electrode. Most frequently the median nerve is stimulated for monitoring the cortical regions representing the upper limbs, and the tibial nerve for the lower limbs respectively. The cathode is placed proximal in order to avoid the anodal block on the ascending potential. Electrical impulses with the help of subcutaneous needle electrodes placed at a distance of approx. 2 cm are emitted. The stimulation is made simultaneously for the 2 upper or lower limbs. The stimulation intensity is progressively elevated until stable and reproducible SEPs are acquired.

The following stimulation parameters were used:

- Stimulus intensity between 50-100 mA;
- Stimulus duration = 0.2 ms;
- Stimulus frequency = 3.6-4.7 Hz;

SEP recording needs signal mediation through repetition up to 200-500 times. SPE updating is done approx. three times per minute in order to obtain a real time monitoring. At the level of the scalp sensory evoked potentials situated at 20 and 23 ms – N20/P23 – for the upper limbs and at 37 and at 45 ms – P37/N45 – for the lower limbs are acquired.

2.3.3.3. The *phase reversal* technique for identifying the central sulcus

The stimulation and parameters are identically as for acquiring SEPs, with recording using a belt of 6-8 electrodes applied epidurally or subdural directly cortically, on 6-8 channels. The electrode belt needs to have been applied perpendicularly on the presumed direction of the central sulcus, near the area corresponding to the hand on the homunculus. The reference electrode was attached to the ipsilateral mastoid and is a needle electrode. PES with N20 of superior quality were obtained on the postcentral circumvolution, while in the neighboring frontal electrode an inverted wave was obtained, P23, which represents phase reversal. Stimulation is made on the median nerve most frequently, others prefer the ulnar nerve, as it has a simpler morphology and ensures higher amplitudes. Stimulation is made with a frequency of 3.17 Hz using stimuli with a duration of 0.3 ms and an intensity ranging between 10-25 mA (6).

2.3.3.4. Direct cortical stimulation for mapping and monitoring of the corticospinal tract

Cortical mapping with the bipolar stimulator is carried through, starting with intensities of 1.5 mA, not exceeding 6 mA. The generator emits rectangular biphasic impulses with a duration of 1.25 ms, in trains of 4 seconds with a frequency of 60 Hz with the help of the bipolar stimulator of 1 mm and distance between the electrodes of 5 mm (Penfield technique) (7).

The golden standard for cortical and subcortical stimulation is the classic Penfield method with the bipolar stimulator at a frequency of 50-60 Hz (8). More recently the anodic unipolar stimulation method with a short train of 3-5 impulses with a frequency of 250 Hz and a duration of the impulse of 0.5 ms was introduced (9,10). The temporal summing of the multiple descending potentials in this type of multi-plus stimulation will determine the occurring of a MEP with a well-defined latency and a quantifiable amplitude. I used both methods in the mapping of the motor areas in patients with supra-tentorial tumors in the proximity of these areas.

2.3.3.5. Mapping of eloquent cortical areas in awake neurosurgery

In awake surgery the stimulation through the Penfield technique for 3 seconds can lead to verbal blockade, if conducted in the eloquent area of the language. The stimulation is repeated three times for reproducibility, it is labelled and a diameter of 1 cm is kept – *"one-centimeter rule"* (11).

I used this method in 2 cases with supra-tentorial l, which were in the proximity of the language areas and needed intervention with awake patient for direct verbal communication. The applied current is rectangular biphasic in the form of impulses with a duration of 1 ms and intensities ranging from 2 to 20 mA, applied for 1-4 s with a frequency of 50-60 Hz. The current was applied using a manual bipolar stimulator with rounded heads separated at a distance of 5 mm. The intensity of the current was elevated with 1-2 mA until a response was acquired, in this cases verbal blockade, anomy or paraphasia.

2.3.3.6 Subcortical intra-lesional monitoring

Subcortical stimulation with a manual stimulator (subcortical mapping) is used in order to locate motor tracts in the profound structure of the white substance in various stages of the tumor resection. For the subcortical stimulation I used a unipolar cathodic stimulator with the reference in the lesion and the stimulation parameters were the same as in obtaining MEP, with intensities under 20 mA.

Important recent studies proved the correlation between the stimulation point and the distance to the CST and the majority set the equivalence of a stimulation threshold for the occurring of a motor response of 1 mA with a distance of 1 mm to the CST as a rule (12, 13).

In this respect I used decreasing stimulation intensities as the resection proceeded, which was stopped when the stimulation threshold reached 1-3 mA or the resection was complete.

Recently a new protocol for subcortical mapping was described, where a tumor suction device is used, to which the unipolar cathodic stimulator is attached. This device allows continuous stimulation during the tumor resection, thus offering real time monitoring attainments, as well as spatial orientation regarding the proximity of CST (14).

2.3.4. IONM in sub-tentorial brain injuries – posterior brain fossa

2.3.4.1. Brain stream auditory evoked potentials (BAEP)

Stimulation is made with intra-auricular transducers, which send out alternant compression and rarefaction clicks with 70 dB and a duration of 100-200 ms.

I used cylindrical silicon auditory insertions, which can be placed in the external auditory channel and covered with impermeable adhesive tape, so that it prevents liquids from getting in. Counter-laterally a background noise is applied in order to prevent the respective ear to participate in the response obtained. Stimuli are applied with a frequency of approx. 12 Hz and a mediation of approx. 500-1000 responses is necessary. It is recorded with the help of some electrodes placed at Ai (mastoid) - Cz, on two channels, for both ears. (4).

As a result of the auditory stimulation successive negative potentials at 1.5 – 6 ms, registered from I to V are obtained, sometimes also the potentials VI and VII appear. The more important waves for monitoring are I, III and V. I continuously observed the latencies of these waves, the interval between them and their amplitude, as well as the modifications as compared to the basic traces.

2.3.4.2. IONM trough spontaneous electromyography of the cranial nerves

I used needle electrodes inserted sub-dermally at the level of the main cranial nerves which needed monitoring. Depending on the type of surgical intervention the recording was made from the facial muscles.

The spontaneous activity on the electromyography was continuously monitored, while significant pathological electrical discharges, which occurred intraoperative, and fibrillations, peaks, groups of peaks or neurotonic discharges were noted.

2.3.4.3. IONM through direct stimulation of the cranial nerves (mapping)

Stimulation was done with the help of a cathodic unipolar stimulator. The stimulator is connected to a power source with constant voltage, which stimulates starting with an intensity of 0.05 mA with stimulation steps of 0.05 mA. The maximum stimulation intensity is of 5 mA, as above this intensity the current can ray off and stimulate other neighboring nerves as well. The stimulation is done with a rectangular impulse with a duration of 0,05-0,1 ms. The recording of the compound motor potentials as a result of the direct nervous stimulation is done at the level of the same muscles used for the spontaneous electromyography. Thus, the eloquent cranial nerves were identified from the operation field and their functionality was verified in real time.

2.3.4.4. Corticobulbar MEP monitoring

Transcranial electrical stimulation with a train of 3-5 stimuli for a duration of 0.5 ms each was used. These stimuli are separated by an interval of 2 ms, while the repetition rate can be of 2 Hz. The stimulus intensity can reach 120 mA. The appliance of the cranial electrodes was with the anode at C3 and C4 respectively and the cathode at Cz for the stimulation of the left and right cerebral hemisphere respectively. The electrical stimulus was applied with the help of corkscrew type electrodes placed subcutaneous at the level of the scalp.

The aim was to obtain corticobulbar motor evoked potentials especially for the trigeminal nerve, the facial and glossopharyngeal nerve, while monitoring the stimulation threshold, the latency threshold, the amplitude threshold and their morphology.

2.3.4.5. Visual evoked potentials VEP

There were two cases of hypophyseal adenomas, which were surgically approached trans-nasal – trans-sphenoidal and which required monitoring of visual evoked potentials. These were acquired through intermittent light stimulation with the help of special glasses provided with LEDs. The stimulation consisted of series of 500-1000 visual impulses with the frequency of 3.3 Hz. VEP recording was done with the help of corkscrew type electrodes placed in points O1, O2, and Oz according to the international EEG 10-20 system with Cz reference electrodes. The VEP latency and amplitude are continuously observed during the surgical intervention.

2.3.5. IONM in spinal cervico-dorsal pathology

The pathology which required IONM in this segment was made up of vertebral and disc degenerative diseases, spinal traumas, malignant or benign extramedullary tumors, malformations.

Within the surgical interventions performed on this segment of the nervous system, I used the following IONM techniques:

- MEP of the lower limbs bilateral;
- SEP of the upper and lower limbs bilateral;
- Spontaneous electromyography in the field of the C5-T1 cervical nervous roots bilateral.

PEM and PES were done using the same parameters described above; I used all four limbs, although the lesion was under the level of radiculo-medullary emergence of the upper limbs for a global control of the potentials obtained and for verifying the efficiency of stimulation. For the spontaneous electromyography I used needle electrodes inserted subdermal at the level of the upper limb muscles innervated on the spinal roots C5-T1.

I observed the intraoperative stability of the stimulation threshold, amplitude, latency and MEP and SEP morphology. Also in certain selected cases the monitoring of the spontaneous electrical activity through electromyography was required.

2.3.6. IONM in vertebro-medullar lumbosacral pathology

I used intraoperative neurophysiological monitoring in this segment in tumors of the cauda equina, lumbosacral dysraphisms with tethered cord syndrome and in vertebral arthrodesis with pedicle screws.

2.3.6.1. Motor evoked potentials through transcranial electrical stimulation

For the MEP monitoring in the lower limbs the primary inferior cortex was activated through transcranial electrical stimulation using a short train of impulses, i.e. the multi-plus method. Short trains of 5-7 stimuli with a duration of 0.5 ms and an inter-stimuli interval of 4 ms, with a repetition rate of 1-2 Hz Ire applied through electrodes places on the scalp at the level of points C1 and C2 according to the international EEG 10-20 system.

2.3.6.2. Sensory evoked potentials

For SEP the tibial nerve was stimulated bilateral consecutive at retro-malleolar level with intensity of 30-40 mA, duration of 0.2 ms and frequency of 3.22- 4.3 Hz, while the recording of the P37/N45 waves was obtained at the level of the scalp with the help of corkscrew type electrodes laid out in Cz'- Fz' arrangement.

2.3.6.3. Spontaneous electromyography in lumbosacral pathology

The spontaneous electromyography was used for recordings from the muscles of the lower limbs of action potentials triggered by the surgical procedures. The recording electrodes for MEP, spontaneous electromyography and mapping were inserted bilateral in the muscles corresponding to the L1-S1 spinal roots. In order to continuously monitor the functional integrity of para-pyramidal motor fibers (for the voluntary control of the anal sphincter) and motor aspect of the pudendal nerves from the anterior horns to the external anal sphincter, in selected cases I attached a pair of needle electrodes at this level, bilateral, corresponding to roots S2-S4.

On the electromyography the spontaneous electrical activity of these muscles innervated by the lumbosacral roots was pursued and the occurrence of peaks or neurotonic discharges was recorded.

2.3.6.4. Direct nervous stimulation of the lumbosacral spinal roots

The direct nervous stimulation was done with the help of the unipolar stimulator with reference at the edge of the lesion or with a bipolar stimulator - concentric or fork-like. The nervous roots at risk or near the cauda equina tumor, as well as the non-neural structures as the filum terminale, which needed to be resected in order to detach the bone marrow were stimulated. In general after the stimulation of a motor root motor responses as CMAP with a quite low threshold of approx. 0.05-0.2 mA were obtained, applying a single stimulus with a duration of 0.2-0.5 ms. Non-functional nervous structures or non-neural structures such as filum terminale did not respond to stimulation of higher intensity than 20 mA.

2.3.6.5. Pedicle screw stimulation in lumbosacral artrodeses

In lumbosacral artrodeses with pedicle screw fixing the electrical stimulation of the entrance gaps, of the evidence and then of the pedicle screws at every level was required, in order to verify the integrity of the pedicle wall and thus the correct position of the screw. In order to save time each channel or screw was tested starting with a stimulation intensity of 8 mA. If no motor response was acquired it was considered that the screw is in the right position. If a CMAP was acquired the intensity of the current was progressively reduced until a stimulation threshold was obtained, which could appreciate the likeliness of a pedicle breach (15).

The channels or screws with a stimulation threshold under 4 mA are susceptible to malpositioning and need be taken out or repositioned; thresholds between 4-6 mA are borderline and the screws need be verified more carefully by the neurosurgeon (16).

2.3.7. TOF technique for the verification of neuromuscular blockade

For a correct monitoring of MEP and the spontaneous electromyographic signals through stimulation it was required that I verify the neuromuscular blockade produced by the curarizing anesthetic substances required at the baseline of the anesthesia for the orotracheal intubation.

The neuromuscular blockade is appreciated with the help of the repetitive stimulation technique *train of four* TOF. This consists of the stimulation with a supramaximal stimuli train of a nerve from the monitored area. A result above 70% is acceptable. The ratio between the amplitude of the first and the last motor response is measured (15).

I stimulated the tibial nerve at retro-malleolar level or the median nerve at the level of the hand neck with a stimulation of 4 successive electrical impulses with an intensity of 30 -40 mA, duration of 0.2 ms and frequency of 2 Hz. At the level of the abductor halucis AH muscle and the abductor policis brevis APB respectively I obtained compound motor action potentials, the amplitude of which was compared and reported.

3. Results

3.1. Case study

I conducted multimodal intraoperative neurophysiological monitoring techniques on 76 consecutive patients during the time frame May 2014 – September 2017. The patients presented neurosurgical pathology, which I divided in four segments of the nervous system: supra-tentorial, infratentorial, cervico-dorsal and lumbosacral. The group I studied consisted of 40 women and 36 men with an average age of 49.57 years. The ages of the patients ranged from 6 months to 84 years.

The postoperative status of the patients was evaluated based on the adapted McCormick scale, which classifies the patients in four stages from a clinical/functional point of view (17).

In our study we had 29 (38.2%) patients in stage I, 34 (44.7%) patients in stage II, 12 (15.8%) patents in stage III and 1 (1.3%) patients in stage IV (Diagram 3.1).

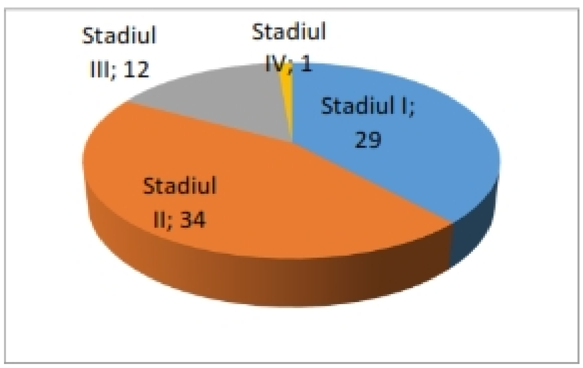

Diagram 3.1. Case status according to the seriousness of the clinical and functional disease

3.2. Monitorability of the performed IONM techniques

Acquiring the motor and sensatory evoked potentials, as well as the other modalities allows the intraoperative neurophysiological monitoring of patients with neurosurgical diseases. The success rate of the acquisition expresses the monitorability of the procedures.

3.2.1. Monitorability of the motor and sensory evoked potentials

For IONM of the 76 patients from the study I conducted MEP for 63 (82.9%) cases and SEP for 63 (82.9%) cases. The success of the procedures is displayed in table 3.II, which describes the monitorability of these techniques depending on the affected segment and the seriousness of the postoperative status.

Out of the 63 cases monitored with MEP in 53 (84.1%) good, reproducible potentials were achieved, in 6 (9.6%) cases the MEPs were low from the baseline and in 4 (6.3%) cases they were not achieved despite maximal stimulation parameters. The 59 cases, where MEPs through transcranial electrical stimulation were achieved, were monitored during the entire surgical procedure (93.7%) (Diagram 3.2).

SEPs were conducted in 63 patients and robust and reproducible potentials were achieved in 57 (90.5%) cases, low potentials from the baseline in 5 (7.9%) cases and only in one case (1.6%) SEP was not achieved. The monitorability of the sensory evoked potentials was of 98.4%, present and monitorable in 62 patients (Diagram 3.2).

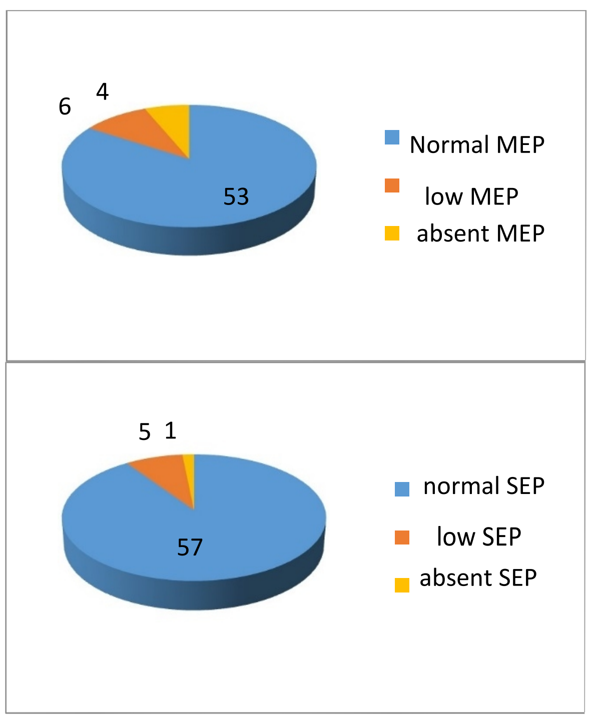

Diagram 3.2. Monitorability of motor evoked potentials MEP and sensory evoked potentials SEP

I conducted MEP and SEP on 63 cases simultaneously, thus monitoring the descending motor pathways, as well as the ascending sensory pathways (table 3.II).

Out of a total of 63 monitored patients with MEP and SEP 50 (79.4%) were in stages I and II, less clinically and functionally affected, whereas 13 (20.6%) were in more serious stages III and IV. Out of the 50 patients in stages I and II only 3 (6.0%) presented low MEPs or absent MEPs at the baseline (2.0%). Out of the 13 patients in stages III and IV 7 (53.8%) patients presented low or absent MEPs, while 5 (38.5%) cases presented low or absent SEPs.

Table 3.II. MEP and SEP monitorability grouped according to segments and stages of clinical seriousness

Technique	MEP				SEP			
	Total	present	low	absent	Total	present	low	absent
Total	63	53 (84.1%)	6 (9.6%)	4 (6.3%)	63	57 (90.5%)	5 (7.9%)	1 (1.6%)
Segment								
ST	25	25 (100%)	0	0	25	25 (100%)	0	0
IT	6	6 (100%)	0	0	6	6 (100%)	0	0
CD	27	18 (66.7%)	5 (18.5%)	4 (14.8%)	27	22 (81.5%)	4 (14.8%)	1 (3.7%)
LS	5	4 (80%)	1 (20%)	0	5	4 (80%)	1 (20%)	0
Stage								
I-II	50 (79.4%)	47 (94.0%)	2 (4.0%)	1 (2.0%)	50 (79.4%)	49 (98.0%)	1 (2.0%)	0
III-IV	13 (20.6%)	6 (46.2%)	4 (30.8%)	3 (23.0%)	13 (20.6%)	8 (61.5%)	4 (30.8%)	1 (7.7%)

Legend: ST=supra-tentorial; IT=infra-tentorial; CD=cervicodorsal; LS=lumbosacral.

In selected cases also other IONM modalities than MEP and SEP were conducted.

3.2.2. Specific IONM modalities for the supratentorial pathology

In supratentorial surgery (27 cases) the cortical mapping was performed using the *phase reversal* technique in order to detect the central sulcus in 14 (51.9%) cases, mapping and motor monitoring through direct cortical electrical stimulation 19 (70.4%) cases and mapping/subcortical monitoring in 14 (51.9%) cases. Two patients underwent awake surgery, benefiting from the anesthesia protocol *asleep-awake- asleep*. For the IONM in these 2 cases I used cortical mapping for the motor and sensatory areas, the phase reversal technique for detecting the central sulcus and last but not least mapping of the language eloquent areas.

3.2.3. Specific IONM modalities for the infra-tentorial pathology

In infratentorial surgery (11 cases) it was required to perform auditory potentials of the brain stem in 7 cases, i.e. in 4 cases of microvascular decompression for trigeminal neuralgia, a clivus tumor, a exophytic tumor of the brain stem and an acoustic nerve neurinoma. BAEP were monitorable in all these cases, only in the case of the neurinoma of the acoustic nerve they were altered from the baseline. A number of 7 cases required spontaneous electromyography for the monitoring of the cranial nerves, especially the facial nerve, trigeminal nerve and glossopharyngeal nerve. In 5 cases the direct nervous stimulation on the facial and trigeminal nerve was used for their intraoperative identification and facilitation. Two cases of hypophysis macroadenoma with trans-nasal/trans-sphenoidal approach were monitored with visual evoked potential.

3.2.4. Specific IONM modalities for the cervico-dorsal pathology

In surgical procedures for the cervico-dorsal segment (27 cases) besides the MEP and SEP monitoring spontaneous electromyography was required in 17 cases which put the cervical spinal roots at risk.

3.2.5. Specific IONM modalities for the lumbosacral pathology

In lumbosacral surgery (11 cases) the stimulation of the pedicle screw and spontaneous electromyography were required in 7 cases for lumbosacral artrodeses. In the other 4 cases, 2 with tumors of the cauda equine and 2 with lumbosacral meningomyelocele MEP, SEP, spontaneous electromyography and mapping of the cauda equine through direct stimulation of the nervous roots were required.

3.3. Utility of multimodal IONM techniques

The warning criteria for SEP consist in the decrease of their amplitude under 50% or the lengthening of the latency with 10%. Referring to MEP a warning criterion is considered the decrease of the amplitude and simplification of the potentials' morphology, but especially their loss, alongside the need to rise the electrical stimulation threshold as compared to the baseline.

3.3.1. Intra-operative modifications of the motor evoked potentials

In 63 monitored cases with MEP I had transitory decreases of the MEP amplitude or simplification of their morphology as compared to the baseline in 18 (28.6%) cases, which reacted positively to early taken measures and/or increase of the intensity of the stimulation current. None of these cases was followed by a new motor deficit. A single case with the total and persistent loss of MEP signals during the surgical intervention was recorded (1.6%), which postoperative presented an aggravated motor deficit as compared to the preoperative condition (diagram 3.7).

3.3.2. Intraoperative modifications of the sensory evoked potentials

Out of 63 cases monitored with SEP in 10 (15.9%) cases the decrease of the potentials' amplitude or less often the lengthening of their latency was recorded, they recovered as a consequence of measures taken by the neurosurgeon. There were no new postoperative sensory deficits in these patients. No persistent decreases or losses of the intraoperative sensory signal were recorded in the patients (diagram 3.8).

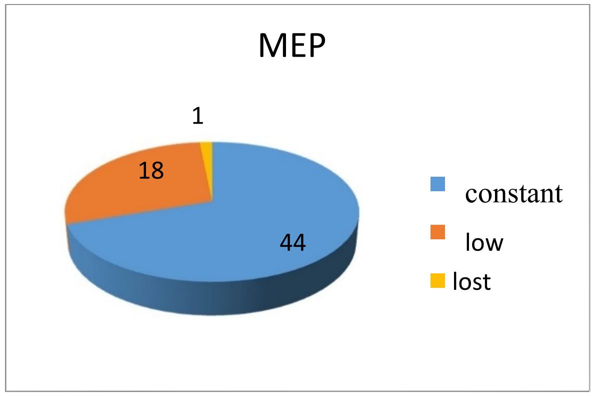

Diagram 3.7. Persistency degree of MEP until the end of the surgical procedure

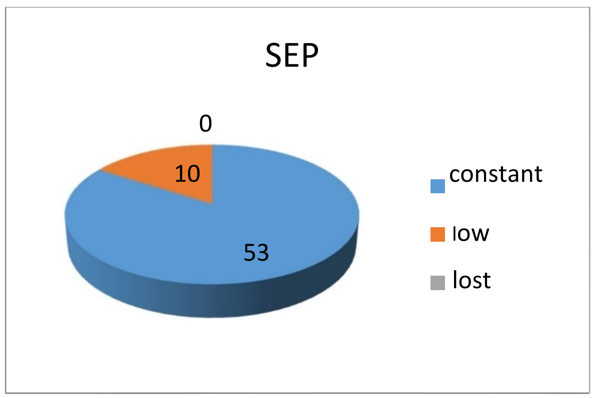

Diagram 3.8. Persistency degree of SEP until the end of the surgical procedure

3.3.3. Modification of the electrical stimulation threshold in subcortical monitoring

In subcortical monitoring of the proximity of the corticospinal tract the decrease of the stimulation threshold in order to obtain a motor response is considered critical around the values of 1-3 mA. Out of the 14 cases of subcortical monitoring of MEP 2 cases presented alarming approaches to the cortical stimulation threshold; it was required that the resection is stopped at that point. Although MEP through direct cortical stimulation did not show their alteration intraoperatively, 1 case presented an accentuation of the preexisting left brachial motor deficit, which nonetheless improved after a recovery period of 30 days.

3.3.4. Language mapping in awake surgery

I had two cases of awake surgery, where after the cortical and subcortical mapping the surgical strategy was adopted for an optimal resection result from an oncological point of view and the point of view of clinical evolution. The first case, a left frontal tumor (low degree astrocytoma) benefited from cortical language with the Penfield method and by identifying the language area through anatomy at repeated stimulation it could be avoided during resection. In the second case, a left parietal tumor (low degree astrocytoma) the stimulation of the parietal eloquent areas allowed the controlled resection, while the continuous subcortical stimulation produced anomy and paraphasia at one point, which led to the resection being stopped as not to cause irreversible lesions of the arcuate fasciculus, which connects the language areas.

3.3.5. Intraoperative modifications of the auditory evoked potentials of the cerebral trunk

BAEP monitors the auditory pathways, which cross the cerebral trunk and an elongation with over 1 ms or a sudden drop of the amplitude of the waves obtained, especially wave V, needs to alert the surgical team. In one single case out of 4 with microvascular decompression for trigeminal neuralgia an BAEP altering was described as an elongation of the latency of wave V with 0.8 ms and a decrease in wave amplitude as compared to the baseline. Postoperatively this patient presented a transitory peripheral vestibular syndrome. The other three cases monitored with BAEP did not present any alterations.

3.3.6. Intraoperative modifications in spontaneous electromyography

In a case with left acoustic nerve neurinoma we had a persistent neuro-tonic discharge of the facial nerve, on the orbicularis and oris muscles, which were postoperatively followed by a paresis of the left facial nerve despite the measures taken. In other 4 infra-tentorial cases there were short spontaneous electrical discharges of neuro-tonic type on the EMG, which were not followed by deficit as a result of early measures taken. In the lumbosacral segment, 3 cases with short neuro-tonic discharges without clinic repercussions were described.

On the spontaneous electromyography of the cranial nerves and the lumbosacral spinal nerves other spontaneous electrical discharges as peaks or group of peaks with no pathological significance were recorded.

3.3.7. Direct electrical stimulation of the cranial nerves

The electrical stimulation of the cranial nerves in infra-tentorial procedures produces prompt motor responses at electrical stimuli intensity of 0.5-5.0 mA, allowing the identification of facial nerves and trigeminal nerves and the verification of their functioning intra- and postoperatively. In all 5 cases, where I used this technique the motor responses were present and stable up to the end of the surgical procedure.

3.3.8. Direct electrical stimulation of the lumbosacral spinal roots

The direct nervous stimulation of the cauda equine roots was followed by prompt responses at intensities of the electric current of 0.5-5 mA and non-responses of the non-neural structures at over 20 mA, which identified this way could be resected. A special case in this respect is a terminal filum tumor, an ependymoma, which was resected together with this non-neural structure when it did not respond to stimulations of intensities over 20 mA.

3.3.9. Electrical stimulation of the pedicle screw

The electrical stimulation of the pedicle screws verifies their proximity as compared to the nervous roots in the spinal channel and a decrease of the stimulation threshold under 4 - 6 mA increases the suspicion of malposition, which requires verification or repositioning eventually. A single case out of the 8 where this technique was used required repositioning after the stimulation threshold was lowered under 6 mA indicated a breach of the pedicle wall at the level of the right L4 root.

3.3.10. General modifications of the neurophysiological parameters

Out of the 76 cases with multimodal monitoring, in 31 (40.8%) cases modifications of the neurophysiological parameters took place, which alarmed the surgical team and which required corrective measures. In 27 (35.5%) cases they were transitory as a result of the early taken measures and 4 (5.3%) cases presented persistent modifications. In the supra-tentorial segment there were 14 such modifications, in the infra-tentorial 5, cervico-dorsal 9 and lumbosacral 3. (diagram 3.15, table 3.IV) The corrective measures were the ones summarized under the acronym *TIP*, namely the temporary halting of the resection, local irrigation with saline solution and eventually the adjustment of arterial pressure (18). Other measures was the increase of the intensity of the stimulation threshold, administration of corticosteroids, repositioning of a limb, anesthesia adjustment, repositioning of a screw and sometimes reconsidering of the surgical strategy, with the limitation or stopping of the resection.

In 45 (59.2%) cases no modifications of the neurophysiological parameters used for IONM occurred (diagram 3.15).

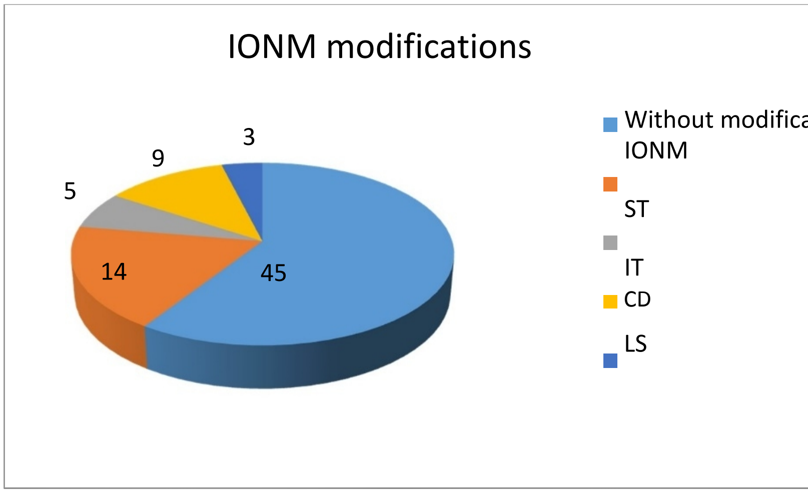

Diagram 3.15. Ratio of occurring of intraoperative modifications of the IONM parameters

3.4. Postoperative clinical evolution

In our series of monitored patients there were only 6 (7.9%) cases which presented different new postoperative motor deficits. The other 70 cases (92.1%) had stationary postoperative evolution – 13 (17.1%) – or towards improving – 57 (75.0%) (diagram 3.16).

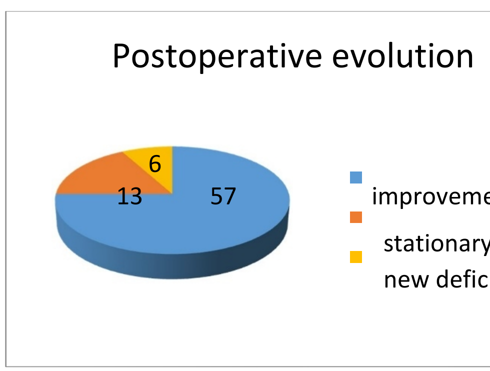

Diagram 3.16.Postoperative evolution of the patients part of the study

In table 3.IV I brought together the data referring to the significant modifications of IONM parameters and the postoperative clinical evolution of the patients. In the group of patients without IONM modifications the two cases with new deficits could not have been prevented, as one was a postoperative complication and the other one a not-monitorable visual field deficit.

In the group of 31 patients with modifications of the IONM parameters 27 cases presented transitory modifications as a result of the early measures applied, whereas the other 4 cases – 2 with paresis and 2 with cranial nerve deficits – were preceded by persistent modifications of these parameters, and were thus predictable.

Table 3.IV. Correlațion between the modification of the IONM parameters and the postoperative evolution

Deficits/segments	ST	IT	CD	LS	Total
Not modified IONM parameters					
NND	11	6	18	8	43
Paresis	0	0	0	0	0
p.o. complications	1	0	0	0	1
CN deficit	1	0	0	0	1
Modified IONM parameters					
NND	12	3	9	3	**27**
Paresis	2	0	0	0	2
p.o. complications	0	0	0	0	0
CN deficit	0	2	0	0	2
TOTAL	27	11	27	11	76

Legend: ST=supra-tentorial;IT=infra-tentorial;CD=cervicodorsal;LS=lumbosacral; IONM= intraoperative neurophysiological monitoring; NND=no new deficit; p.o.=postoperative; CN= cranial nerves.

Through the modifications of the neurophysiological parameters and the consecutively applied measures in the studied group the intraoperative monitoring prevented the occurring of new neurological deficits in 27 (35.5%) of the 76 cases.

3.5. Security of the IONM procedures

In our study, I noticed that besides the intraoperative neurophysiological modifications we also experienced some rare complications in 4 (5.3%) cases: 3 cases with generalized convulsive seizures and a case of tongue biting (diagram 3.17). The convulsive seizures occurred in patients with supratentorial tumors, which presented preoperative epileptic morbidity and required direct cortical stimulation, which probably lowered the convulsant threshold even under anesthesia. All 3 cases responded rapidly to local cortical irrigation with cold saline solution and anticonvulsant treatment. The isolated case of tongue biting was due to the transcranial electrical stimulation in order to acquire MEP and possibly due to a concomitant dental asymmetry, subsequently it had a favorable evolution.

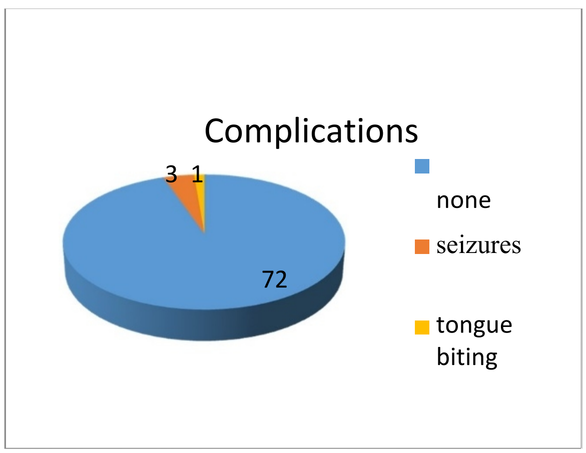

Diagram 3.17. Complication rate during the IONM procedures

The duration of an intraoperative neurophysiological monitoring was of 4.77 hours on average, ranging from 3 to 8 hours.

5. Conclusions

1. The motor and sensory evoked potentials were efficiently acquired from patients under anesthesia; the MEP monitorability was of 93.7%, and the SEP monitorability was of 98.4%. The success rate of acquiring these evoked potentials was influenced by the severity of the preoperative morbid state.
2. The intraoperative monitoring technique of the MEP is specific and sensible for the appreciation of the motor cortex functionality and the functionality of the corticospinal tract. The irreversible deterioration and disappearance of MEP were events indicating a postoperative motor deficit in a case part of the group studied (1.6%). The reversible alteration of MEP in 18 cases (28.6%) was not followed by motor deficit, like in the case of patients without modifications of the MEP parameters.
3. The combined utilization of MEP monitoring through direct cortical stimulation for remote vascular lesions (19 cases; 70.4%) with subcortical mapping with the help of the suction device alongside the unipolar stimulator (14 cases; 51.9%) provided real time functional feedback during the resection of the cerebral tumors from the eloquent motor and language areas.
4. The combined utilization of SEP and MEP in 63 cases (82.9%) ensured a coverage of a monitoring of the sensory and motor pathways, so that IONM is more efficient. The loss of proprioceptive sensitivity of the lower limbs, which could be detected by SEP, can cause important disturbances in walking and orthostatism. I detected reversible alterations of the sensory evoked potentials in 10 patients (15.9%) without them developing sensory or postoperative deficit.
5. The *phase reversal* technique for the identification of the central sulcus and thus of the cortical motor area has proven useful as it reduces the time for cortical mapping and continuous monitoring initiation of the MEP through direct cortical stimulation in 14 patients part of our study (51.9%).
6. Direct electrical stimulation allowed the identification of the anatomic position of cranial nerves and their route in 5 of the infra-tentorial procedures. The spontaneous electromyography of the cranial nerves conducted in 7 patients offered real time warning through the occurring of spontaneous electrical discharges of neuro-tonic type, which prevent or predict a neurologic deficit.

7. The intraoperative neurophysiological monitoring was useful for the 4 procedures of microvascular decompression in trigeminal neuralgia. IONM consisted of spontaneous electromyography and mapping of the facial nerve and the trigeminal nerve, as well as in the conduction of auditory evoked potentials. The modifications in these IONM techniques warned the surgeon, which then took early measures in order to avoid difficult postoperative deficits, especially hypoacusis and peripheral facial paresis.

8. IONM during spinal surgery is a complex process, during which information are acquired that contribute to the surgical decision in real time. The combined usage of SEP, MEP and pedicle stimulation in 27 cases with cervicodorsal pathology allowed the neurosurgeons to operate more securely, avoiding dangerous manipulations and instrumentations neighboring the nervous structures. No intraoperative events took place and the patients did not present new deficits postoperatively.

9. IONM during the 11 cases of lumbosacral surgery proved useful for identifying potential lesions of spinal nervous roots. Through spontaneous electromyography, electromyography associated with the stimulation of the pedicle screw and radicular mapping conducted in 7 cases, the establishment of a motor or sensory deficit of radicular type was prevented. Through the meticulous mapping of the cauda equina roots it was prevented that they be damaged and filum terminale in the cases of tumors of this non-neural structure (2 cases) and in cases of "tethered cord" were identified (2 cases).

10. Both the absence and the presence of SEP and MEP modifications as a result of surgical procedures represented useful indicators. SEP and MEP modifications, as well as modifications of the other modalities of intraoperative neurophysiological monitoring led to changing the surgical strategy in 35.5% of the cases, allowing an optimal resection of the pathological process, while at the same time preserving the healthy nervous tissue. This fact proved the utility of IONM in the prevention of the occurring of iatrogenic nervous lesions by applying successful corrective measures.

11. Even when no modification of the parameters used for monitoring occurred, this gave the neurosurgeon more confidence and allowed a more radical resection within security limits. The utility of IONM was proven by the favorable postoperative evolution of the patients, as 92.1% of them presented improvement or stationary evolution.

12. The multimodal intraoperative neurophysiological monitoring procedures were safe, during the surgical interventions of only 4 cases (5.3%) slight complications occurred.

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