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INTRAOPERATIVE MONITORING OF VISUAL EVOKED POTENTIALS: EXPERIENCE OF 240 OPERATIONS

E.A. Levin, M.G. Kilchukov, A.A. Glushaeva

E.N. Meshalkin National Medical Research Center, Ministry of Health of Russia; 15 Rechkunovskaya St., Novosibirsk 630055, Russia

Contacts: Evgeny Andreevich Levin *e_levin@meshalkin.ru*

Background. Intraoperative monitoring (IOM) of visual evoked potentials (VEPs) is used to inform surgeons about impacts on the visual system in order to prevent iatrogenic visual impairment. The VEP monitoring use become widespread only in the last decade; nowadays, there is no generally accepted methodology for its implementation, and the effectiveness of VEP monitoring and the factors determining it have not been sufficiently studied.
Aim. The aim of the study was to investigate the factors influencing the VEP monitoring feasibility and effectiveness.
Materials and methods. Data from 240 consecutive neurosurgical operations performed using VEP monitoring were retrospectively reviewed. IOM data (registration parameters, presence and type of VEP changes), patient characteristics (gender and age, tumor type and location, presence of preoperative visual dysfunctions), anesthesia parameters and postoperative changes in vision were studied. Statistical analysis was performed using χ^2 and Mann–Whitney tests.
Results. VEPs were obtained in 91.3 % of eyes with completely or partially preserved vision. The main factors reducing the chances to record VEPs successfully are preoperative visual disorders and the use of inhalation anesthesia. A personalized approach to the selection of reference electrodes and frequency filtering parameters makes it possible to reduce the number of averagings required for VEP recording and accelerate informing surgeons.
With successful monitoring 59.1 % of eyes had no noticeable VEP changes; 5.8 % of eyes had signs of intraoperative improvement; 35.1 % had signs of deterioration. Among the last category, 60.7 % of eyes had full VEPs recovery afterwards. After surgery, new visual disorders were detected in 2.6 % of eyes without signs of intraoperative deterioration, in 6.7 % – with temporary deterioration, and in 19.3 % – with signs of deterioration persisted until IOM is finished. Assessing the sensitivity and specificity of VEP monitoring is hampered by the possibility of complications in the early postoperative period and IOM influence on the course and results of the operation.
The proportion of total resections was maximal when VEP monitoring was successful. In the subgroup without preoperative visual impairments, the alarms during monitoring were associated with decrease in proportion of total resections proportion due to increase in proportion of subtotal resections.
Conclusion. VEP monitoring with a personalized approach allows effective monitoring of visual functions preservation during neurosurgical operations.

Keywords: intraoperative neurophysiological monitoring, visual evoked potentials, personalized approach, iatrogenic disorder, surgical radicality

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BACKGROUND

Neurosurgical operations performed near the visual pathways and visual cortex carry a risk of their damage which can cause partial or even complete loss of vision. Visual evoked potentials (VEPs) reflecting the response of the visual cortex to light stimulation of the retina allow to evaluate integrity of visual function. VEP control during surgery allows to detect reduced visual function and, in many cases, prevent development of severe irreversible visual loss. For a long time, intraoperative monitoring (IOM) of VEPs was represented only through pilot studies, many of which showed instability of VEP registration and weak correlation of their changes with postoperative visual disorders [1, 2]. Good reproducibility of VEPs during their monitoring was achieved only about 10 years ago [3–6]. Consecutively, in contrast to other types of evoked potentials, currently there are no standards for IOM VEP. Different authors have described various techniques of IOM VEP. The position of reference electrodes varies: they can be located in the frontal [4, 7] or central [6] area or on the left and right mastoid processes [3, 5, 8, 9]; different frequency filter bandwidths are used: from 1–5 to 100 Hz

(corresponding to the standard for clinical VEPs) [4, 5], from 10–20 to 500 Hz [3, 9], from 2 to 400 Hz [6], from 0.1 to 200 Hz [8]. Most commonly single flashes are used as stimuli but other types of stimulation such as illumination cessation [8, 10] and double flashes with 50 ms interval [9] have been described. Therefore, currently there are not only no standards for IOM VEP but no universal techniques for it.

Between 2015 and 2022, at the Neurosurgical Division of the E.N. Meshalkin National Medical Research Center, 240 neurosurgical operations with VEP monitoring were performed. The accumulated experience allowed us to develop an approach taking into account patients' individual characteristics and ensuring effective VEPs monitoring. We present this experience in this article.

Aim. The aim of the study was to analyze the factors affecting IOM VEP feasibility and effectiveness.

MATERIALS AND METHODS

Patients. Data on 240 sequential neurosurgical operations performed under VEP control between 2015 and 2022 were retrospectively analyzed. In 155 cases, patients were female, in 85 – male; 17 surgeries were performed in children and adolescents, 223 in adults. The most common were interventions in the area of the optic nerves and/or chiasm (86 %), postchiasmal elements of the visual system accounted for 14 % of interventions. In 102 (42.5 %) surgeries, transnasal approach was used; in 138 (57.5 %), trepanation was performed. Among neoplasms, the most common were pituitary adenomas (99 (41 %) surgeries), meningiomas (86 (36 %) surgeries), and gliomas and intracerebral metastatic lesions (28 (12 %) surgeries). Preoperative visual impairment was observed in almost half of the cases (235 of 480 eyes); the most common were loss of visual filed (100 eyes) and decreased visual acuity (92 eyes); in 19 cases, complete loss of vision was observed (amaurosis); in 14 cases, vision was severely impaired (light perception, "hand motion").

The retrospective study and accompanying patient data collection were approved by the local ethical committee of the E.N. Meshalkin National Medical Research Center (extract No. 06-5 from the protocol of the ethical committee meeting No. 5 from 14.07.2023).

VEP monitoring. VEPs were evoked through closed eyelids using flashes with intensity 25,000 lx, duration 10 ms, frequency about 1 Hz generated by red LEDs. The averaging number was 50–100 (in 2015) or 20–50 (in 2016–2022). Spiral subcutaneous electrodes for VEP registration were installed in O1, O2, Oz, A1, A2, CPz, Fz leads of the 10–20 system (Fig. 1, *a*). At the first stage of monitoring, various electrode combinations were tested and electrodes demonstrating the best reproducibility of VEP curves were selected for further monitoring. If possible, 3 channels were monitored for VEPs from each eye (left, right and medial; active leads O1, O2 and Oz, respectively). Parameters of frequency filters were also selected after registration of the first 3–5 VEPs at the start of monitoring. The main criteria of selection were the possibility of accurate identification of peaks during the 70–140 ms time interval from the moment of stimulus and maximal reproducibility of the obtained curves. In most cases, these were achieved with the lower bandwidth limit of 10–20 Hz and upper of 200–400 Hz (Fig. 1, *b*) (see also the "Results" and "Discussion" sections).

The ISIS IOM (Inomed Medizintechnik GmbH, Germany) system with NeuroExplorer 4.4 software from the same manufacturer were used for monitoring. Alarm was raised when VEP peak latency increased by more than 10 % and/or VEP amplitude decreased by 50 % or more, or in cases of less dramatic changes if they were unilateral. Simultaneously, background electroencephalogram (EEG) and somatosensory evoked potentials were registered to control possible changes associated with anesthesia depth and other systemic parameters. VEP monitoring was started at the stage of preparation for surgery. Baseline parameters were updated after dissection of the sella turcica floor during transnasal approach and after dissection of the dura mater in trepanation surgeries. If prior to this moment VEPs for stimulation of one or both eyes could not be obtained, the surgeons were informed about the absence of control. Monitoring was completed after tamponade of the nasal passages during transnasal interventions and after closure of the dura mater in other cases.

Anesthetic management. At the main surgical stage, in 188 patients total intravenous anesthesia (TIVA) was used (propofol 10–60 mL/h + fentanyl); in 16 patients, inhalation anesthesia was used (sevoflurane 0.4–0.8 MAC); in 36 patients, combined anesthesia was used. The latter was performed at the request of anesthesiologists if sevoflurane was administered at a steady level of 0.5 MAC or less and anesthesia regimen was switched to TIVA in cases of low VEP reproducibility.

Analyzed data and analysis methods. The IOM data (registration parameters, presence and type of VEP changes), patient characteristics (sex, age, presence of preoperative vision impairment, lesion type and location, type of surgical approach), anesthesia parameters, postoperative changes in visual function and surgical radicality were analyzed. to evaluate the effectiveness of VEP monitoring in the context of iatrogenic complication prevention, contingency tables for intraoperative VEP changes and postoperative visual changes were used. The tables allowed to calculate sensitivity, specificity and positive and negative predictive values (PPV and NPV, respectively). Surgical radicality was evaluated based on the level of space-occupying lesion resection according to postoperative magnetic resonance imaging: total (>99 %), subtotal (90–99 %), and partial (<90 %).

Statistical analysis was performed using the χ^2 and Mann–Whitney tests (depending on data type) in the Statistica (StatSoft Inc., USA) software.

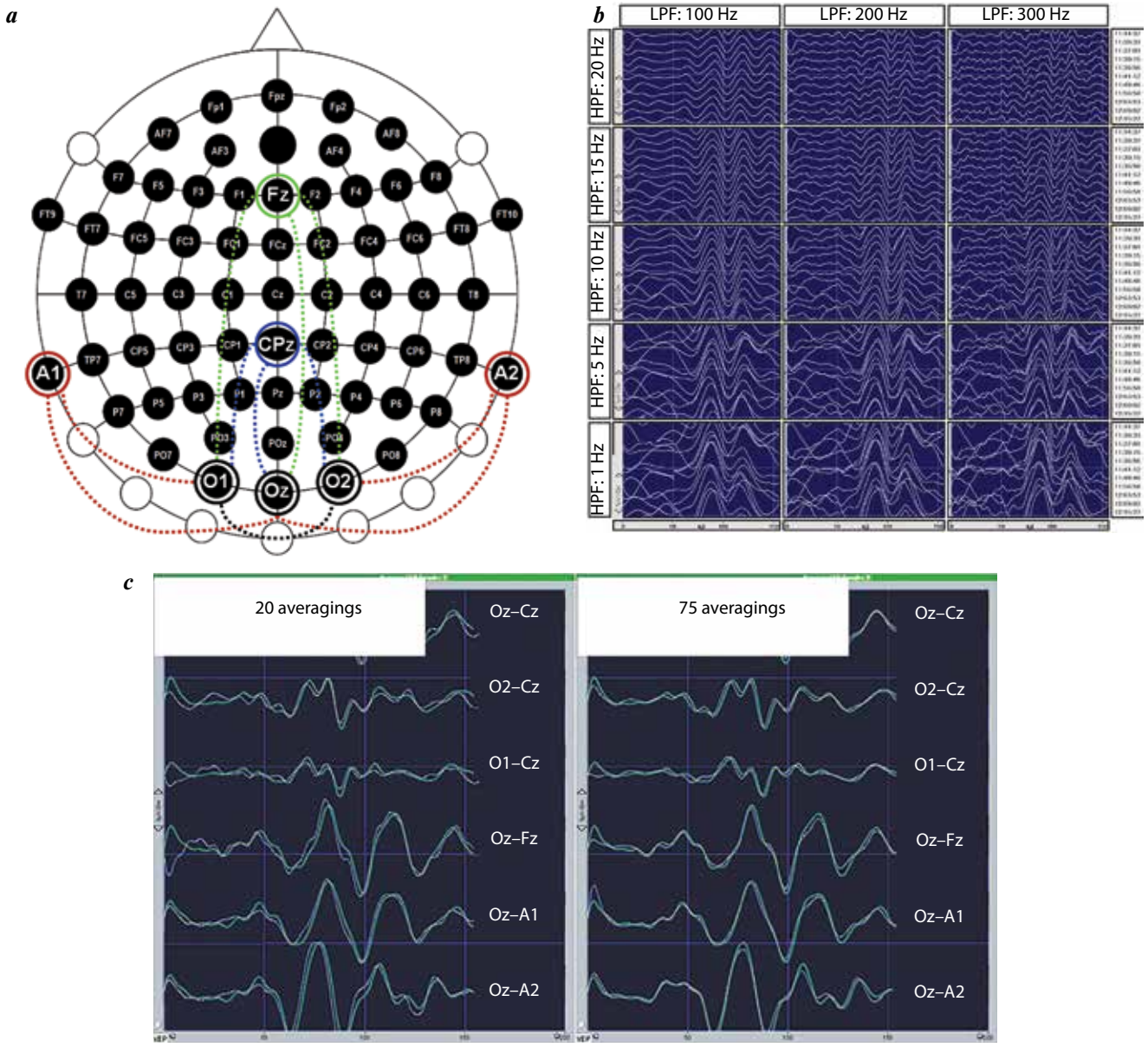

Fig. 1. *Selecting personalized parameters for visual evoked potentials (VEP) monitoring: a – options for recording electrodes placing. Before monitoring begins, electrodes are placed in positions O1, O2, Oz, Fz, CPz, A1, A2 according to the 10/10 EEG electrode placement system. Active electrodes in all cases are O1, O2 and Oz; for reference electrodes, one of three options is selected (Fz, CPz, or A1/A2) according to the criteria of best reproducibility and maximal amplitudes of the main VEP peaks basing on the first 3–4 recordings; b – example results of applying high-pass (HPF) and low-pass (LPF) filters to the same set of raw VEP recordings. Patient: woman with meningioma of the sphenoid wing, lead Oz–CPz. Differences in the shape, amplitude and reproducibility of the curves are clearly visible. The criteria for choosing a frequency filter for monitoring were the reproducibility and the amplitude of the main VEP peaks; c – reduction of the number of averagings required to obtain reproducible VEPs when using personalized monitoring parameters. Left panel: with just 20 averagings, the curves obtained under unchanged conditions (thinner lines) are almost undistinguishable from the baslines (thicker lines, obtained earlier with 100 averagings). Right panel: further accumulation of averagings does not change the result. The graphs also show differences in the amplitude and shape of responses in different leads. A frequency filter passband of 15–300 Hz was used*

RESULTS

Feasibility of VEP registration. VEPs from both eyes were registered at the beginning of 184 (76.7 %) surgeries. Initially, responses from 1 of the eyes were absent in 43 (17.9 %) surgeries: in these cases, preoperative visual impairment in these eyes was present; 16 of them had amaurosis. In subfrontal approach, during 5 (2.1 %) surgeries uni- or bilateral disappearance of VEPs after cutaneous flap bending was observed. Reproducible VEPs from both eyes could not be initially registered in 8 (3.3 %) surgeries. The number of eyes for which VEPs were registered at the beginning of surgery was 421 (91.3 %) (here and from now on percentages are calculated excluding 19 eyes with preoperative amaurosis); at the end of the main surgery stage, 413 (89.6 %); for 6 eyes, the possibility of VEP registration ceased after cutaneous flap bending; for 2 eyes, after necessary switch to sevoflurane anesthesia.

Effect of patient characteristics on feasibility of VEP registration. Feasibility of VEP registration did not significantly depend (p >0.15 in all cases) on patient's sex and age, operation area (prechiasmal area, chiasm, visual tracts and/or visual cortex), or type of space-occupying lesion (pituitary adenoma, meningioma, glial tumors, et al.). However, statistically significant ($\chi^2 = 22.3$, df = 2, $p = 0.000014$) effect of the type of approach was observed. In approaches to the base of the anterior cranial fossa (subfrontal, supraorbital), VEPs were not registered in 24 (18.3 %) of 131 eyes without amaurosis; in transnasal approach, in 12 (6.0 %) of 200 eyes; in pterional and other projection approaches, in 4 (3.1 %) of 130 eyes. More expected was statistically highly significant dependance ($\chi^2 = 40.2$, df = 3, p <0.000001) of IOM VEP feasibility on the presence of visual impairment prior to surgery: without it VEPs could not be registered in only 6 (2.4 %) of 255 eyes; with loss of vision fields, in 11 (11.0 %) of 100; with significant decrease in visual acuity, in 18 (19.6 %) of 92 eyes; with vision at the level of "hand motion" or light perception, in 5 (35.7 %) of 14 eyes.

Effect of anesthesia on VEP registration feasibility. Among 360 eyes without amaurosis and VEP registration during TIVA, VEPs could not be obtained for 29 (8.1 %) eyes, 26 of which had preoperative visual impairment. For inhalation anesthesia, among 31 eyes without amaurosis, VEPs could not be obtained for 6 (19.4 %) eyes, 3 of which had preoperative vision impairment. The difference is statistically significant: $\chi^2 = 4.47$, df = 1, $p = 0.034$. Surgeries performed using combined anesthesia were not included into comparative analysis because they were performed under condition of switching to TIVA if VEPs were difficult to obtain. This creates systematic sampling error without the possibility of correct the evaluation of the fraction of VEP registration failures during combined anesthesia. More detailed description of the effect of anesthesia on VEP monitoring is presented in another our publication [11].

VEP registration parameters. As stated above, VEP registration parameters were selected individually for each patient to decrease the necessary averaging number. The optimal reference electrodes in many cases were the following 3: A1 and A2 (on the left and right mastoid processes) in 112 (47 %) surgeries, CPz (medial parietal region) in 55 (23 %) surgeries, and Fz (medial frontal region) in 57 (24 %) surgeries. The O1, O2 and Oz electrodes were active. In the first alignment, A1 reference electrode was used to monitor the left hemisphere, A2 – the right; for the medial region, CPz or Fz was used as the reference electrode. For approach through the occipital region, active electrodes sometimes had to be moved relative to the standard position but in all of these cases VEPs were registered. During 8 (3 %) surgeries with distant reference electrode location due to significant interference, reproducible VEPs were obtained only from the O1–O2 electrode pair. Finally, in 8 (3 %) cases VEPs could not be obtained for any electrode combination: neither form the left or right eye.

The frequency filtration parameters and the number of eyes they were applied to are presented in Table 1. Only cases of successful VEP registration are presented. Frequency filtration parameters for the left and right eye could differ in the same patient. The most common value was 200 Hz for low frequency filter and 10 Hz for high frequency filter but combination of these specific values was used in only 46 % of cases.

Intraoperative clinically significant VEP changes. At the start of the main surgical stage, VEPs were registered for 413 of 480 eyes (examples of different VEP dynamics during surgery and dependencies of VEP changes on intraoperative events are presented in Fig. 2). Among them, clinically significant intraoperative VEP changes (decreased peak amplitude and/or increased latency not associated with anesthesia regimen changes (see Fig. 2, *b–e*)) were observed in 145 (35.1 %) eyes including complete response cessation in 4 eyes (see Fig. 2, *c*). In all cases, the neurosurgeons were notified, and, if possible, measures were taken to alleviate the negative effect on the visual system (retractor position change, less aggressive electrocoagulation, etc.) after which in the majority of cases VEP characteristics restored. At the end of monitoring, full restoration (see Fig. 2, *b, c*) was observed in 88 (60.7 %) of 145 eyes, partial (see Fig. 2, *d*) in 40 (27.6 %) eyes, no restoration was observed (see Fig. 2, *e*) in 17 (11.7 %) eyes. Signs of intraoperative visual improvement (increased amplitude and/or decreased latency (see Fig. 2, *f*)) were observed in 24 (5.8 %) eyes, no signs of improvement (see Fig. 2, *a*) were observed in 244 (59.1 %) eyes. VEP changes caused by anesthesia regimen change were considered clinically insignificant and they weren't included in these statistics.

Correlation between intraoperative VEP changes and postoperative visual changes. Eyes under monitoring were divided into 4 groups depending on intraoperative VEP changes: group 1 had no clinically significant amplitude decrease and/or latency increase (response slowdown); in group 2, temporary response decrease, slowdown or disappearance was observed with subsequent full restoration; in group 3, response decrease, slowdown or disappearance were observed without full restoration at the end of monitoring; in group 4, VEPs could not be obtained initially or the ability to monitor was lost during surgery due to increased anesthesia depth or technical difficulties.

Four types of vision changes (outcomes) after surgery were identified: 1) vision improved; 2) no change; 3) decreased acuity, loss of fields, or vision loss; 4) postoperative vision evaluation was unavailable due to severe non-vision complications. Distribution of outcomes depending on VEP changes is presented in Table 2. Intergroup differences were statistically significant both if all groups and outcomes were included in the analysis ($\chi^2 = 85.7$, df = 9, p <0.000001), and if group 1 was compared to all other groups ($p = 0.0021$; p <0000001; p <0.000001 for groups 2, 3 and 4, respectively).

Table 1. *Low- and high-pass filters that were used for the visual evoked potentials (VEP) monitoring in the analyzed group of patients*

High-pass filter, Hz	The number of eyes for which VEPs were recorded using the specified frequency filters, *n*						Total, *n*
	Low-pass filter, Hz						
	100	150	200	250	300	350–400	
5	1	6	29	1	0	0	37
10	2	47	196	13	26	2	286
15	2	4	74	6	7	1	94
20	0	2	1	0	0	1	4
Total	*5*	*59*	*300*	*20*	*33*	*4*	*421*

Note. *The table cells show the number of eyes for which the bandwidth determined by the values of the high- and low-pass filters was used when recording VEP. In some cases filter values other than multiples of 5 or 50 (respectively) were used. These cases were counted in the cells corresponding to the nearest multiple of 5 or 50.*

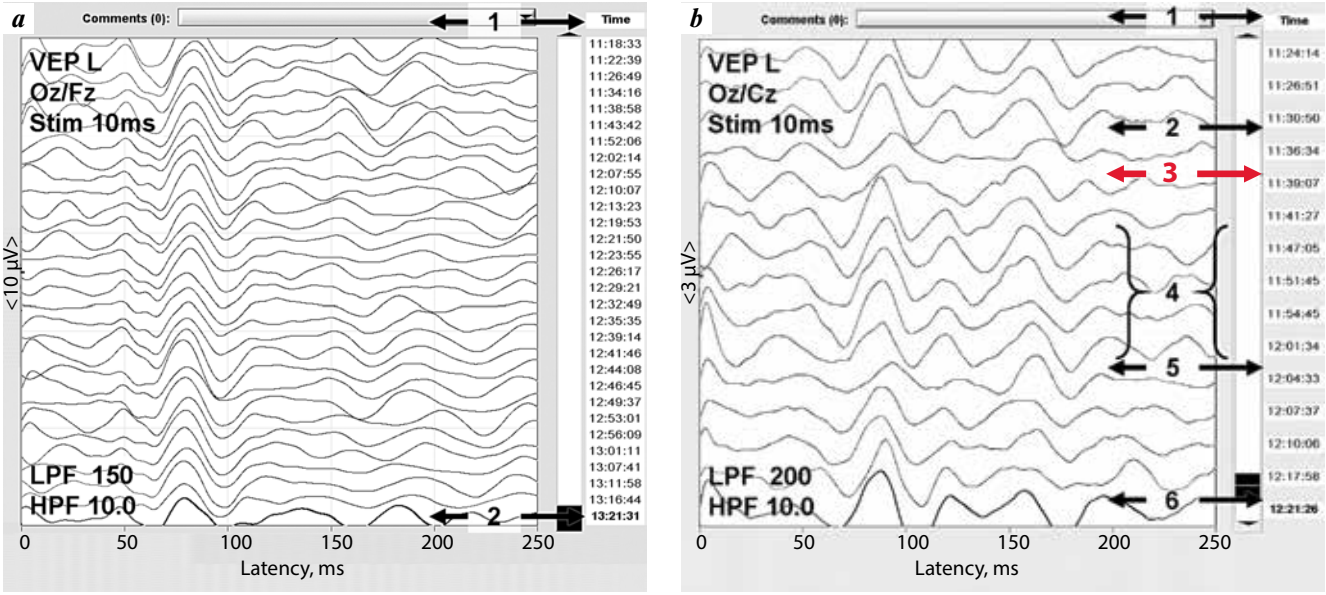

Fig. 2. *Examples of different variants of the dynamics of visual evoked potentials (VEP) characteristics during operations and the relationship between changes in VEPs and intraoperative events: a – no intraoperative changes in VEPs. Female patient, about 55, meningioma in the area of the right wing of the sphenoid bone; before surgery there was no vision in the right eye, the left was not impaired. Pterional approach. No significant changes in the VEPs were observed during monitoring – from the beginning of the operation (1) to the closure of the bone defect (2). Subtotal tumor removal. Vision after the surgery is unchanged; b – temporary decrease in VEP amplitudes with full recovery. Female patient, about 65, meningioma in the area of the left anterior clinoid process; vision was not impaired before surgery. Pterional approach. A reversible decrease of the VEP peaks amplitude associated with the insertion of retractors (2); recovery of responses after changing the position of the retractors (3). No changes in VEPs during removal of the tumor (4). During hemostasis, with coagulation near the optic nerve (5), a short-term VEP decrease occurred followed by complete recovery. At the end of the monitoring session (closure of the dura mater, 6), VEP characteristics were at the initial level. Total tumor removal. Vision after the surgery is unchanged; c – temporary disappearance of VEPs with complete recovery. Male patient, about 55, pituitary macroadenoma; normal vision before surgery. Transnasal approach. After opening the sellar floor (1) and the dura mater incision (2), there were no VEP changes. After opening the tumor cyst (3), its contents were suctioned quickly, then VEPs disappeared (4). Tumor removal was suspended, in 20 minutes VEPs were restored, and removal was continued (5). After reconstruction of the sellar region, a Foley catheter was placed to provide temporary support, but its inflation (6) led to the disappearance of VEPs. The catheter was removed (7) and in 10 minutes VEPs were restored. After support was provided with another method and nasal tamponade was performed (8), VEPs were at the initial level. Partial tumor removal. Vision after the surgery is unchanged; d – significant decrease in VEP amplitudes with partial recovery. Male patient, about 60, olfactory neuroblastoma, vision was normal before surgery. Projection approach. When surgery began (1) VEPs were well-identified, with moderate reproducibility. During removal of the tumor, there was a significant decrease in VEP amplitudes to the right eye stimulation (2), and subsequently unstable low-amplitude responses, reduction to indistinguishability (3). Under hemostasis (4), partial recovery to 40–50 % of the initial level occured. Partial tumor removal. Vision after the surgery is unchanged; e – significant decrease in VEP amplitudes without recovery. Female, more than 70, cavernous malformation in the occipital lobe, episodes of visual impairment on the left before surgery. Projection approach. From the beginning of the operation (1) until the dural opening (2), the VEPs were stable. Under further approach, removal of the malformation, and hemostasis (3), N100 peak amplitudes decreased unilaterally by approximately 50%; this change persisted through the stages of dural closure and cranioplasty (4) and until completion of the operation. Total malformation removal. After the surgery there was left-sided upper quadrant hemianopsia; f – increase in amplitudes and decrease in latencies of VEPs. Female patient, about 30, pituitary adenoma; before surgery, vision acuity was reduced in both eyes, and visual fields were partially lost bitemporally. Transnasal approach. From the beginning of the operation (1) VEPs were with moderate*

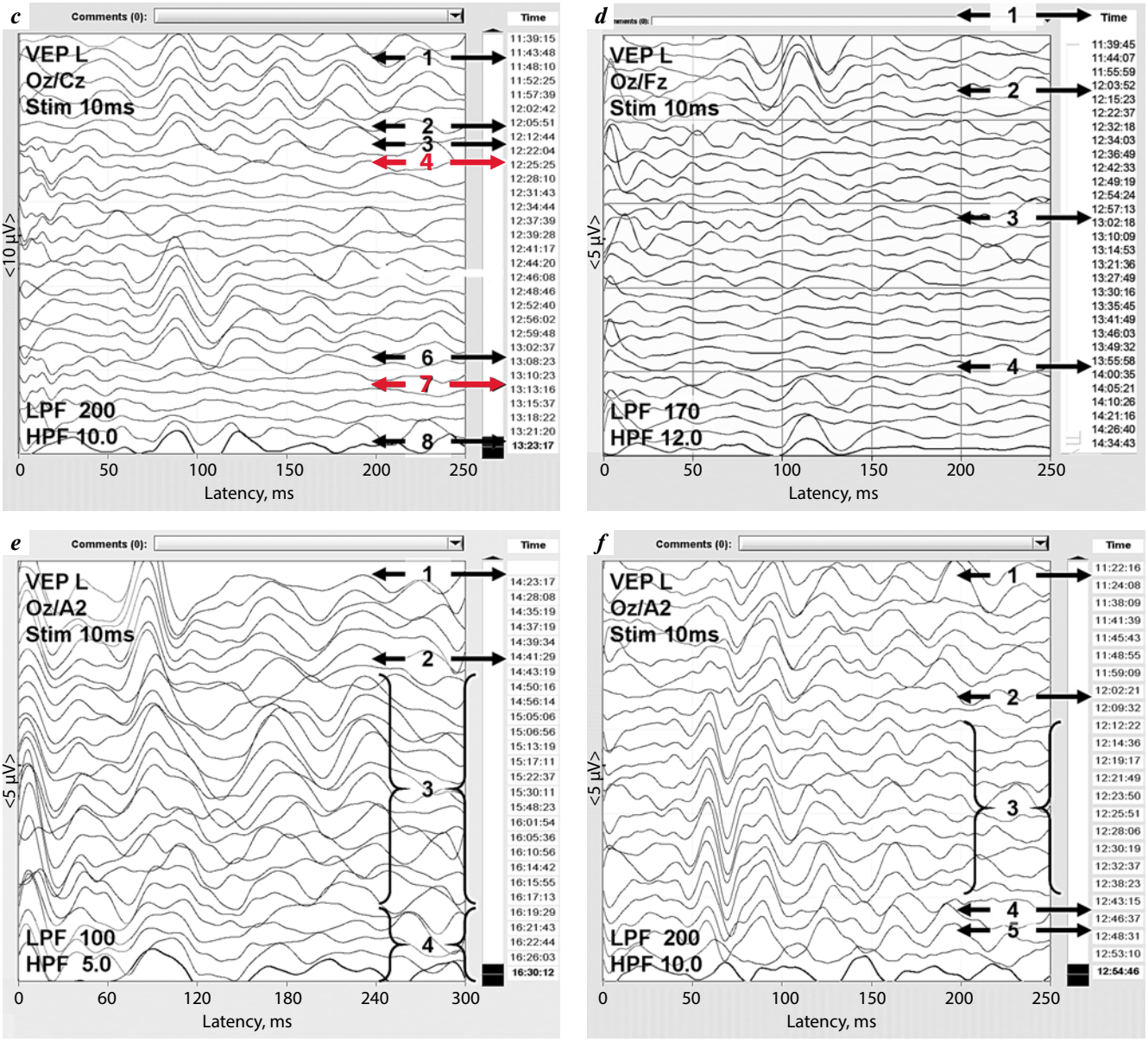

Fig. 2. *(continuation) reproducibility, without significant changes. After opening the bone (2), the amplitudes of VEP increased and the latencies decreased (presumably due to decompression of the chiasm). During adenoma removal and hemostasis (3), VEPs did not change significantly until switching to sevoflurane anesthesia (5) after the bone window closure (4). As the respiratory circuit was saturated with sevoflurane, the amplitudes of VEP peaks decreased and the latencies increased. Total tumor removal. After the surgery, visual acuity improved and visual fields were restored*

The difference in outcomes between groups 2 and 3 was also statistically significant ($\chi^2 = 19.5$, df = 2, $p = 0.0002$).

Sensitivity, specificity and predictive value of intraoperative VEP monitoring. For evaluation of VEP monitoring effectiveness, data on 397 eyes were used for which VEP could be registered during the whole operation and vision could be evaluated in the postoperative period. VEP registration during IOM is performed multiple times, therefore VEP changes can be interpreted differently: all cases of decreased and/or slowed VEPs (1st variant) or only changes that persisted by the end of monitoring (2nd variant) can be considered "positive" changes (registration of signs of visual impairment). This leads to significant differences in characteristics of IOM VEP effectiveness. In the 2nd variant, sensitivity value is relatively low (45.8 %) while specificity value is high (90.9 %). In the 1st variant, both values are intermediate (70.8 and 69.7 % for sensitivity and specificity, respectively). The 1st and 2nd variant are presented on the lower curve in Fig. 3. NPV value is high (97.4 and 96.3 %), while PPV value is low (13.1 and 24.4 %) in both cases (1st and 2nd variants, respectively).

Radicality of space-occupying lesion resection with and without monitoring. Among 240 surgeries, total resection was achieved in 106 (44.2 %) cases, subtotal in 64 (26.7 %) cases, partial in 70 (29.2 %) cases. Considering VEP monitoring characteristics, the surgeries were divided into

Table 2. *Interactions between intraoperative visual evoked potentials (VEP) monitoring results and postoperative changes in vision*

Intraoperative VEP changes	Postoperative changes in vision, *n* (%)				Total, *n*
	Improved	No changes	Worsened	No data*	
No signs of new impairments in vision (group 1)	17 (6.3)	243 (90.7)	7 (2.6)	1 (0.4)	268
Signs of temporal impairments with subsequent full recovery (group 2)	10 (11.2)	69 (77.5)	6 (6.7)	4 (4.5)	89
Signs of impairments with no or partial recovery (group 3)	1 (1.8)	33 (57.9)	11 (19.3)	12 (21.1)	57
VEP monitoring unavailable (group 4)**	4 (8.5)	31 (66.0)	8 (17.0)	4 (8.5)	47
Total, n	*32*	*376*	*32*	*21*	*461*

**Evaluation of vision after surgery was impossible due to severe complications unrelated to the visual system developed in the postoperative period. **VEPs either became unobtainable during surgery due to excessive deepening of anesthesia or technical problems, or were unobtainable from the beginning of surgery.*
Note. *The table cells represent the number of eyes for which a certain combination of intraoperative VEP changes and postoperative changes in vision were observed. The percentages of certain postoperative outcomes for each type of intraoperative VEP changes are indicated in parentheses. 19 eyes with preoperative amaurosis were excluded from the analysis.*

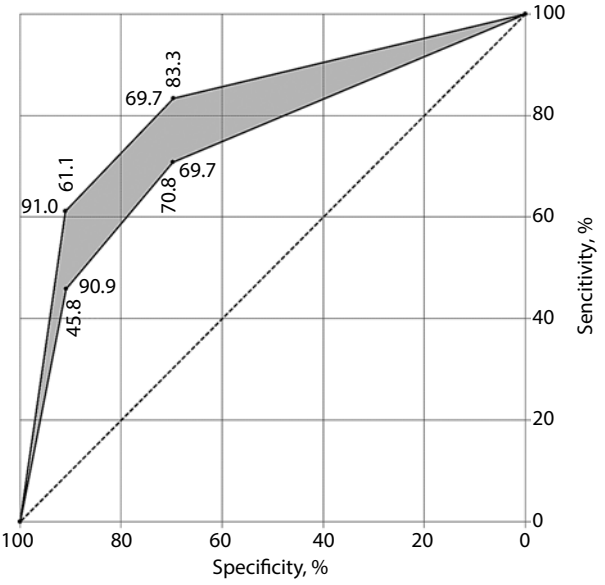

Fig. 3. *Sensitivity and specificity estimates for intraoperative visual evoked potentials (VEP) monitoring with different variants of monitoring results interpretation. Lower graph: all cases of postsurgical new visual dysfunctions with lacking signs of disturbed visual function during VEP monitoring are interpreted as false negatives. Upper graph: cases with early postoperative complications that can cause visual disturbances are excluded from the false negative subgroup. Left points in both graphs: only cases with clinically significant decrease of amplitudes and/or increase of latencies of VEPs persisted until the end of VEP monitoring, are considered the positive cases. Right points in both graphs: all the cases with the abovementioned VEP changes, including the cases with changes being temporary and followed by full VEP recovery, are interpreted as positive cases. Filled area represent possible locations of sensitivity/specificity graphs for interjacent variants of interpretation of VEP monitoring results*

3 groups: 1) successful monitoring for both eyes (or 1 if the second was diagnosed with amaurosis prior to surgery), alarm signals were absent; 2) successful monitoring, alarm signals were present; 3) monitoring is unavailable for 1 or both eyes. Characteristics of surgical radicality for each group are presented in Fig. 4, *a*. With monitoring, the percentage of radical surgeries was significantly higher than when it was unavailable; if monitoring for at least 1 eye was unavailable, almost half of the surgeries achieved only partial resection. Intergroup differences were statistically significant with inclusion of all groups into analysis ($\chi^2 = 12.7$, df = 4, $p = 0.013$) and between groups 1 and 3 ($\chi^2 = 12.5$, df = 2, $p = 0.0019$); differences between surgery groups 2 and 3 had a level of a trend ($\chi^2 = 5.66$, df = 2, $p = 0.059$), and the differences between surgery groups 1 and 2 were insignificant ($\chi^2 = 1.88$, df = 2, $p = 0.39$).

DISCUSSION

Factors affecting feasibility of intraoperative VEP monitoring. Intraoperative VEP monitoring was performed in 90 % of eyes without preoperative amaurosis including 98 % of eyes without visual impairment prior to surgery. Other authors report similar results: between 85 and 97 % for all eyes and up to 100 % for eyes without preoperative visual impairment [12]. It should be noted that we had attempted to control VEPs in all surgeries associated with risk to the visual system and did not exclude patients with severe visual impairment and surgeries using sevoflurane out of necessity. Both factors, expectedly, significantly decreased probability of successful intraoperative VEP registration (to 62 and 81 %, respectively). Other modern publications on IOM VEP always emphasize that propofol TIVA is preferable to inhalation anesthesia [12, 13].

The significant effect of approach type was more unexpected: for approaches to the anterior cranial fossa (subfrontal, supraorbital), the percentage of unsuccessful attempts of VEP monitoring (18.3 %) was 3–6 times higher than for other approaches. Additional analysis had shown that anesthesia regimens in different types of approach did not differ significantly, while there were intergroup differences in preoperative vision impairment which, however, do not explain the differences in successfulness of VEP monitoring. While the percentage of eyes with

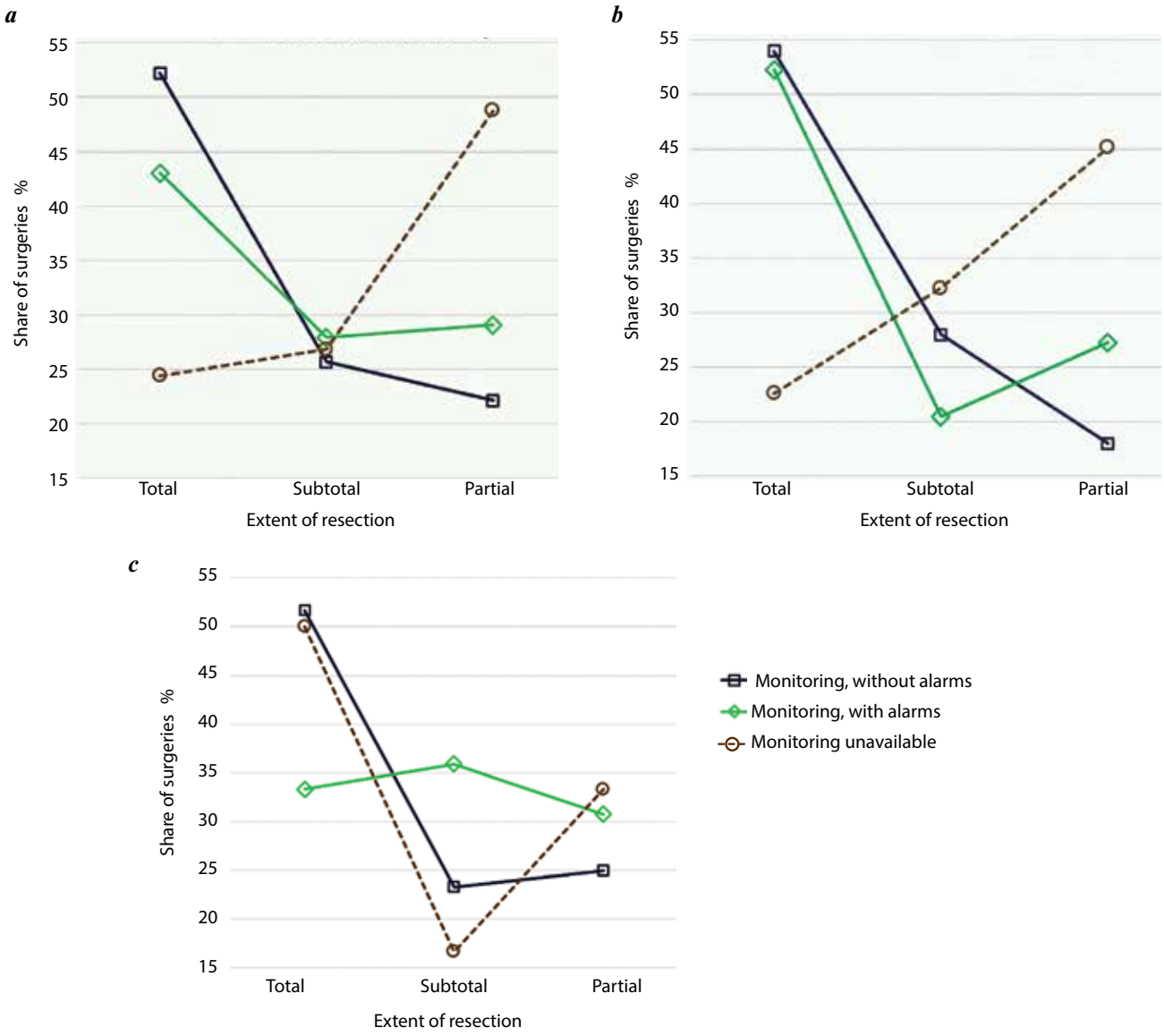

Fig. 4. *Interaction between surgical radicality and intraoperative visual evoked potentials (VEP) monitoring obtainability and results: a – data for all surgeries; b – data for the surgeries in patients with preoperative visual dysfunctions (excluding the eyes with amaurosis); c – data for the surgeries in patients without preoperative visual dysfunctions (excluding the eyes with amaurosis). Solid blue line (all panels): VEP monitoring was successful for both eyes (or one, if there was preoperative amaurosis in the other); no clinically significant signs of new visual dysfunctions were observed in the VEPs. Solid green line: the same as above, but clinically significant signs of new visual dysfunctions were observed in the VEPs with alarm issued for the surgeons. Dashed line: VEP monitoring attempt failed for at least one eye without amaurosis*

preoperative visual impairment was significantly higher in subfrontal and supraorbital approaches (48 %) compared to pterional and projection (23 %) approaches, for transnasal surgeries it was even higher (57 %). Additional information is necessary to explain the correlation between the type of approach and the probability of successful VEP monitoring. On the other hand, histological type of the resected lesion, patient sex and age did not show significant correlation with feasibility of VEP monitoring.

Personalized approach to selection of registration parameters and signal processing during VEP monitoring. The standards for intraoperative VEP monitoring have not been yet developed, and there is no consensus on the optimal parameters for signal registration and processing during such monitoring. In the majority of publications, the authors describe their techniques without explanation of their choices. In our work, we have used personalized approach to VEP monitoring which allowed us to select conditions suitable for each specific surgery. For this purpose, as described in the "Materials and methods" section, we selected bandwidth for frequency filter and reference electrode. Both of these selections had the same goal: to increase the signal/noise ratio. It is important to note that in the context of IOM VEP, noise includes not only external interferences, but also spontaneous bioelectric activity of the brain not associated with processing of visual

stimuli (in particular, EEG rhythms). Better signal/noise ratio allowed to increase VEP reproducibility and decrease the averaging number necessary to evaluate VEPs. As a result, we were able to decrease intervals between subsequent VEP registrations and warn surgeons about the signs of negative effects on the visual system earlier. Consequently, this increases the probability of surgical tactics correction before these effects become irreversible.

The selected upper and lower limits of frequency filter bandwidth were quite wide in the analyzed patient group (see Table 1) which can be explained by significant variability of background EGG rhythms [14] with added variability caused by the effect of anesthesia [15, 16]. Additionally, characteristics of VEPs themselves varied between patients; in particular, period of the main oscillation also limited filter values, especially for the high frequency filter. Essentially, the goal was to find the right balance between maximally possible noise suppression and reasonably low VEP suppression. Conversely, higher frequency filter in many cases cut low-frequency VEP components which changed response shape (see Fig. 1, *b*) compared to the shape obtained using the standard frequency filter bandwidth (1–100 Hz) used for clinical VEP registration. However, this is not a problem in the context of IOM as the goal is to prevent iatrogenic neurological abnormalities. Identification of intraoperative changes of functional condition of the visual system requires only registration of VEP changes compared to the initial values, and there is no need to compare these values with the reference values. Analysis performed by us earlier [17] showed that VEP amplitudes and latencies change similarly due to manipulations affecting transmission along the visual pathways in a wide range of frequency filter settings. For high frequency filter 10–20 Hz, reproducible VEP peaks can be obtained after only 20–50 averages in most cases (see Fig. 1, *c*), while at 1–5 Hz same reproducibility requires 50–100 averages. It happens because when the lower limit of frequency filter bandwidth is increased, the highest amplitudes of background EEG activity in the range are cut [18]. This significantly increases the signal/noise ratio, and the required averaging number is inversely proportional to the square root of this ratio [19]. Therefore, increasing the lower limit of the frequency filter bandwidth to 10–15 Hz allows to decrease the time interval between consecutive checks of the functional condition of the visual system approximately 2–3-fold without decreasing sensitivity.

Another approach to improve the signal/noise ratio is selection of active and reference electrode pairs. In guidelines on clinical VEP registration, Fz electrode (medial frontal region) is recommended to be used as reference, while Oz, O1 and O2 electrodes (medial, left and right parietal zones, respectively) should be used as active [19, 20]. However, under propofol anesthesia, anteriorization of α rhythm is observed, i. e. its weakening in the parietal region with significant amplification in the frontal region [21]; sevoflurane can also cause this effect but only in some patients [15]. In the temporal regions, these changes do not occur, and installation of reference electrodes there can decrease the noise level as was done by several authors [3, 8, 18] but without explanation of such selection. Meanwhile, if motor functions (for example, of the nerves of the oculomotor group) have to be monitored, low myorelaxation level must be maintained and, in this case, spontaneous myographic activity of the temporal muscle can create noise in reference electrodes located in the temporal region. In this case, medial anterior occipital area (CPz electrode) can be better as it is sufficiently removed from the head muscles and is located at the periphery of increased α activity. Reference electrode in this area was used by E. M. Gutzwiller et al. [6]. We have tested all 3 variants of reference electrode locations during VEP monitoring. At individual level, in many cases one was clearly superior compared to the others but in group analysis there is no preferential location for reference electrodes: the numbers of surgeries for each of the 3 variants were similar.

Therefore, both lead pairs and frequency filter bandwidths should be selected individually to maximize VEP reproducibility in each specific patient. This requires 2–4 curves for each eye obtained in identical conditions. The selection itself takes some time, so it is preferable to be able to perform VEP registration after patient setup before the start of the surgery.

Apart from the above described methods of signal/noise reduction, in some cases (if signs of response attenuation were present), we also decreased light stimulation frequency from ~1 to 0.5–0.7 Hz. Unfortunately, this practice was not always registered in the protocol and cannot be analyzed.

Evaluation of VEP monitoring effectiveness in the context of detection and prevention of iatrogenic visual impairment. The results of analysis of the data presented in Table 2 indicate a significant correlation between signs of intraoperative visual impairment detected through VEP and postoperative visual impairment.

To evaluate the effectiveness of VEP monitoring we tried to use traditional characteristics of effectiveness of diagnostic methods: sensitivity, specificity, PPV and NPV. Our NPV value (>96 %) and specificity (70 or 90 % depending on the choice of intraoperative criteria) are quite high while PPV value and sensitivity could cast doubt on the effectiveness of VEP monitoring. In fact, while IOM VEP sensitivity estimates measured in our study (71 or 46 % depending on the calculation methos) are similar to data from other studies where it was 47.2 % [22], 66.7 % [6] and 75 % [23], percentage of "missed" abnormalities remains high. However, analysis of medical histories showed that in the early postoperative period complications that could lead to visual impairment were observed in 6 of 13 cases while IOM results were interpreted as false negative (in 4 of 7 cases without decreased VEP and/or slowdown and in 2 of 6 cases in which VEPs completely restored after temporary decrease and/or slowdown). If vision worsened due to these complications and not due to intraoperative

manipulations, then these cases should be considered not false negative but true negative. In this case, sensitivity estimates are significantly higher (upper curve in Fig. 3) and other characteristics of IOM VEP effectiveness change insignificantly.

Formal evaluation of IOM VEP specificity and PPV can also be significantly undervalued due to another reason: postoperative outcomes are not independent from VEP monitoring data. In fact, when surgeons receive information about VEP increased latency or decreased amplitude they, if possible, change intervention tactics to decrease the negative effect upon the visual system. If this allows to avoid postoperative visual impairment, neuromonitoring successfully achieved its goal. However, according to formal approach, this case would be categorized as false positive signal which decreases PPV and specificity estimates. Unfortunately, in medical documentation these cases of changing tactics were not always noted which prevents statistical analysis. The link between surgical tactics alteration and prevention of iatrogenic damage is apparent in cases of VEP restoration after such change. Illustrative examples of such cases are presented in Fig. 2, *b, c*.

Effect of VEP monitoring on radicality of space-occupying lesion resection. At the group level, percentage of radical surgeries was significantly higher with monitoring than without it. The usual explanation for this result is that surgeons are more assured of the safety of their manipulations when monitoring is present [24]. However, location of lesions in close proximity to the visual pathways unidirectionally affects both feasibility of VEP monitoring and possibility of radical surgery, and this effect can explain the observed pattern. An indirect sign of such lesion localization can be the presence of preoperative visual impairment. To make up for this effect, we divided patients into subgroups without impairment, with moderate impairment, and with severe impairment. The number of cases of VEP monitoring unavailability sufficient for statistical analysis was found only in the subgroup with moderate impairment. In this subgroup (Fig. 4, *b*), the pattern of association between surgical radicality and VEP monitoring remains the same as for all patients (see Fig. 4, *a*) which indicates a correlation between the presence of monitoring and increased surgical radicality. Meanwhile, in the subgroup without preoperative visual impairment, another statistically significant correlation was found (Fig. 4, *c*): if alarms were raised during monitoring, the percentage of subtotal resections increased at the expense of the number of total resections. Supposedly, in this subgroup preservation of visual function was more important than surgical radicality.

Study limitations. Our study is limited by its retrospective character and the fact that it was performed at a single center. However, a traditional randomized trial to compare effectiveness of various VEP monitoring techniques is not possible due to ethical considerations. Nevertheless, search for the optimal parameters of bioelectric signal processing (filtering parameters, selection of electrode combinations) can be performed through comparison of these options using previously recorded data which does not pose ethical problems. to achieve this, complete unprocessed initial data should be recorded in parallel with IOM. Currently, we are performing such study.

Additionally, we did not use some of the methods to increase IOM VEP effectiveness proposed by other authors. In particular, we did not use alternative techniques to achieve VEP such as off-response (reaction to cessation of light stimulus) [8, 10] and double stimulation [9]; did not use mydriatics [25] and additional light-intercepting coverings [6] to increase intensity and contrast of the retinal stimuli. The effects of these methods on feasibility and quality of intraoperative VEP registration require further research.

CONCLUSION

Generally, VEP monitoring was an effective method of intraoperative control of the visual system functioning. Direct evaluation of the number of prevented iatrogenic impairments due to IOM VEP is complicated but there are indirect signs that it is quite high. Moreover, VEP monitoring increases both surgical safety and radicality. Personalized parameter selection maximizing VEP reproducibility minimizes averaging number and time to obtain VEPs. This allows surgeons to obtain information about the signs of abnormalities earlier and alter surgical tactics before irreversible damage occurs.

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Authors' contribution
E.A. Levin: research design development, data processing and analysis, writing the article, editing the article;
M.G. Kilchukov: data obtaining and analysis;
A.A. Glushaeva: data obtaining and analysis, editing of the article.

ORCID of the authors
E.A. Levin: https://orcid.org/0000-0002-1338-5881
M.G. Kilchukov: https://orcid.org/0000-0002-2395-7177
A.A. Glushaeva: https://orcid.org/0009-0000-1145-3732

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