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Perioperative Neuroprotection with Systemic Hypothermia During Carotid Endarterectomy

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Summary

Prevention of brain injury during carotid endarterectomy (CEA) remains a significant challenge. Moderate controlled systemic hypothermia may serve as a potential neuroprotective measure during these procedures.

Aim of the study. To investigate the neuroprotective effects of moderate systemic hypothermia during CEA.

Materials and methods. Fifty-nine patients undergoing CEA under combined anesthesia were included. Patients were divided into two groups: the hypothermia group (N=33) and the normothermia control group (N=26). Both groups received standard measures to prevent cerebral ischemia. The hypothermia group received additional moderate systemic hypothermia aimed at a temperature range of 34–35°C. Cognitive function was assessed preoperatively and at 2, 5, and 30 days postoperatively using neurocognitive tests. Statistical analysis was performed with IBM SPSS Statistics.

Results. The incidence of cognitive impairment was 21.1% in the hypothermia group and 26.9% in the normothermia group. Postoperative cognitive impairment was more common in the normothermia group: 15.38% on day 5 and 11.5% on day 30 postoperatively compared to 12.1% and 6.1% in the hypothermia group (P<0.05).

Conclusion. This study demonstrated the neuroprotective effects of hypothermia, manifested by a reduced severity of cognitive impairment in the hypothermia group. Further research is needed to identify high-risk patients who would benefit most from this neuroprotective strategy and to optimize hypothermia protocols.

Keywords: neuroprotection by systemic hypothermia; therapeutic hypothermia; moderate hypothermia; carotid endarterectomy

Conflict of interest. The authors declare no conflict of interest.

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Introduction

Carotid artery stenosis accounts for 20–40% of all strokes [1–3]. Carotid endarterectomy (CEA) remains the primary surgical intervention for secondary stroke prevention [4, 5]. However, this procedure is not without risk and may independently contribute to cerebrovascular complications, including transient or permanent neurological deficits. This necessitates efforts to minimize surgical risks and improve procedural safety [4, 5].

Beyond acute cerebrovascular events, there are less severe but equally concerning postoperative outcomes, such as cognitive dysfunction, that significantly impact patients' quality of life. Current data suggest that up to 25% of patients, and possibly more in some reports, experience postoperative

cognitive dysfunction (POCD) following CEA [6]. The etiology of these disorders is multifactorial, often involving intraoperative factors. These may include intraoperative ischemia, microembolism, transient hypoperfusion, or reperfusion injury after restoration of blood flow to the internal carotid artery [6]. A combination of these factors is often observed.

A large meta-analysis of cognitive dysfunction after CEA, which included 60 studies and 4.823 cases, showed an association between the development of cognitive impairment and evidence of hypo- and hyperperfusion during the procedure. Furthermore, cognitive dysfunction was more common in patients with prolonged internal carotid artery clamping, highlighting the role of surgical factors in its development [7].

Preventing and treating cognitive dysfunction during the perioperative period, regardless of its etiology, remains a critical responsibility of anesthesiologists [8, 9].

Extensive experience has been gained in clinical practice worldwide in the use of various methods to protect the brain from ischemia and hypoperfusion. These include maintaining elevated arterial blood pressure during internal carotid artery (ICA) clamping, ensuring a high fraction of oxygen in the ventilated gas mixture (especially during general anesthesia with mechanical ventilation), placement of temporary intraluminal shunts, and the use of metabolic neuroprotective agents, among others [10]. However, these methods do not guarantee protection against brain injury and in some cases may even increase its likelihood [11].

A potential additional measure in the neuroprotective armamentarium is controlled moderate hypothermia. The therapeutic effects of hypothermia have been well documented in areas such as neonatal hypoxic-ischemic encephalopathy, post-cardiac arrest syndrome, and as part of comprehensive ischemic stroke therapy using local hypothermia [12, 13]. Several mechanisms underlying the neuroprotective effects of cooling in such contexts have been discussed [14]. Reports have highlighted the successful application of local cerebral hypothermia in reducing brain injury volume in ischemic stroke [13]. In addition, this method of neuroprotection has been studied in carotid endarterectomy, where it has been shown to affect brain metabolism during unilateral ICA occlusion. However, the use of cerebral hypothermia devices during surgery can be challenging due to procedural technical limitations [15].

To address intraoperative neuroprotection in carotid surgery, the use of controlled systemic hypothermia within a temperature range of 34.0°C to 35.0°C appears promising [16]. However, data on its protective properties remain inconsistent [17, 18]. Furthermore, neither the optimal hypothermia protocol nor its duration to achieve maximal neuroprotective effects has been definitively established. It is possible that the beneficial neuroprotective effects of hypothermia in previous studies were offset by confounding factors related to the depth of hypothermia, its complexity and/or invasiveness, and other methodological nuances. These considerations highlight the need for further research.

Materials and Methods

The effectiveness of systemic hypothermia was evaluated at the L. G. Sokolov North-Western District Scientific and Clinical Center (Sokolov NWDSCC, St. Petersburg) from September 2022 to November 2023. A pilot, single-center, randomized trial was conducted and approved by the local ethics committee of the Sokolov NWDSCC (LEC protocol No. 6 dated August 22, 2022).

The inclusion, exclusion, and post-randomization withdrawal criteria are shown in Table 1.

Based on the above criteria, 59 patients who underwent surgery for atherosclerosis of the brachiocephalic vessels were included in the study. The preliminary sample size calculation was performed using the following formula:

$$n = \frac{z^2 p(1-p)}{E^2}$$

where:

— n is the calculated sample size;

— z is the confidence coefficient;

— p is the expected proportion of patients with postoperative cognitive impairment;

— E is the margin of error.

For the calculation, the z coefficient for standard conditions (with a 95% confidence level) was set at 1.96. The expected proportion of patients with postoperative cognitive impairment was 15% (the expected rate based on the available literature at the time of the final screening). The margin of error used was 5%.

The initial result was then adjusted for the population of up to 100 patients expected to be screened during the study period using the following formula:

$$n = \frac{n_0}{1 + (n_0 - 1)/N}$$

where:

— n_0 is the sample size calculated using the previous formula;

— N is the population size;

— n is the adjusted sample size for the population.

The population was limited to the estimated number of patients eligible for screening within the study period.

As a result of the calculation, the sample size was determined to be 67 patients.

The primary endpoint of the study was the incidence of cognitive impairment in the groups. Secondary endpoints included the development of stroke, length of hospital stay, and mortality. None of these outcomes were observed in the enrolled patients. The endpoint used for calculation was the incidence of cognitive impairment in the groups.

All patients underwent carotid endarterectomy. Eight patients were excluded: three patients withdrew from the study, four refused cognitive testing, and one patient was discharged on the day of surgery due to the development of an acute respiratory illness. Patients were randomized into two groups using an envelope method: the main group, which underwent moderate systemic hypothermia (*N*=33), and the control group (*N*=26), in which normothermia was maintained without any temperature-maintaining measures. Opaque envelopes and double-blinding were used for randomization. Block randomization was not used. The enrollment process is shown in Fig. 1.

Group characteristics are shown in Table 2.

Anesthesia and pharmacologic agents used during anesthesia may contribute to cognitive decline [19, 20]. Therefore, all patients underwent carotid endarterectomy under combined anesthesia: cervical plexus block with 0.5% ropivacaine under ultrasound guidance combined with general anesthesia. Induction of general anesthesia was performed routinely in both groups with fentanyl (1.5–2.0 μg/kg), propofol (1.5–2.0 mg/kg), and muscle relaxation with rocuronium (0.6–0.8 mg/kg). Maintenance anesthesia was achieved with sevoflurane (0.8–1.0 MAC) or propofol at 3–4 mg/kg/h. The choice of maintenance anesthetic was left to the anesthesiologist. The study did not use double randomization.

Because hypothermia can affect the pharmacokinetics of propofol and muscle relaxants, their doses were adjusted in the main group based on data from the depth of anesthesia monitor and neuromuscular transmission monitoring.

During the intraoperative period, in addition to the Harvard standard for monitoring, the following methods were used: invasive arterial blood pressure measurement, depth of sedation monitoring (GE Healthcare M-Entropy), neuromuscular transmission monitoring (NMT GE Healthcare), registration of cerebral oximetry data using near-infrared spectroscopy (Somanetics Invos), and assessment of acid-base balance and blood gas parameters at all stages of hypothermia (before initiation, at target level, and before rewarming). Coagulation status (activated coagulation time, ACT) and mechanical ventilation parameters were also monitored. For thermometry, temperature sensors were placed in the retropericardial segment of the esophagus and in the axillary region.

Patient awakening and recovery from anesthesia were assessed using the Aldrete scale. The main characteristics of surgery and anesthesia in both groups are shown in Table 3.

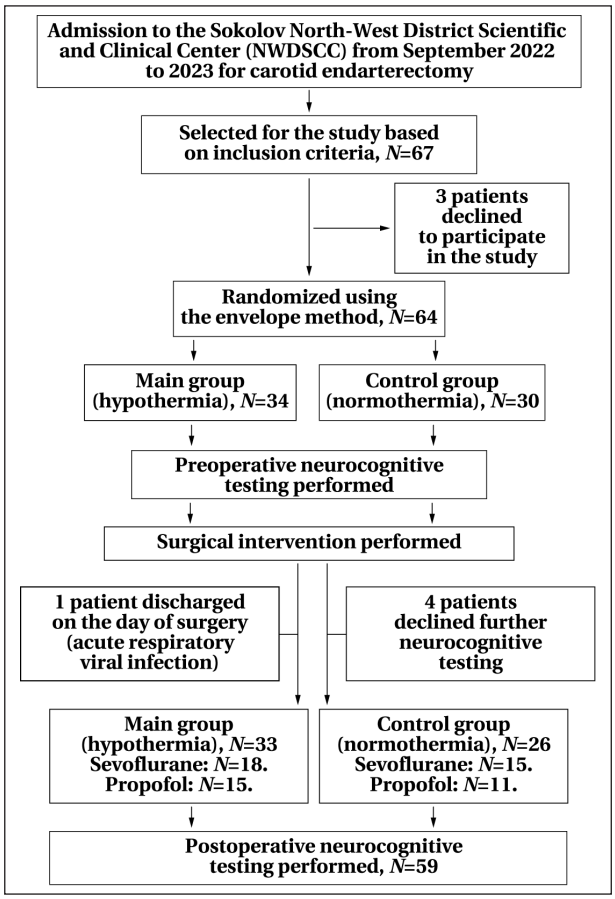

Fig. 1. Flowchart of Patient Selection in the Study.

Table 1. Criteria for Patient Selection in the Study.

Criteria of		
inclusion	**exclusion**	**post-randomization exclusion**
1. Patients with atherosclerosis of the brachiocephalic arteries (BCA) indicated for carotid endarterectomy. 2. Men and women over 18 years of age. 3. Patient consent to participate in the study.	1. Individuals unable to understand the goals and objectives of the study. 2. Patients with severe neurological deficits precluding neurocognitive testing. 3. Patients with terminal stages of chronic diseases. 4. Patients with critical ischemia of the lower extremities. 5. Patients with BMI greater than 30. 6. Patients participating in other studies. 7. Use of pharmacological neuroprotectors.	1. Withdrawal of informed consent by the patient. 2. Refusal to participate in further neurocognitive testing stages.

Table 2. Characteristics of patient groupsв, *Me (Q25–Q75)* or *N* (%).

Parameter	Values in the groups					*P*-value
	Hypothermia, *N*=33		Normothermia, *N*=26		Z-score*, *N*=30	
	Propofol	Sevoflurane	Propofol	Sevoflurane		
Age, years	69.5 (64.75–75.5)	68 (65.5–75)	71 (69–75.5)	68.5 (64–73)	69 (61–71.5)	0.659
Sex						
male	10 (66.67)	13 (72.22)	7 (63.64)	10 (66.67)	17 (56.67)	0.860
female	5 (33.33)	5 (27.78)	4 (36.36)	5 (33.33)	13 (43.33)	
Smoker	6 (40)	10 (55.56)	5 (45.45)	9 (60)	18 (60)	0.708
Stroke/TIA	5 (33.33)	6 (33.33)	4 (36.36)	5 (33.33)	7 (23.33)	0.898
Diabetes mellitus	3 (20)	3 (16.67)	2 (18.18)	4 (26.67)	9 (30)	0.825
Hypertension	13 (86.67)	17 (94.44)	9 (81.82)	12 (80)	25 (83.33)	0.782
Hyperlipidemia	4 (26.67)	6 (33.33)	5 (45.45)	9 (60)	13 (43.33)	0.402
CHD	10 (66.67)	9 (50)	6 (54.54)	6 (40)	11 (36.67)	0.383
Arrhythmias	2 (13.33)	1 (5.56)	0	3 (20)	4 (13.33)	0.510
Symptomatic stenosis	4 (26.67)	6 (33.33)	5 (45.45)	4 (26.67)	1 (3.33)	0.026
Neurological deficit	2 (13.33)	3 (16.67)	1 (9.09)	3 (20)	0	0.203
Overweight	2 (13.33)	1 (5.56)	1 (9.09)	2 (13.33)	10 (33.33)	0.106

Note. * — patients not undergoing surgery or anesthesia, matched for age and testing interval to patients in the normothermia and hypothermia groups.

Description of the hypothermia technique. In the main group, after induction of anesthesia and placement of temperature sensors in the retropericardial segment of the esophagus and the axillary region, controlled hypothermia was initiated using the Hypoterm device (Medmos, Russia) with a target core temperature of 34.0–35.0°C. Cooling was performed with a heat-exchange mattress and blanket. The hypothermia device was set to the coolant and target cooling temperatures, and the cooling process was stopped when the target temperature was reached. The temperature was then maintained within the target range. In most cases, the target cooling temperature was reached by the time the carotid artery was clamped. Hypothermia was maintained until the internal carotid clamp was removed. Monitoring parameters during cooling (core and peripheral body temperatures, coolant temperature, adverse events) were recorded in the protocol every 10 minutes. The hypothermia technique was based on established national and international practices [12, 21].

The rewarming process was then initiated with a target temperature of 36.0°C. Due to the inertia of the cooling process, rewarming did not begin immediately, and the rate of rewarming was limited to no more than 0.5°C per hour. After surgery, rewarming was continued in the intensive care unit using convective warming devices.

In both groups, cerebral protection against hypoperfusion was performed using routine methods described in the literature: maintaining systemic arterial pressure at 20–25% above baseline, increasing the oxygen concentration in the gas mixture to FiO_2 0.9, and placing a temporary intraluminal shunt when cerebral oxygenation fell below 15% of baseline. In equivocal cases, additional monitoring of retrograde pressure in the internal carotid artery stump was performed [11, 10]. Adverse events related to hypothermia were recorded intraoperatively and postoperatively (e. g., coagulation disorders, electrolyte imbalances, arrhythmias, postoperative shivering, perioperative infectious complications) according to the ESAIC perioperative complications list [22].

Cognitive function was assessed using standard scales: MMSE, MOCA, and TMT (Trail Making Test) at baseline and on postoperative days 2, 5, and 30. The assessments were performed by an vascular

Table 3. Surgery and anesthesia characteristics, *Me (Q25–Q75)* or *N* (%).

Parameter	Values in groups						*P**
	Hypothermia, *N*=33			Normothermia, *N*=26			
	Total	Sevoflurane	Propofol	Total	Sevoflurane	Propofol	
Duration of surgery, min	130 (107.5–145)	135 (115–159)	125 (110–132)	120 (111.3–135)	120 (105–145)	120 (115–140)	0.738
Duration of anesthesia, min	220 (145–236.3)	225 (175–245)	205 (170–212.5)	200 (177.5–210)	195 (145–227.5)	192.5 (176.25–207.5)	0.289
Duration of internal carotid artery clamping, min	53 (38.8–61.3)	60 (45–72.5)	40 (40–50)	40 (40–55)	50 (35–57.5)	45 (40-55)	0.257
The use of temporary intraluminal shunt	3 (9.09)	2 (13.33)	1 (9.09)	3 (11.54)	1 (5.56)	2 (13.33)	0.655
Classical carotid endarterectomy technique	3 (9.09)	1 (6.67)	2 (18.18)	3 (11.54)	2 (11.11)	1 (6.67)	0.705
Eversion carotid endarterectomy technique	30 (90.91)	17 (94.44)	13 (86.67)	23 (88.46)	13 (86.67)	10 (90.91)	0.299
Blood loss, mL	40 (30–50)	50 (35–55)	50 (35–55)	40 (30–50)	40 (27.5–50)	40 (30–50)	0.523
Aldrete score	9 (8–9.3)	9 (8.5–9.5)	9 (8.5–10)	9 (8–10)	9 (8–9.5)	9 (8–10)	0.894

Note. * — Intergroup comparison based on the total values in the «Total» column.

neurologist who was unaware of the patient's group assignment.

Because cognitive assessment tests have different dimensions, Z-scores were used to compare test results [23]. A third group (Z-score, *N*=30) of patients in the same age range who had not undergone surgery or anesthesia was tested at the same intervals as the normothermia and hypothermia groups.

The standardized Z-score for each patient was calculated from the raw test result using the formula:

$$Z = \frac{x - X}{SD}$$

where:

x is the raw test result for a given patient,

X is the mean,

SD is the standard deviation for the particular test.

Postoperative cognitive impairment (POCI) was defined as Z-scores that differed from baseline by –1.96 SD or more on at least two tests. If these changes persisted for more than 30 days, the patient was considered to have postoperative cognitive dysfunction (POCD). If detected earlier, it was classified as delayed neurocognitive recovery [24].

Statistical Analysis. Data were analyzed using IBM SPSS 26 with nonparametric statistical methods. Results were presented as medians (Me) and interquartile ranges *(Q25–Q75)*. The Kruskal–Wallis test was used to compare quantitative variables between groups, and the Mann–Whitney *U* test was used for pairwise comparisons of two independent groups. Pearson's χ^2 test was used for categorical variables. A $P<0.05$ was considered statistically significant. A two-tailed *P*-value was used.

Results and Discussion

The groups were homogeneous with respect to baseline characteristics. Among the patients studied, 24 (41%) had right carotid stenosis and 35 (59%) had left carotid stenosis.

The most common comorbidities in this cohort were arterial hypertension (86.4%), coronary artery disease (57.6%), and diabetes mellitus (20.3%). In the main and control groups, 10 and 9 patients, respectively, had a history of transient ischemic attack or stroke in the operated artery territory.

The study results demonstrated that systemic cooling to a target temperature of 34.0–35.0°C, initiated prior to carotid clamping and maintained during clamping, is technically feasible and safe.

There was no statistically significant difference in the duration of surgery and carotid clamping time between the groups: 120 (111.3–135) minutes in the control group and 130 (107.5–145) minutes in the main group. Carotid artery occlusion time was 53 (38.8–61.3) minutes in the main group and 40 (40–55) minutes in the control group (*P*=0.78). There was no significant difference in the dosage and duration of sympathomimetic support between the groups. Mean arterial pressure during carotid occlusion was maintained above baseline in both groups, taking into account cerebral oximetry data. None of the patients experienced infectious complications while receiving the standard regimen of antibiotic prophylaxis.

One patient in the main group and one in the control group experienced paroxysmal atrial fibrillation (AF) in the early post-operative period, both had a history of paroxysmal AF. One patient in the control group required prolonged norepinephrine administration due to persistent hypotension, but the need for vasopressors was resolved within the first few hours. Five patients in the overall cohort required narcotic analgesia during the first postoperative day. The rest of the patients received analgesia with nonsteroidal anti-inflammatory drugs.

Overall, no significant differences were found between the groups based on standard criteria for perioperative complications. However, specific characteristics related to hypothermia were noted.

The incidence of postoperative cognitive impairment (POCI) is shown in Fig. 2. These impairments mainly manifested as delayed neurocognitive recovery. On postoperative day 2, the incidence of POCI was 21.2% in the hypothermia group and 26.9% in the normothermia group. POCI were observed more frequently in the normothermia group, occurring in 15.4% of patients on day 5 and 11.5% on day 30, compared to 12.1% and 6.1%, respectively, in the hypothermia group ($P<0.05$).

One month after surgery, improvement in cognitive function was observed in 4 patients (12.1%) in the hypothermia group, while only 1 patient (3.8%) in the normothermia group showed improvement.

Within each group, the effects of anesthetic maintenance agents (sevoflurane or propofol) were

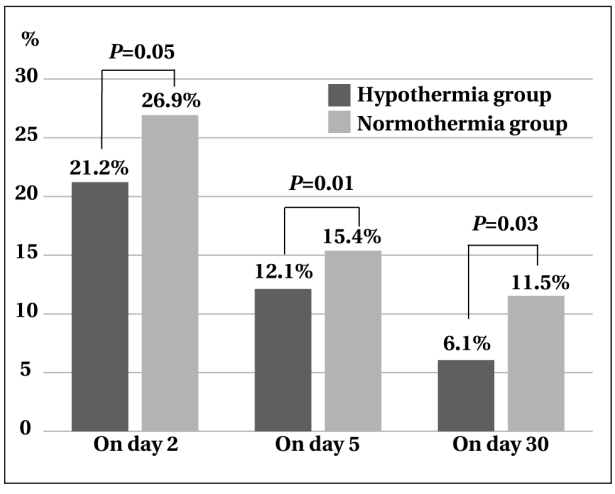

Fig. 2. Frequency of postoperative cognitive impairment.

also analyzed. A trend toward a higher incidence of cognitive impairment was observed in patients receiving sevoflurane. In the hypothermia group, POCI developed in 2 patients receiving sevoflurane, whereas no cognitive impairment was observed in patients receiving propofol. A similar trend was observed in the normothermia group: POCI was identified in 2 of 15 patients receiving sevoflurane compared to 1 of 11 patients receiving propofol.

The results obtained regarding the safety of moderate hypothermia during carotid endarterectomy are consistent with the existing literature. For example, S. Candela et al. [15] cooled patients to 34.5–35.0°C using an invasive thermoregulation device. The authors concluded that hypothermia within this temperature range does not cause clinically significant adverse effects and that shivering can be effectively managed with medication. Similar conclusions were reached by the authors of studies on the use of «mild» hypothermia in neurosurgery [25].

However, in the study by M. Todd et al., which focused on the use of therapeutic hypothermia during surgery for clipping cerebral aneurysms, a higher incidence of bacteremia was reported in the hypothermia group, along with a more frequent need for prolonged mechanical ventilation due to insufficient rewarming after the hypothermic phase. However, it should be noted that their cooling protocol reached 33.5°C, which is below the target range in our study.

Controlled hypothermia is a relatively simple method of neuroprotection during carotid endarterectomy. The duration of the procedure eliminates the risk of an excessively long hypothermic period, thereby minimizing potential adverse effects.

Overall, the incidence of POCI observed in this study is comparable to data reported by other investigators. According to a meta-analysis by P. Aceto et al. on cognitive impairment after CEA, the overall incidence of POCI was 14.1%, with delayed cognitive recovery occurring in 20.5% of cases. However, in individual studies included in the analysis, this rate was higher, reaching up to 45% [26].

It is noteworthy that the frequency of POCI one month after CEA reported in this study is lower than in some other studies. For example, in K. Relander's study, cognitive deficits persisted in 44% of patients three months after surgery [26]. This high detection rate of cognitive dysfunction may be due to the use of a more extensive battery of neuropsychological tests. Similarly, in a study by T. Klypa on POCI in cardiac surgery patients, varying degrees of cognitive dysfunction were observed in 30–70% of patients in the early postoperative period using a battery of four tests [27].

Undoubtedly, cognitive impairment in this patient population is not only influenced by intraoperative risk factors. Additional contributing factors may include suboptimal pharmacological treatment of atherosclerosis and comorbidities, progression of other serious systemic diseases, preexisting central nervous system disease, and others [26]. However, based on the results of this study, it can be assumed that intraoperative risks and their potential modification contribute significantly to treatment outcomes.

The use of hypothermic neuroprotection during surgery, in combination with other conventional methods of protecting the brain from injury, was found to reduce the severity of cognitive impairment compared with the normothermia group. In the normothermia group, delayed neurocognitive recovery was more common in asymptomatic patients than in symptomatic patients. In the hypothermia group, however, no such differences were observed between symptomatic and asymptomatic patients.

In a study by Trae R. Robison et al., the authors found no significant differences in the incidence of cognitive impairment between symptomatic and asymptomatic patients. However, they highlighted that the beneficial effects of statins and aspirin on the development of POCI were particularly pronounced in asymptomatic patients. This suggests that asymptomatic patients may be particularly vulnerable and, as such, may require enhanced neuroprotection. This is particularly important considering that surgical treatment of asymptomatic patients tends to yield better results in preventing ischemic events compared to symptomatic patients [28, 29].

A trend toward increased incidence of POCI was observed with the use of sevoflurane in both groups. Although our data did not reach statistical significance due to the small sample size, they are consistent with the findings of other investigators. For example, a meta-analysis of 34 studies involving 4.314 elderly patients reported a postoperative neurocognitive disorder rate of 16.8% in the propofol group and 24.0% in the sevoflurane group [31].

According to the literature, shivering is the most common adverse effect observed during controlled hypothermia [30], and this was clinically confirmed in our study. During the early postoperative period, shivering was observed in 4 patients (12%) immediately after awakening. Of these 4 patients, 2 received excessive cooling (i. e., beyond the target temperature range) during surgery (down to 33.5°C), which prolonged the rewarming process. The excessive cooling was attributed to the inherent inertia of the cooling method used. No other serious adverse effects related to hypothermia were observed.

The literature describes the use of meperidine, magnesium sulfate, and tramadol to lower the shivering threshold [30]. As shivering can have potentially adverse effects on the patient, it was promptly

treated by slow intravenous administration of a 25% magnesium sulfate solution.

The issue of rewarming patients after hypothermia deserves special attention. Some investigators in their studies did not awaken patients and extubate the trachea until normothermia was achieved. In particular, M. Todd et al. awakened patients in the ICU several hours later [25]. This approach may have contributed to a higher incidence of infectious complications in their observations. However, other authors report that mild hypothermia within the specified temperature range is well tolerated by patients without anesthesia: discomfort caused by this regimen can be alleviated with moderate sedation and anti-shivering medications [30].

In a review by S. Inoue on the use of therapeutic hypothermia during the intraoperative period, the author concludes that extubation can be performed in the operating room if there are no other contraindications. If necessary, sedation should be continued until the patient is fully rewarmed [21]. Similarly, we proceeded with awakening and tracheal extubation while gradually rewarming the patient, without waiting for normothermia to be fully restored. The residual sedation remaining in patients after anesthesia helped to mitigate any potential subjective discomfort caused by hypothermia. In addition, a key consideration in rewarming is to prevent the development of hyperthermia in the postoperative period. Even mild hyperthermia significantly exacerbates ischemic brain injury and can potentially worsen neurocognitive test scores [13].

The low incidence of adverse events was likely related to both the hypothermic protocol and the short duration of its use. In addition, the small surgical site and lack of significant blood loss during the procedure made the hypothermic process well controlled, avoiding excessive cooling or prolonged rewarming in most cases.

The lack of a registered protocol in a clinical registry is a limitation of the study. Nevertheless, to minimize the risk of subjective modifications and interpretations, the protocol approved prior to the clinical trial was strictly followed. Out of 64 randomized patients, neurocognitive testing was not performed in 5 cases, which could have influenced the assessment of the severity of POCI.

Conclusion

Controlled hypothermia is a safe and easily reproducible neuroprotective method in carotid endarterectomy with a minimal number of adverse effects.

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