

ROMANIAN
NEUROSURGERY

Vol. XXXIV | No. 4 December 2020

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Mihaela Coşman,
Andreea Atomei,
Nina Straticiuc,
Alexandru Caragea,
Mihai Soare,
Alina Mihaela Neacşu



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Mihaela Coşman¹, Andreea Atomei², Nina Straticiuc³,
Alexandru Caragea¹, Mihai Soare¹,
Alina Mihaela Neacşu^{1,4}

¹ Emergency County Hospital, Braila, ROMANIA

² Student. "Grigore T. Popa" University of Medicine and Pharmacy, Iasi, ROMANIA

³ Department of Anaesthesia and Intensive Care. "N. Oblu" Emergency Clinical Hospital, Iaşi, ROMANIA

⁴ "Carol Davila" University of Medicine and Pharmacy, Bucharest, ROMANIA

ABSTRACT

Intraoperative neurophysiological monitoring (IOM) and especially motor evoked potentials represents an important tool in the evaluation of the nervous system integrity and particularly of the motor tracts. A real and correct registration of the potentials with a proper interpretation of the modification is mandatory for an optimal outcome in eloquent areas, tumours, brainstem and medullary lesions. For all this to happen a suitable anaesthetic protocol must be used. Even though there is a large spectrum of anaesthetic agents at our disposal it is imperative to know their effect on the IOM signals recordings and the fact that some of them are dose-dependent. Drugs effects and physiological changes produced intraoperatively must be corrected before a shift in the direction of the surgical lesion resection it is taken. We present an overview of the action of the anaesthetic agents, most used protocols and the physiological alteration encountered in the operative theatre.

INTRODUCTION

Nowadays tumors located in functional areas of the brain, brainstem and medullary lesions still represents a challenge for many neurosurgeons because of the high risk of postoperatively permanent neurological deficits, but the technological development comes in our aid and the golden standard of maximal resection with minimal neurological disfunction can be reached more often using functional technique perioperatively [12,34,35,41,46].

Considering those date, intraoperative neurophysiological monitoring (IOM) represents a suitable modality for the assessment of the integrity of the nervous system with a real time feedback [32,45,52].

Keywords

intraoperative neurophysiological monitoring, motor evoke potentials, eloquent areas, propofol, volatile agents, intravenous anaesthesia



Corresponding author:
Andreea Atomei

"Grigore T. Popa" University of
Medicine and Pharmacy, Iasi,
Romania

atomei_andreea96@yahoo.com

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ISSN online 2344-4959
© Romanian Society of
Neurosurgery



First published
December 2020 by
London Academic Publishing
www.lapub.co.uk

This technique includes various evaluation possibilities e.g., direct cortical / subcortical stimulation and monitoring modalities like motor evoked potentials (MEPs), somatosensory evoked potentials (SSEPs), brainstem auditory evoked potentials (BAEPs), electromyography / free running EMG. For proper recording of the motor / sensitive response special anesthetic drugs are used with differences between the induction step and the stage of maintaining of the sedation [4,9,24]. In order to record the motor response, the drugs used during surgery have a major role in data accuracy [11].

The vast majority of anesthetic drugs decrease the synaptic activity, this effect being dose dependent. They have a direct action on synaptic pathways or indirect effect by altering the influence of inhibitory or excitatory mediators: some anesthetic agents may bind to gamma-aminobutyric acid-a receptors, others may block the excitatory effect of glutamic acid and another group act at the neuromuscular junction level at the "n-type" acetylcholine receptors [43].

Anesthetic agents' effects on intraoperative evoked potentials.

Volatile anesthetic agents (Sevoflurane, Desflurane, Halothane, Nitrous Oxide), dose dependently suppress the MEPs by inhibiting the pyramidal activation of spinal motor neurons, they increase the latency and decrease the amplitude (Figure 1). MEPs are more sensitive to their action in comparison with SEPs [43]. Some studies say that a concentration under 0,5-1 at the alveolar level (MAC) it is safe for IOM recording. Nevertheless, for patients with preoperative neurologic disfunction, motor/sensitive alteration or neuropathy, lower doses may impede or even abolish the potentials [55].



b.

Figure 1. a) cork-screw electrodes placement for transcranial MEPs recordings; **b)** morphology of MEPs from tibialis anterior muscle and abductor hallucis muscle: red star - time of the stimulus application, yellow arrow - latency (unit: seconds), red arrow - amplitude (unit: volts) (images form dr. Coşman M. personal collection).

Between sevoflurane and desflurane the former has a bigger impact on decreasing the amplitude of MEPs. The recordings from the lower limbs seem to be more sensitive to anesthetics than the upper limbs [8]. The action mechanisms of desflurane are on different levels: on pre-postsynaptic receptors, on cellular ionic channels and on serotonin type 3 receptors [33,47] hence its capacity of maintaining proper anesthesia and amnesia at 0,5 MAC [16].

Sevoflurane, halothane, isoflurane are considerate "potent" agents and nitrous oxide is less "potent" being used at higher concentration. The latter is used for IOM in combination with other drugs e.g. nitrous-narcotic technique and the effect depends on the agent already present [43]. His action determines a decrease in amplitude and no effect on cortical potentials latency, without changing the wave morphology [5,42].

Intravenous agents such as Propofol interact with SEPs and MEPs recordings, dose dependent, but in a smaller extent compared with volatile agents [44]. By comparison with the baseline the latency of the evoked potentials is prolonged and the amplitude is decreased after both isoflurane or propofol is administrated, but the former has a bigger inhibitory effect on IOM than the latter [7].

Propofol is been used commonly in TIVA technique (Calanci *et al.* 2001, Deletis 2002, Langeloo *et al.* 2003, Chen *et al.* 2004, MacDonald *et al.* 2006, Sala *et al.* 2006, Szeleny *et al.* 2007, Lieberman *et al.*

2017, Marafona et al.2018, Toossi et al. 2019) [6,7,10,18, 20,24,27,39,49,51] or with inhalant anesthetic agents to decrease their dosage [14,17,25,44]. Although is the preferred drug in IOM procedures, in a study from 2017 it was concluded that hemorrhage may alter the pharmacokinetic properties, the reduction of the cardiac output was associated with increase of the serum concentration which had the capacity to generate false positive results [20].

Etomidate influence only the cortical SEPs (increases the amplitude) and ketamine enhance the response of both potentials, making those agents a good choice for patients with preoperatively functional deficit. Nowadays the former is not used so frequently because of the risk of increasing the intracerebral pressure. Etomidate produces the less depression over potentials amplitude but utilized in continuous infusion may induces adrenocortical suppression [30,42].

Barbiturates (Thiopental) influence significantly the MEPs, but they do not affect the SEPs registration so strongly. Benzodiazepines – Midazolam decreases the potential recordings, especially of MEPs but has an advantage by inducing amnesia [30].

Dexmedetomidine ensure analgesia and sedation acting on α_2 agonist receptors with minimal respiratory depression. In a study from 2015 published by Rozet it is shown that this agent does not have a significant effect on the potential's latency and amplitude [36].

As an adjuvant, when propofol is utilized for IOM anesthesia, dexmedetomidine determine smaller changes on MEPs recordings in comparison with midazolam but alters in a bigger way the hemodynamical parameters [1]. Also in a randomized double blinded study the use of dexmedetomidine before induction (1 $\mu\text{g}/\text{kg}$ over 10 minutes) and at the maintenance stage (0,2 $\mu\text{g}/\text{kg}/\text{hr}$) was associated with a need of lower doses of propofol and stable hemodynamical parameters [48].

From opioids, fentanyl may even improve the myogenic reaction when utilized for IOM by reducing the spontaneous muscular contraction from the background [43]. Another intravenous agent, remifentanil can be used in infusion, being an ultra-short action narcotic, but he has the disadvantage of opioid-induced hyperalgesia [14].

Muscular relaxants have little effect on SEPs recordings but interact with MEPs registration. Partial muscular blockade has the advantage of reducing the patient movements and facilitate the tissue retraction. To determine the degree of blockage we can use two methods: we measure the amplitude produced by supramaximal stimulation of the peripheral motor nerve – T1 (M wave) and compare with the baseline value obtained after the drugs where administrated. Another technique requires to evaluate the motor response after 4 stimuli are delivered at 2 Hz rate [43].

Various anesthetic techniques were used and some combination have been tested with the aim of minimum effect on IOM recordings. It was observed that at the same MAC concentration volatile drugs have a greater suppression effect. However, the best protocol is still controversial [9,54]. However, it is important to know that: the most resistant type of potential at anesthetic drugs are BAEPs, visual evoked potentials are the most sensitive, MEPs can be totally blocked by skeletal muscle relaxants and the recordings of SEPs depends on type of the anesthetic drugs [15]. Sometimes to assess the depth of the anesthesia can be a challenge for the anesthesiologist because the placement of the electrodes may coincide with the skin incision and so the type of the anesthesia must be chosen keeping in mind the site of the operation and the general status of the patient [17].

A summary of medications interactions with neurophysiological monitoring, especially with the MEPs recordings is presented in **Table 1**.

Table 1. Aesthetic drugs influence on Motor Evoked Potentials [15,22,30].

Anesthetic drug	MEP - Latency	MEP- amplitude	Observation
Sevoflurane	Increase	Decrease	Use: MAC – 0,5
Nitrous oxide	Increase	Decrease	Strong effect, should be avoided
Fentanyl	Preserved	Slight depression	Dose dependent
Remifentanyl	Preserved	Decrease	Rapid metabolism – rapid titration
Propofol	Increase	Decrease	Dose dependent;

			Rapid metabolism – rapid titration
Thiopentone	High increase	High decrease	Marked suppression
Etomidate	Decrease	Increase	Enhances the potentials
Ketamine	Increase	Increase	Enhances the potentials
Midazolam	High increase	High decrease	Marked suppression; indicated only in premedication administration
Dexmedetomidine	Increase	Decrease	Use to lower other TIVA agents dose

A combination of those drugs may be used as well with proper sedation and without impairing the IOM measuring's. Gunter presented in 2016 a protocol which includes inhalant agent at a MAC= 0,5 associated with remifentanil and dexmedetomidine. This technique has the advantage of a quick emergency from the general anesthesia due to the latter drug, which produces the sedation effect by acting in locus ceruleus [14].

Another study presented by Isik *et al.* in 2017, where optimal potentials recordings were obtained by using desflurane (0,5 MAC) with remifentanil (0,05-0,3µg/kg/min at 50% O₂) considers this association safe and an alternative for more used TIVA technique [16].

In a randomized survey published by Martin *et al.* in 2014 a comparison has been made between the two classes of drugs: the total intravenous technique (Propofol – Remifentanil) with volatile agents (Desflurane – Remifentanil). The results showed the necessity of a higher voltage to elicit response in volatile agent anesthesia [14,28]. Similar results have been found by Velayutham *et al.* in a study on spinal cord tumors from 2019 where the stimulation applied was 205 ± 55 Volts for propofol anesthesia (6-8mg/kg/hr) and 274 ± 60 Volts for isoflurane [53].

Sloan *et al.* presents in 2015 a combination of inhalant and intravenous anesthesia (0,5 MAC Desflurane with Propofol) with good results regarding electrophysiological monitoring and this technique may be an advantage for patients with opioid tolerance [3,44].

In a retrospective cohort study published in 2020 by Oh *et al.* it was evaluated the postoperatively liver function in patients with preoperative transaminase alteration comparing the group cases operated using total intravenous anesthesia (Propofol) with those operated using inhalator agents (Sevoflurane). The halogenated inhalational drugs are frequently used but they are associated with hepatotoxicity which is less encountered in latest anesthetic agents like sevoflurane or desflurane. The study concluded that the changes in liver enzyme levels were obviously lower for patients from the TIVA group and this type of anesthesia is indicated in neurosurgical intervention especially because of the longer time of the operation [2,31,37].

Other study from 2020 presented by Grau *et al.* discusses de impact of the anesthesia type on tumors recurrence and how the surgical stress can affect the mechanisms of the immune response inducing a vulnerable perioperative period. The idea started from the results obtain in vitro, where anesthetic drugs acted over tumor cells culture. Propofol induced apoptosis in contrast with isoflurane which increased proliferation of glioblastoma stem cells, however the results have not been consistent because of the differences induced by the cell line [29,38]. The conclusion that Grau *et al.* have reached shows no difference between volatile agents and TIVA regarding glioblastoma recurrence (volatiles 8 vs. propofol 8,4 months) or overall survival (volatiles 16,9 vs. propofol 17,4 months) [13].

Another thing to keep in mind when there is a oscillation between TIVA and inhalational anesthesia is the fact that in a study from 2014 published by Tamkus *et al.* volatile drugs were associated with obviously higher false positive responses (15% vs. 3,2%) compared with intravenous agents, when recording transcranial MEPs [50].

Modification in potentials amplitude and the need of a higher voltage to elicit the same result was observed as independent of anesthetic drugs concentration during the intervention, phenomenon named "anesthetic fade". This situation is produced by a long exposure of the nervous system to the drugs action [23]. In contrast with this decrease effect, it was observed and an increase impact called "anesthetic fade-in". This may happen if the baseline measurements of the MEPs were recorded before the surgical procedure started and before the effect

of the myorelaxants drugs used at induction disappeared [19].

Therefore, the mainstay in anesthesia protocols are synthetic opioid (fentanyl, sufentanyl) and propofol which under continuous administration have the capacity to maintain a constant serum concentration. Due to their pharmacokinetic properties the influence on amplitude, latency of MEPs and direct cortical stimulation is negligible [30]. This makes TIVA (Lo et al.2006, Martin et al. 2014, Tamkus et al. 2014, Sloan et al.2015, Malcharek et al. 2015, Velayutham et al. 2019, Oh et al.2020) more suitable for MEPs recording than inhalant anesthesia [21,26,28, 31,44,50,53].

Physiological changes on intraoperative evoked potentials.

Temperature. Cortical SEPs are the most vulnerable to temperature changes. Brain irrigation with cold serum affects the potential recordings [15]. Hyperthermia decrease the latency of MEPs where the hypothermia increases the latency. The effect of temperature on the conduction velocity of both MEPs and SEPs is raised in case of hyperthermy and reduced in case of hypothermia [27,40].

Ventilation. On the one hand the most visible alteration induced by hypoxemia is on SEPs, on the other hand hypocapnia has a smaller effect on SEPs and MEPs [15]. Hypercapnia has inhibitory effect on anterior horn cell and on cortical level, but the registration of the potential is altered only when extreme level of CO₂ is reached [22].

Blood rheology. The blood viscosity and oxygenation depend on hematocrit values. Studies have shown that mild anemia is associated with increase in SEPs amplitude, but no results are cited about MEPs [22,43].

Intracranial pressure. Intracranial hypertension decreases the amplitude of SEPs and prologs the latency. When the uncal herniation occurs the brainstem response is lost and MEP signal can no longer be recorded [22,43].

Blood pressure. Of all the above, hypotension may induce severe potential alteration. At first when the perfusion pressure is raised again the changes

restore to baseline. If the perfusion pressure is decreased under 15 ml/ min/100g tissue there are important changes, severe alteration and even the evoked potentials may be abolished [40]. Usually mild to moderate changes do not affect MEPs values [22]. Sometimes systemic blood pressure values may not predict regional ischemia induced by local factors like: prolong tissue retraction, vasospasm, positioning, head extension which can be discovered by potentials alterations [15,40,43].

CONCLUSION

A good neurological outcome for lesion located in eloquent area or for those with medullary development depends on the correct interpretation of the IOM signals and surgical maneuvers. But all of those are interconnected with proper anesthesia management and a teamwork. So far, a standard anesthetic protocol is missing, but general recommendations have been made. Even though the intravenous agents are more appropriate, the use of volatile anesthetic agents or a combination of them it is up to the anesthesiologist and the particularity of the case.

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