Research paper

The utility of intraoperative neurophysiological monitoring in surgical treatment for spinal arteriovenous malformations: A historical control study

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\textbf{Abstract}

Objectives: This study sought to investigate the utility of intraoperative neurophysiological monitoring (IONM) in the surgical treatment for spinal arteriovenous malformations (SAVMs).

Methods: We retrospectively reviewed the data of 39 patients who underwent surgical treatment for SAVMs. Twenty-eight patients who received multimodal IONM (transcranial electrical motor-evoked potentials [MEPs], somatosensory-evoked potentials, continuous electromyography, and bulbocavernous reflex [BCR]) between 2011 and 2020 were compared to 11 historical controls between 2003 and 2011. The rates of postoperative neurological deficits (PNDs), neurophysiological warnings, and their characteristics were analyzed.

Results: PNDs were developed in 10.7% and 54.5% of patients in the IONM and historical control (non-IONM) groups, respectively \((p = 0.008)\). Moreover, not applying IONM was the only significant risk factor for the development of PNDs in the logistic regression analysis \((\text{odds ratio } 10.0, p = 0.007)\). In the IONM group, a total of three electrophysiological warnings were observed, and two of these were true positives; one patient complained of leg motor weakness after surgery with loss of the abductor hallucis MEPs. The other patient experienced disappearance of the BCR during surgery and newly developed urinary retention. Overall, the sensitivity, specificity, positive predictive value, and negative predictive value of IONM warnings for detecting PNDs were 66.7%, 96.0%, 66.7%, and 96.0%, respectively.

Conclusions: The neurological outcome of the IONM group was significantly better than that of the historical control group in the surgical treatments for SAVMs.

Significance: Multimodal IONM could be a useful tool to detect neurological damage with relatively high accuracy in this type of surgery.

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1. Introduction

Spinal arteriovenous malformations (SAVMs) are extremely rare and are present in only 3% of all spinal cord lesions (Khrings, 2010, Lakhdar et al., 2019, Ortega-Suero et al., 2018). SAVMs cause progressive neurological complications once symptoms occur, leading to venous hypertension and dysregulation of spinal blood flow (Chung et al., 1997, Ghadirpour et al., 2018, Lakhdar et al., 2010, Narvid et al., 2008, Takai et al., 2015, Taskiran et al., 2019). There are two main approaches for the treatment of SAVMs (Eskandar et al., 2002, Flores et al., 2017, Mourier et al., 1993). Although recent advances in endovascular treatments have significantly improved operative outcomes, surgical treatment is a straightforward procedure with a high success rate and low recurrence rate (Ghadirpour et al., 2018, Koch et al., 2004, McCutcheon et al., 1996, Morimoto et al., 1992, Tacconi et al., 1997). Long-term postoperative neurological deficits (PNDs) of surgical treatment were reported to have an incidence of 6% (Saladino et al., 2010).

Multimodal intraoperative neurophysiological monitoring (IONM) in surgical treatment for SAVMs is being applied to reduce these PNDs. However, unlike in endovascular treatment, there remains a lack of evidence in support of the clinical significance of multimodal IONM in SAVM surgical treatment (Jahangiri et al., 2014, 2019).
Although some cases revealing the usefulness of IONM in surgical treatment have been previously reported (Ghadirpour et al., 2018, Gopalakrishna et al., 2020), a study comparing outcomes with those of a control group has not been carried out. Therefore, this study aimed to investigate the utility of IONM in SAVM surgical treatment by comparing it with a historical control group.

2. Methods

2.1. Ethics

This study was approved by the appropriate institutional review board. All procedures were performed in accordance with the Declaration of Helsinki.

2.2. Participants

We retrospectively reviewed the data of 39 patients who underwent surgical treatments for SAVMs. The 28 patients who underwent multimodal IONM (transcranial electrical motor-evoked potentials [tcMEPs], somatosensory-evoked potentials [SSEPs], continuous electromyography [EMG], and the bulbocavernous reflex [BCR]) from May 2011 to August 2020 were classified as the IONM group. The 11 historical controls that did not undergo IONM from July 2003 to April 2011 were classified as the non-IONM group. Demographic and clinical data, including age, sex, body mass index, presence of myelopathy, types of SAVMs, lesion location and extent, symptom duration, operation time, estimated blood loss, pre- and postoperative neurological state classified according to the Aminoff–Logue Disability Scales for Gait (G-ALS) and Micturition (M*ALS) (Ghadirpour et al., 2018), and follow-up period, were analyzed. The lesion extent was evaluated by the number of vertebral bodies in which high signal intensities were observed on the T2 sagittal view of preoperative spinal magnetic resonance imaging.

2.3. Anesthesia

Total intravenous anesthesia regimens with propofol (3.0–4.0 µg/mL) and remifentanil (1.5–4.0 µg/mL) were applied in all patients. Neuromuscular blockage (rocuronium 0.5–1.0 mg/kg) was only used on anesthesia intubation and not during surgery to minimize confounding effects on IONM parameters.

2.4. IONM and warning criteria

A neurophysiologic workstation (Xltek protector 32 IOM system; Natus Medical Inc., Oakville, ON, Canada) was used to record tcMEPs, SSEPs, EMG, and BCR signals. A commercially available electrical stimulator (D185 stimulator; Digitimer Ltd., Welwyn Garden City, Hertfordshire, UK) was applied for tcMEP stimulation.

2.4.1. tcMEP

Subcutaneous needle electrodes were placed following the international 10–20 electroencephalography system to deliver stimulation. The C3-anode/C4-cathode pairs or the C1-anode/C2-cathode pairs were used for stimulation of the unilateral hemisphere, and the reverse arrangement was used for stimulation of the other hemisphere. Five square-wave electrical pulse stimuli in inter-stimulus intervals of 2–4 ms were delivered with a 50-µs pulse width at an intensity of 250–500 V. For the upper limbs, tcMEPs were recorded in the bilateral abductor pollicis brevis muscles. For the lower limbs, tcMEPs were recorded in the bilateral vastus lateralis (VL), tibialis anterior (TA), and abductor hallucis (AH) muscles to monitor corticospinal tract function. A permanent loss of tcMEP signals was considered reflective of significant changes.

2.4.2. SSEPs

SSEPs were triggered by stimulation of the bilateral median and posterior tibial nerves. Square-wave electrical pulses of 0.3 ms in duration and 10–20 mA in intensity were used for the upper extremities and pulses of 20–30 mA in intensity were used for the lower extremities at a frequency of 2.31 Hz. Recording electrodes were placed at C3’ (2 cm posterior to C3); C4’ (2 cm posterior to C4), and Cz’ (2 cm posterior to CZ) referenced to FPz via scalp electrodes according to the international 10–20 system. SSEPs were assessed every 60 s during surgery. A permanent decrease in SEP amplitude of more than 50% compared to baseline and/or a tendency toward an increased latency by more than 10% were considered reflective of significant changes.

2.4.3. Continuous EMG

EMG activities in the bilateral VL, TA, AH, and anal sphincter muscles were recorded using stainless steel 25-mm paired needle electrodes. Sustained neurotonic EMG activities were considered reflective of significant changes.

2.4.4. BCR

The BCRs were monitored according to the technique described by Deletis et al. (Deletis and Vodusek, 1997). One set of surface electrodes was used to stimulate the dorsal penile or clitoral nerve. We elicited stable BCR responses using a train of 4–8 constant-current stimuli with an inter-stimulus interval of 2 ms, a duration of 0.1 ms, and an intensity of 20–40 mA. Two pairs of needle electrodes for bipolar recording were subdermally inserted into the bilateral external anal sphincter muscles. Significant change was defined as a persistent loss of unilateral or bilateral BCR responses.

2.5. Evaluation of postoperative neurological deficits

PNDs were defined as any newly observed postoperative motor or sensory deficit or urinary difficulty lasting until discharge. A postoperative motor deficit was defined as a score increasing by more than 1 point in the G-ALS. Worsening sensory function was defined when the severity or extent of symptoms increased to levels exceeding those prior to surgery or when sensory symptoms newly occurred. A urinary-function deficit was defined as a score increasing by more than 1 point in the M-ALS. The postoperative neurological status was evaluated at 1 month, 6 months, and 1 year after surgery.

2.6. Data analysis

We classified patients into four groups in accordance with electrophysiological warnings during operation and postoperative outcomes. These consisted of true-positive, false-positive, true-negative, and false-negative groups. Baseline characteristics of patients were analyzed using a Mann–Whitney U test and Fisher’s exact test. Chi-squared test was used to compare the rate of deficits between the groups. We conducted a multivariate logistic regression analysis including variables with p values less than 0.10 in a univariate logistic regression analysis and used a forward selection approach. Statistical analyses were carried out using the IBM Statistical Package for the Social Sciences (software version 22, Armonk, NY, USA). A p value <0.05 was considered statistically significant.
3. Results

3.1. Demographic and clinical characteristics

In total, 28 patients in the IONM group and 11 patients in the non-IONM group underwent surgical treatment for SAVMs during the study period. Thirty male patients and nine female patients were enrolled in the study, and their mean age (± standard deviation) was 55.1 ± 14.2 years (range, 22–77 years). No significant differences were observed in demographic features between the groups for all variables except for age. The demographic features of the IONM and non-IONM patients who underwent surgical treatment for SAVMs are presented in Table 1.

Table 1
Demographic and clinical characteristics of IONM and non-IONM patients who underwent surgical treatment for SAVMs.

|                      | IONM group (n = 28) | non-IONM group (n = 11) | p value |
|----------------------|---------------------|-------------------------|---------|
| Sex (male)           | 22                  | 8                       | 0.69    |
| Age (years)          | 58.1 ± 13.7         | 47.4 ± 13.2             | 0.04    |
| Body mass index (kg/m²) | 23.5 ± 3.4        | 22.2 ± 3.3              | 0.30    |
| Types of SAVMs       |                     |                         |         |
| Dural AVF            | 15                  | 4                       |         |
| Perimedullary AVF    | 13                  | 7                       | 1.00    |
| Location of lesion   |                     |                         |         |
| Cervical             | 2                   | 0                       |         |
| Thoracic             | 16                  | 7                       |         |
| Lumbosacral          | 7                   | 3                       |         |
| Extent of lesion     | 2.2 ± 1.4           | 1.9 ± 0.7               | 0.55    |
| With intramedullary  | 1/28                | 1/11                    | 0.49    |
| hemorrhage           |                     |                         |         |
| With myelopathy      | 21/28               | 10/11                   | 0.40    |
| Operation time (minute) | 260.5 ± 141.9     | 249.6 ± 66.3            | 0.81    |
| Estimated blood loss (ml) | 644.6 ± 1500.1   | 559.1 ± 960.2           | 0.83    |
| Duration of symptom  | 17.2 ± 33.5         | 33.0 ± 46.1             | 0.24    |
| (month)              |                     |                         |         |
| Preoperative G-ALS   | 2.2 ± 1.5           | 1.7 ± 1.8               | 0.45    |
| Preoperative M-ALS   | 0.9 ± 0.9           | 1.2 ± 0.8               | 0.37    |
| Follow up period (month) | 21.5 ± 21.5      | 41.9 ± 68.9             | 0.13    |

SAVMs, spinal arteriovenous malformations; AVF, arteriovenous fistula; G-ALS, Aminoff-Logue Disability Scale for Gait; M-ALS, Aminoff-Logue Disability Scale for Micturition; IONM, intraoperative neurophysiological monitoring.

3.2. Postoperative neurological deficits

PNDs were observed in three patients (10.7%) in the IONM group and in six patients (54.5%) in the non-IONM group (p = 0.008). PNDs in the IONM group developed in three patients with leg weakness and sphincter changes (one, both leg weakness, and two, voiding difficulty). Details of neurological deficits in the IONM and non-IONM groups are shown in Table 2. Regarding the serial changes in G-ALS/M-ALS after surgery compared to the initial scores (before surgery) in the IONM and non-IONM groups (Table 3), no significant differences were observed between the groups; however, these results showed that the IONM group tended to have a better prognosis than the non-IONM group. Additionally, we analyzed the associated factors, including the application of IONM for the development of PNDs using a multivariate logistic regression model (Table 4). The application of IONM was the only variable that was significantly associated with PNDs after adjustment. Non-application of IONM increased the risk of newly occurring PNDs (odds ratio: 10.0, p = 0.007, 95% confidence interval: 1.85–53.98).

3.3. Characteristics of IONM warnings

In all 28 patients in the IONM group, 13 were monitored with tcMEPs and SSEPs and eight were monitored with triple modalities comprising tcMEPs, SSEPs, and continuous EMG. The seven remaining patients were monitored with quadruple modalities, including tcMEPs, SSEPs, continuous EMG, and the BCR. In total, three warnings were observed during IONM. Of these, one patient had a tcMEP warning, one had a tcMEP and a SSEP warning, and one had an isolated BCR warning. Two of these cases were true positives (Patients 1 and 2 in Table 2) and the one remaining case was a false positive. In the false-positive case, both the MEP and SSEP of the unilateral leg had disappeared. However, significant PNDs were not observed in this patient. In contrast, there was one false-negative case (Patient 3 in Table 2). The patient had newly observed voiding difficulty after surgery and needed clean intermittent catheterization (CIC) for approximately 1 year postoperatively. In this case, triple modalities except the BCR were applied, and there were no changes in IONM parameters, including EMGs of the anal sphincter muscles. Overall, the sensitivity, speci-
ficity, positive predictive value (PPV), and negative predictive value (NPV) of IONM warnings for detecting PNDs in our study were 66.7%, 96.0%, 66.7%, and 96.0%, respectively (Table 5).

3.4. Illustrative case

Case. A 45-year-old man (Patient No.2 at Table 2) presented with right leg weakness and sensory change in the right side below T10 segmental level that occurred three weeks ago. Preoperative spine magnetic resonance imaging demonstrated engorged perimedullary vessels from T12 to S1 level accompanied by venous infarction at T10 to T12 level (Fig. 1-A). Spinal angiography revealed the perimedullary arteriovenous fistula (AVF) supplied by the anterior spinal artery from the left T8 level (Fig. 1-B). The laminotomy and ligation of AVF were performed with multimodal IONM. The tcMEPs of bilateral AH showed a significant decrement in the amplitude of more than 80% from the baseline after the temporary clipping, and bilateral BCR disappeared after a few minutes. After the tcMEP and BCR changes were notified, the surgeon removed the temporary clipping, irrigated the surgical field, and released the retractors. After a while, the amplitudes of tcMEPs of AH were fully recovered at the right side and partially recovered to 30% from the baseline. However, the bilateral BCR was not recovered until the end of surgery (Fig. 1-C). Bilateral SSEPs (not shown) and tcMEPs recording at other limb muscles (abductor digiti quinti and tibialis anterior) did not show significant changes beyond the alarm criteria from the baseline. The patient had severe urinary retention after surgery and needed CIC from discharge to 6 months postoperatively. Furthermore, a urodynamic study suggested neurogenic bladder dysfunction.

4. Discussion

Although some cases and a descriptive study that showed the usefulness of IONM in surgical treatment have been reported, there have been no studies showing the usefulness of IONM compared to a non-IONM historical group. A previous study by Ghadirpour et al. included a total of 12 consecutive patients who received surgical

| Table 3 |
| The changes in G-ALS/M-ALS at 1 month, 6 months, and 1 year after surgery compared to the initial score in the IONM and non-IONM groups. |

|                  | IONM group (n = 28) | non-IONM group (n = 11) | p value  |
|------------------|---------------------|-------------------------|----------|
| Preoperative G-ALS | 2.2 ± 1.5           | 1.7 ± 1.8               |          |
| Preoperative M-ALS | 0.9 ± 0.9           | 1.2 ± 0.8               |          |
| Postoperative (1 month) G-ALS | 2.1 ± 1.7       | 2.0 ± 1.3               |          |
| Postoperative (1 month) M-ALS | 1.0 ± 1.0        | 1.3 ± 0.8               |          |
| A1 month G-ALS | -0.1 ± 0.4          | 0.3 ± 1.7               | 0.45     |
| A1 month M-ALS | 0.1 ± 0.5           | 0.1 ± 0.5               | 0.91     |
| Postoperative (6 month) G-ALS | 2.1 ± 1.7        | 1.8 ± 1.5               |          |
| Postoperative (6 month) M-ALS | 1.0 ± 0.9        | 1.7 ± 0.5               |          |
| A6 months G-ALS | -0.2 ± 0.6          | 0.3 ± 1.5               | 0.45     |
| A6 months M-ALS | -0.0 ± 0.6          | 0.3 ± 0.5               | 0.15     |
| A1 year G-ALS | -0.1 ± 0.5          | 0.3 ± 1.3               | 0.48     |
| A1 year M-ALS | -0.1 ± 0.5          | 0.3 ± 0.5               | 0.11     |

G-ALS, Aminoff-Logue Disability Scale for Gait; M-ALS, Aminoff-Logue Disability Scale for Micturition; IONM, intraoperative neurophysiological monitoring; A1 month, score changes between before the surgery and one month after surgery; A6 months, score changes between before the surgery and six months after surgery; A1 year, score changes between before the surgery and one year after surgery.

Table 4

| Univariate analysis | Multivariate analysis |
|--------------------|----------------------|
|                     | p value | OR  | 95% CI, lower | 95% CI, upper |
|                     | p value | OR  | 95% CI, lower | 95% CI, upper |
| *Non-application of IONM (n = 11) | 0.007   | 10.0 | 1.85          | 53.98         |
| Age                 | 0.33    |     |               |               |
| *Male (n = 30)      | 0.08    | 0.08 |               |               |
| *Types of SAVMs (spinal dural AVF, n = 19) | 0.07    | 0.12 |               |               |
| Extent of lesion    | 0.11    |     |               |               |
| Absence of myelopathy (n = 8) | 0.43    |     |               |               |
| Operation time      | 0.42    |     |               |               |
| Estimated blood loss| 0.37    |     |               |               |
| Symptom duration    | 0.58    |     |               |               |
| Preoperative G-ALS  | 0.69    |     |               |               |
| Preoperative M-ALS  | 1.00    |     |               |               |

IONM, intraoperative neurophysiological monitoring; SAVMs, spinal arteriovenous malformations; AVF, arteriovenous fistula; OR, odds ratio; CI, confidence interval; G-ALS, Aminoff-Logue Disability Scale for Gait; M-ALS, Aminoff-Logue Disability Scale for Micturition.

* Covariate with p < 0.10 in univariate analysis (n = 3) were entered in a multivariate logistic analysis model, method stepwise forward (LR).

Table 5

| The accuracy of IONM warnings for detecting postoperative neurological deficits. |
|-------------------------------------|------------------|------------------|------------------|------------------|
| PNDs (–)                            | IONM change (–)  | 24 (true negative) | 1 (false negative) | 25               |
| PNDs (+)                            | IONM change (+)  | 1 (false positive) | 2 (true positive)  | 3                |
| Total (n)                           |                  | 25               | 3                | 28               |

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treatment under multimodal IONM, including tcMEPs, SSEPs, and D-wave for SAVMs; no significant warning of IONM occurred during surgery, and there were no newly observed PNDs in any of the patients. As such, the authors suggested that multimodal IONM would reflect whether PNDs occur or not, and patients with improved IONM parameters after the occlusion of the fistula had greater chances of postoperative improvement ($p = 0.025$) (Ghadirpour et al., 2018). However, this study included a limited number of patients and did not investigate the usefulness of IONM by comparison to a defined control group.

We found a statistically significant relationship between the application of IONM and the occurrence of PNDs in SAVM surgical treatment. In our study, PNDs were observed less frequently in the IONM group than in the historical control group. Moreover, the non-application of IONM was the only significant variable associated with PNDs in the multivariate regression analysis, with a high odds ratio. This result could support the usefulness of multimodal IONM in terms of its ability to reduce PNDs in the surgical treatments for SAVMs. However, in an analysis of the changes in G-ALS/M-ALS scores at 1 month, 6 months, and 1 year after surgery compared to the initial score, no significant differences were observed between the IONM and non-IONM groups, although these results showed that the IONM group tended to have a better prognosis than the non-IONM group. We considered that this might be attributed to the small number of subjects and characteristics of the G-ALS/M-ALS, commonly used in SAVMs. In particular, the range of the G-ALS for each score is broader than that of other scales used to evaluate motor function, such as Medical Research Council grading. Therefore, further studies that address these limitations are needed.

In terms of the accuracy of multimodal IONM in our study, there were one false-positive and one false-negative case resulting in the relative lower sensitivity/PPV compared to specificity/NPV. In the false-positive case with loss of tcMEPs and SSEPs in the right leg, the G-ALS of the patient was already at the lowest score (5) due to severe leg weakness before surgery and could not be counted as a significant PND according to our definition. For the false-negative case, the patient had newly observed voiding difficulty as a significant PND according to our definition. For the false-positive case with loss of tcMEPs and SSEPs in the right leg, the G-ALS of the patient was already at the lowest score (5) due to severe leg weakness before surgery and could not be counted as a significant PND according to our definition. For the false-negative case, the patient had newly observed voiding difficulty as a significant PND according to our definition. The BCRs began to be monitored 2 years later at our center; thus, BCR monitoring was not available in this case. We considered that the application of BCR monitoring could have allowed detecting neural damage related to bladder function in this patient.

Saladino et al. analyzed the PNDs and prognoses in 154 consecutive patients with a spinal dural AVF who underwent surgical treatment as the sole or primary treatment modality. Approximately 15% of patients experienced immediate PNDs after surgery, and, of these, long-term neurological deficits were confirmed in 6% (Saladino et al., 2010). In our study, the rate of PNDs at the time of discharge was 23.1% (IONM group, 10.7%; non-IONM group, 54.5%), and the rate of PNDs after 1 year was 15.4% (IONM group 7.1%, non-IONM group 36.4%). The main reason for the higher rate of PNDs in our cohort compared to that of Saladino may be due to the different compositions of SAVMs. While patients with only a spinal dural AVF were included in the previous study, we enrolled patients with other types of SAVMs, such as a perimedullary AVF, which is known to have a lower obliteration rate than dural AVF (Cho et al., 2013). Approximately half of our patients (51.3%) had a perimedullary AVF, and most PNDs occurred in this group (7 out of 9 cases). Although the proportion of SAVMs type between the IONM and non-IONM groups was not different significantly ($p = 0.48$), and there was no statistically significant relationship between the types of SAVMs and PNDs in our study, the further studies will be needed with a larger sample size to dissect the effect of IONM according to SAVMs type precisely.

Our study has several limitations. First, since we performed a retrospective analysis with a historical control group, we could not measure and reflect the effect of clinical factors except the application of IONM, such as the learning curve effect and introduction of new intraoperative adjuncts (ex. ICG fluorescence), among others. To minimize the influence of these factors other than the application of IONM, a prospective randomized study should be conducted. However, designing prospective randomized controlled studies in the IONM field is unlikely and may evoke ethical concerns because the advocates of IONM techniques point toward the lack of poor outcomes as proof that these monitoring tools have clinical value. In addition, there is increasing evidence regarding the benefits of IONM in various types of surgeries. Consequently, there have been no previous control studies in the IONM field thus far, except for a few historical control studies (Radtke et al., 1989, Sala et al., 2006). Second, the number of subjects in our study was relatively small, and the study was performed at a single tertiary center. If the sample size increases, the relationship between the application of IONM and prognosis according to pathology-related factors, including lesion location and, especially,
type of SAVMs could be meaningfully analyzed. Third, IONM modalities were not identically applied in all patients. BCRs began to be applied in our center in 2015; therefore, they were not applied to patients in the IONM group who underwent surgeries before then. Fourth, we did not evaluate the sensory symptoms using an objective scale. Since sensory symptoms are common in SAVMs, it is necessary to examine for changes in sensory symptoms after surgery. Detailed scales that can objectively evaluate the sensory system are needed in SAVMs in future studies.

5. Conclusions

This study was performed to evaluate the utility of IONM in the surgical treatment for SAVMs. In our study, PNDs were observed less frequently in the IONM group than in the historical control group, and the accuracy of IONM for detecting PNDs was relatively high. In conclusion, this is the first study to reveal the usefulness of multimodal IONM to reduce the risk of PNDs by comparing with a non-IONM historical control group in the surgical treatment for SAVM.

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Conflict of interest

The authors have no relevant financial or non-financial interests to disclose.

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