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Impact of multimodal neuromonitoring in carotid endarterectomy surgery neurologic outcomes

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A systematic review

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Resumo

Enquadramento: A endarterectomia carotídea (EC) é uma cirurgia realizada para diminuir o risco de acidente vascular cerebral em indivíduos com doença aterosclerótica carotídea extracraniana conhecida. Como cirurgia vascular está associada a complicações neurovasculares, como acidente vascular cerebral, disfunção cognitiva e *delirium*. A neuromonitorização na EC é um assunto que não reúne consenso dentro da comunidade científica, nomeadamente em relação aos parâmetros a monitorizar e sobre o impacto que esta monitorização trará. Várias técnicas foram já propostas e são utilizadas noutros contextos.

Objetivos: A presente revisão sistemática tem como objetivo identificar, avaliar, selecionar e resumir toda a evidência de boa qualidade sobre a neuromonitorização no perioperatório da cirurgia de endarterectomia carotídea.

Métodos: Para a elaboração da revisão sistemática foram identificadas as publicações com recurso ao repositório do PubMed. Foi construída uma questão PICO para cada técnica de monitorização (TCD, EEG, NIRS, monitorização neurofisiológica intra-operatória) e *outcome* (AVC, disfunção cognitiva, *delirium*). estudados que terá guiado a seleção dos artigos. Foram incluídos todos os tipos de artigos, desde que de acordo com a PICO.

Resultados: Foram incluídos vinte e cinco artigos na revisão: 21 sobre AVC no perioperatório com diversos métodos de monitorização (9 TCD, 8 EEG, 4 NIRS) e 5 sobre Disfunção Cognitiva e Delirium, 2 dos estudos utilizando monitorização NIRS abordaram ambos os *outcomes* (AVC e disfunção cognitiva).

Conclusão: As três técnicas de neuromonitorização estudadas (TCD (MES ou MCA-V), EEG e NIRS) mostraram-se capazes de prever a ocorrência de isquemia cerebral e de AVC no período perioperatório. A combinação de diferentes métodos de neuromonitorização aumenta a sua sensibilidade e especificidade, para deteção das complicações neurológicas. O *Delirium* e a Disfunção Cognitiva são possíveis complicações da CEA, ainda que pouco abordados no contexto, com uma incidência considerável e aparentemente previsíveis com a utilização de neuromonitorização. Desta forma se recomenda a realização de mais estudos sobre o tópico bem como adoção de neuromonitorização, como rotina, durante a CEA. Mantém-se também a necessidade de estabelecer um consenso sobre a melhor combinação de técnicas de neuromonitorização bem como os *cut-offs* ideais a utilizar.

Palavras-chave: *Endarterectomy, Carotid; Intraoperative Neurophysiological monitoring; Transcranial Doppler; Electroencephalogram; Spectroscopy, Near-Infrared; Ischaemic stroke; Cognitive Dysfunction; Delirium.*

Abstract

Background:

Carotid endarterectomy (CEA) is a surgery performed to decrease the risk of stroke in a patient with known extracranial carotid atherosclerotic disease. As a vascular surgery it has some neurovascular complications, such as stroke, cognitive dysfunction and delirium. Several neuromonitoring techniques have been proposed to detect and prevent these neurologic events and are already used in other contexts. Currently, there's no agreement in the scientific community about the best neuromonitoring techniques to improve the safety of the surgery and reduce the undesired neurologic outcomes.

Objectives: This review aims to analyze the scientific evidence regarding neuromonitoring during the perioperative period of CEA

Methods: A systematic literature search related to CEA was conducted in PubMed. The selection of studies was made based on a PICO question developed to each neuromonitoring technique (TCD, EEG, NIRS, Intraoperative Neurophysiological Monitoring) and clinical outcome studied (stroke, cognitive dysfunction, delirium). All types of study design, following the PICO established, were included.

Results: Twenty-five studies were included in the review: 21 regarding perioperative Stroke with several, monitoring methods (9 TCD, 8 EEG, 4 NIRS) and 5 regarding Cognitive Dysfunction and Delirium. 2 of the studies using NIRS monitoring addressed both outcomes: stroke and cognitive dysfunction.

Conclusion: TCD (MES or MCA-V), EEG and NIRS are capable of predicting cerebral ischaemia and stroke on the perioperative period. The combination of several methos increases their sensitivity and specificity. Delirium and Cognitive Dysfunction are outcomes with a considerable incidence, apparently predictable with neuromonitoring and so, further studies are encouraged. Multimodal neuromonitoring should be adopted as routine during CEA, although consensus about the methods and its thresholds should be established.

Keywords: Endarterectomy, Carotid; Intraoperative Neurophysiological monitoring; Transcranial Doppler; Electroencephalogram; Spectroscopy, Near-Infrared; Ischaemic stroke; Cognitive Dysfunction; Delirium.

List of abbreviations

CAM	confusion assessment method
CEA	Carotid Endarterectomy
CVC	Cerebrovascular complications
DSM-V	Diagnostic and Statistical Manual of Mental Disorders fifth edition
EEG	Electroencephalogram
ESO	European Stroke Organisation
ESVS	European Society for Vascular Surgery
GA	General anaesthesia
MA	Meta-analysis
MCA-V	Middle cerebral artery blood flow velocity
MES	Microembolic signals
MMSE	Mini Mental State Examination
MoCA	Montreal Cognitive Assessment
NA	Not applicable or not available
NASCET	North American Symptomatic Carotid Endarterectomy Trial
NIRS	Near-infrared spectroscopy
PCS	Prospective cohort study
PICO	Population, Intervention/Index test, Comparator test, Outcome
POCD	Postoperative cognitive dysfunction
POCI	Postoperative cognitive improvement
POD	Postoperative delirium
PPV	Positive predictive value
RA	Regional anaesthesia
RCS	Retrospective cohort study
RCT	Randomized clinical trial
rSO_2	regional oxygen saturation
SP	Stump pressure
SR	Systematic review
SSEP	Somatosensorial evoked potentials
Sx	Symptoms
TCD	Transcranial Doppler
TIA	Transient ischemic attack

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Introduction

Carotid Endarterectomy

Extracranial Carotid Atherosclerotic Disease and associated carotid stenosis progression is a strong predictor of stroke in multiple natural history studies.[3] Management of extracranial cerebrovascular disease has been the focus of intense investigation and debate by multiple vascular specialists since the introduction of carotid endarterectomy (CEA) as a therapeutic modality for the prevention and treatment of stroke. CEA is a surgery performed to decrease the risk of stroke in a patient with known extracranial carotid atherosclerotic disease. The procedure entails removing the atherosclerotic plaque from the common carotid artery and/or internal carotid artery to improve blood flow and remove potential embolic material. Carotid artery reconstructions began in the early 1950s, and techniques for carotid endarterectomy procedures, as well as indications to perform them, have evolved.[4]

Surgery indications are based on the severity of the stenosis calculated by imaging techniques, as well as on the presence of symptoms. European Society for Vascular Surgery (ESVS) Guidelines (2017) considers a symptomatic patient someone who has suffered a carotid territory symptom within the preceding 6 months. Carotid territory symptoms include (1) hemi-sensory impairment (numbness, paraesthesia of face/arm/leg) (2) hemimotor deficits (weakness of face/arm/leg, or limb clumsiness), and (3) higher cortical dysfunction (dysphasia/aphasia, visuospatial problems).[2]

Both ESVS (2017) and European Stroke Organisation (ESO) (2021) Guidelines strongly recommend that patients with ≥70% symptomatic carotid artery stenosis (Class I, Level A; High level of evidence) and ≥60% asymptomatic carotid artery stenosis considered to be at increased risk of stroke on best medical therapy alone (Class II, Level B; Moderate level of evidence), should undergo CEA.[5,6]

As for imagologic methods for measuring stenosis severity, the European Carotid Surgery Trial [7] (ECST) and North American Symptomatic Carotid Endarterectomy Trial [8] (NASCET) diverge (Figure 1). Each method provides different measures of stenosis severity, and this has been a source of confusion as to whether interventions should be based on "50%" or "70%" thresholds.[2] Nevertheless, either ESVS[2] (2017) and ESO[6] (2021) Guidelines adopted the same NASCET measurement method.

There are two main surgical techniques for carotid endarterectomy: the classical/conventional method and the eversion method. With the eversion method the internal carotid artery is transected at its origin at the bifurcation, and a cylinder of atheroma “expelled” via eversion of the outer media and adventitia. The distal intimal step is examined for residual flaps, which are then excised. The ICA is shortened as required and reanastomosed to the CCA.[2] The advantages of the eversion method include the absence of the need for patch closure therefore eliminating the risk of prosthetic infection, and the overall shorter carotid clamping time and total operative time. Conventional CEA is indicated in the cases where the carotid plaque is extended more than usual, as well as, in the cases where usage of external shunt is necessary.[9]

External Shunt is used to avoid the haemodynamic neurologic deficits associated with temporary interruption of cerebral perfusion during carotid clamping. ESVS[2] (2017) guidelines recommend that the choice of shunting (routine, selective, never) should be left to the discretion of the operating surgeon.

As for the anaesthetic technique there is no significant difference between locoregional and general anaesthesia and therefore ESVS guidelines recommends that the choice of anaesthesia should be left to the surgical team’s discretion.[2]

Despite its superiority to medical treatment, in particular in symptomatic patients, carotid endarterectomy has some undesirable outcomes.[2,6,10] The main outcomes identified are perioperative stroke, restenosis, myocardial infarction, postoperative cerebral hyperperfusion syndrome and death.[10-12] Recently, there has been some evidence of cognitive decline after CEA emphasising the lack of knowledge about its pathophysiology as well as the means to prevent it.[13]

Perioperative Stroke

Perioperative stroke is defined by the Society for Neuroscience in Anaesthesiology and Critical Care Consensus Statement (2014) as a brain infarction of ischemic or haemorrhagic aetiology, which occurs during surgery or within 30 days after surgery, including the development of stroke after recovering from anaesthesia.[14]

Ischaemic stroke is a known complication of CEA, limiting its benefit.[15] There are several risk factors already established as independent for the development of perioperative stroke such as: older age, previous history of stroke or transient ischemic attack (TIA), smoking, hypertension, diabetes mellitus, ischemic heart disease, atrial fibrillation, and mitral valve disease.[16] Based on known and modifiable risk factors a healthy diet, smoking cessation and physical activity are recommended for all patients with symptomatic carotid disease. [2]

It should also be remembered that all the patients with carotid stenosis proposed to carotid endarterectomy either are symptomatic (had a previous stroke or TIA) or are asymptomatic with a significantly high risk of having a stroke.[10] From that point of view, these are high risk patients, in a high risk surgery. Concerning high-risk surgeries, such as carotid endarterectomy, perioperative stroke is one of the main complications to avoid.[14,17] The very same procedure whose goal is to prevent strokes has at the same time risk of causing them.[18] As life expectancy increases and older people are being submitted to surgical procedures, we expect a growth of the incidence of perioperative stroke in the future.[14]

The NASCET, a big multicentric trial involving 1745 patients who underwent carotid endarterectomy, reported an overall rate of perioperative stroke and death of 6.6%. The majority of these events were ipsilateral to the manipulation and occurred after the procedure, particularly within 6 hours. Most strokes were non disabling, with 30 days rates of: 3.5% nondisabling, 1.8% disabling strokes and 1.1% resulting in death.[8]

As it is known patients experiencing a stroke after carotid revascularization have significant reductions in survival over the first 1 and 5 years compared with patients experiencing neither complication.[19]

During the surgery itself, these patients are prone to neurologic events of ischaemic aetiology. Several preoperative tests can be performed to predict the risk of cerebral ischaemia, knowledge that will influence revascularization decision-making.[20] These complications can be caused by cerebral hypoperfusion, mainly after carotid cross clamping, embolization after the initial dissection, due to atheromatous plaque disruption or, more recently aborded, hyperperfusion syndrome.[15,17,21-23]*Most (80%) intraoperative ischemic changes are due to embolization, and a small percentage (20%) are due to hemodynamic factors.*[15,17,21-23]

Cognitive dysfunction

Cognitive impairment is described by the Diagnostic and Statistical Manual of Mental Disorders latest edition (DSM-V) as an intermediate clinical state between normal cognition and dementia.[24] At the same time, mild cognitive impairment may appear also as a reversible complication of certain diseases, interventions, or medications.[25]

The cognitive function may be accessed through neuropsychological tests that can be divided into seven functional domains: learning, delayed memory, working memory, executive functioning, speed, motor dexterity and reasoning.[26] Some of the most used tests due to their simplicity of application are the Mini Mental State Examination (MMSE) and Montreal Cognitive Assessment (MoCA).[27] Several studies and systematic reviews on the topic have emphasized the need for standardisation of an optimal battery of neurocognitive tests to diagnose cognitive dysfunction.[26,28] Although the National Institute of Neurological Disorders and Stroke (NINDS) recommends a neurocognitive battery of tests - the NIH Toolbox – it is not established globally and the scientific literature remains heterogeneous.[28]

Cognitive impairment is related with early mortality and has a huge negative impact on quality of life (QoL),[28,29] even in a mild level, thus the importance to recognize its existence and prevent it when possible.

There is a significant association between carotid endarterectomy and cognitive dysfunction, but a direct aetiological relationship has not yet been proved.[27,28] A cohort study from 2021 involving 43 patients clarified the importance of measuring the postoperative cognitive changes both in an acute phase (4 days after) and in a stable phase (3 months after), showing that postoperative cognitive dysfunction (POCD) at 3 months after CEA has an association with a five times higher mortality rate, after a follow up of 12 to 14 years, as compared to the acute phase that didn't show any association with survival.[26]

There are several possible aetiologies for cognitive impairment in the context of carotid stenosis, such as chronic brain hypo-perfusion and microinfarction of the brain tissue cause by microemboli from an unstable carotid plaque.[28] As carotid endarterectomy is shown to be the best interventional treatment for carotid stenosis, one would expect an improvement on cognitive function. However over the last years carotid endarterectomy has been associated with POCD and improvement (POCI).[26] A systematic review on the topic, from 2022, concluded that there is a significant neurocognitive improvement at one month post CEA in executive function and processing speed domains. This affects directly QoL in a positive way,[28] improving daily functioning and working ability.[26]

A meta-analysis regarding cognitive decline after CEA found cerebral perfusion as the key factor for cognitive decline after CEA.[13] The rationale behind this is that the sudden hyperperfusion after CEA on a hypoperfusion adapted brain is beyond the metabolic demands of the brain tissue. Some authors defend that this phenomenon, even when asymptomatic, will lead to postoperative cognitive impairment.[13]

Delirium

Delirium is defined by DSM-V as a disturbance in attention and awareness, followed by several diagnostic criteria.[24] It can be broadly described as an acute brain dysfunction, that can include a variety of symptoms like disorientation, perceptual disturbances, emotional dysregulation, or sleep disturbances.[30]

The pathophysiology of delirium is not yet understood, however there are two main theories: the first relates delirium with inflammation, based on the action of cytokines on the blood-brain barrier and the impact of chronic stress on cytokine and cortisol levels, while the second attributes it to the neurochemical imbalances that affect neurotransmission.[30]

Some diagnostic tools have been created, such as the confusion assessment method (CAM), the Memorial Delirium Assessment Scale (MDAS) and the Delirium Rating Scale Revised 98, in order to make the detection of delirium by non-psychiatric medical professionals quicklier and more effective. All the three were considered reliable for diagnosis and discriminating from other psychiatric disorders, such as dementia.[31-34] The CAM instrument includes four elements: (1) acute onset and fluctuating course of mental state, (2) inattention, (3) disorganized thinking, and (4) altered level of consciousness. The test should be completed in less than 5 minutes and delirium is diagnosed when elements (1) and (2) are present.[31] The MDAS and the DRS-R-98 target the severity of delirium, being more time-consuming, and more applicable on scientific investigation rather than on the clinical context.[33,34]

Postoperative delirium (POD) is a common complication, with incidence ranging from 0 to 73%, depending on the type of surgery and perioperative risk factors.[35-37] It can happen at any age, although the elderly have a higher risk, and it is estimated to happen in the recovery room or up to five days after surgery.[30,38-40] The European Society of Anaesthesiology (ESA) developed an evidence-based list of risk factors for delirium in the perioperative period to raise awareness and reduce its incidence. The risk factors include advanced age, cerebrovascular and cardiovascular comorbidities, intraoperative bleeding, and pain.[40] POD has been associated with vascular surgery and particularly with carotid procedures, although not extensively studied.[41]

Although POD is frequently taken as a temporary attenuation of brain function, it is widely demonstrated that it is related with mortality and (longer term) morbidity and has a significant impact on QoL.[38,40,42] The ESA points out some efforts that should be made to decrease delirium incidence, being one of them the use of neuromonitoring intraoperatively to avoid excessively deep anaesthesia. Electroencephalogram (EEG) has already been suggested by other studies to detect delirium.[43]

Neuromonitoring

Aware that any patient proposed to a carotid endarterectomy has already elevated risk of developing a stroke or cognitive dysfunction,[13,16] intraoperative monitoring turns out as the crucial point that can influence decision making intraoperatively[27] and eventually reduce complications. The use of a combination of different modalities for detection of cerebral ischemia in high-risk procedures, such as CEA, is already recommended in the literature, especially in patients under general anaesthesia, which is the most common practice for CEA.[27,44]

Hence the need for neuromonitoring. There are several techniques capable of predicting cerebral function intraoperatively under general anaestheia, such as: Transcranial Doppler (TCD), electroencephalogram (EEG), stump pressure (SP), Near-infrared spectroscopy (NIRS) and somatosensorial evoked potentials (SSEP).[17] On this review, we will address: TCD, EEG, NIRS and Intraoperative Neurophysiological Monitoring.

The ideal monitor should have high sensitivity and specificity, be easy to interpret, and, more importantly, provide real-time information with a sufficient therapeutic time window to allow treatment implementation to alter outcome.[18]

It is important to address that, if the patient show signs of hypoperfusion during the surgery the first move is to implement a shunt. The shunt itself, which amis to prevent ischaemia, can cause an embolic event by dislodging debris.[45]

When the surgery is performed under locoregional anaesthesia, the clinical examination is the chosen method to evaluate cerebral function.[17]

Objectives

The current systematic review aims to analyse the literature regarding neuromonitoring during the perioperative period of the CEA and establish whether the use of neuromonitoring would be capable of predict, prevent, and reduce the incidence of perioperative stroke, postoperative cognitive dysfunction, or delirium.

Methods

A systematic review was conducted according to the recommendations of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA)[1].

A PICO (Population, Intervention/Index test, Comparator test, Outcome) question was developed to each neuromonitoring technique and clinical outcome.

This resulted in 12 PICO questions identified with the letters from h) to s), as shown in Table I.

h) [(Carotid Endarterectomy) AND (Transcranial Doppler)] **AND** [(Carotid Endarterectomy) AND (Ischemic Stroke)]
i) [(Carotid Endarterectomy) AND (Electroencephalography (+ Electroencephalogram)] **AND** [(Carotid Endarterectomy) AND (Ischemic Stroke)]
j) [(Carotid Endarterectomy) AND (Spectroscopy, Near-Infrared)] **AND** [(Carotid Endarterectomy) AND (Ischemic Stroke)]
k) [(Carotid Endarterectomy) AND (Intraoperative Neurophysiological Monitoring)] **AND** [(Carotid Endarterectomy) AND (Ischemic Stroke)]
l) [(Carotid Endarterectomy) AND (Transcranial Doppler)] **AND** [(Carotid Endarterectomy) AND (Cognitive dysfunction)]
m) [(Carotid Endarterectomy) AND (Electroencephalography (+ Electroencephalogram)] **AND** [(Carotid Endarterectomy) AND (Cognitive dysfunction)]
n) [(Carotid Endarterectomy) AND (Spectroscopy, Near-Infrared)] **AND** [(Carotid Endarterectomy) AND (Cognitive dysfunction)]
o) [(Carotid Endarterectomy) AND (Intraoperative Neurophysiological Monitoring)] **AND** [(Carotid Endarterectomy) AND (Cognitive dysfunction)]
p) [(Carotid Endarterectomy) AND (Transcranial Doppler)] **AND** [(Carotid Endarterectomy) AND (Delirium)]
q) [(Carotid Endarterectomy) AND (Electroencephalography (+ Electroencephalogram)] **AND** [(Carotid Endarterectomy) AND (Delirium)]
r) [(Carotid Endarterectomy) AND (Spectroscopy, Near-Infrared)] **AND** [(Carotid Endarterectomy) AND (Delirium)]
s) [(Carotid Endarterectomy) AND (Intraoperative Neurophysiological Monitoring)] AND [(Carotid Endarterectomy) AND (Delirium)]

The study population consists of adults with carotid stenosis who undergo CEA. Any specific study focusing on a subpopulation of patients would be excluded.

The index diagnostic tests are the four neuromonitoring techniques analysed in this study: Transcranial Doppler, EEG, NIRS, Intraoperative Neurophysiological Monitoring.

The Comparator test would be the gold standard diagnostic method for each of the 3 clinical outcomes: ischemic stroke, cognitive dysfunction, and delirium.

The search queries built with these PICO questions (Table I) were applied to the online database PubMed, last consulted on the 22ndMarch 2022. We used the identified key concepts, combined as mentioned before, searching in "all fields".

Selection of studies was based on methodologic criteria (PICO question of the study) and clinical criteria. During the screening phase an initial evaluation of all records obtained in the search was performed. Decisions were based on the title and abstract. In the inclusion phase a detailed assessment of potential eligible studies was done, based on the reading of the works/articles.

All the 148 results from the search were added to the Citation Manager (EndNote) and 24 duplicates were removed, leaving 124 for screening. The titles and abstracts were independently screened to determine the applicability, based on the PICO question previously established. Thirty-four studies were excluded for not meeting the population criteria, either for studies conducted in children, in patients with carotid stenosis but not proposed to carotid endarterectomy or some comparing medical and surgical treatment.

The intervention is the monitoring with one of the chosen methods: Transcranial Doppler, EEG and NIRS. We included all the studies who used at least one intraoperatively, thus excluding 36 results.

We included the studies measuring at least one of the outcomes desired, being them perioperative stroke, cognitive dysfunction, and delirium. Based on those 21 results were excluded.

A flowchart explaining the selection process can be found on Figure 2.

Results and Discussion

Tables II to VI display all the studies included in this review, identifying for each one of them authors and year of publication, sample size (number of patients included), percentage of symptomatic patients, type of anaesthesia, stroke rate, monitoring modalities, decision to shunt, registered changes in monitoring, significative findings (sensitivity and specificity) and recommendations for the future. The tables are divided by themes TCD, EEG, NIRS, Cognitive Dysfunction and Delirium, corresponding to Tables II, III, IV, V and VI, respectively.

Stroke and cerebral ischaemia

Nowadays neuromonitoring techniques are mainly used for shunt placement indication, not as much as predictors of cerebrovascular events.[11]

Even though there is no evidence supporting regional or general anaesthesia, a meta-analysis from 2013 considered that, during CEA, physical examination under RA is superior to any cerebral monitor in detecting cerebral ischaemia. Among the available methods, the most favourable results were given by a combination of stump pressure and either TCD or EEG.[46] However GA remains as the most common practice for CEA.[44]

Transcranial Doppler

Transcranial Doppler can be used in two different ways: either to measure the blood flow velocity on the middle cerebral artery (MCA-V) or to detect microembolic signals (MES), both being pointed out as capable of predicting cerebral ischemia.[21,47]

As the main cause of stroke during CEA is embolism[48], it would be expected that, by using Transcranial Doppler to detect MES, we would be able to prevent these neurologic events. It is known that cerebral MES detected by transcranial Doppler are frequent during CEA, what remains to clarify is the potential harmful effects on the brain.[49,50] Muller et al.[48] suggest that, even excluding the lesions with clinical deficits, there are several small areas of the brain tissue at risk for irreversible ischaemia during CEA and detecting MES can have a high impact in preventing these events. Skjelland et al.[50] (2009) showed that there is a significant association between solid (p=.027) and gaseous (p=.037) microemboli during carotid revascularization and procedure-related ipsilateral ischemic strokes. Concerning this association, they suggest that the number of these microemboli, both solid and gaseous, should be monitored and reduced to a minimum during CEA.

Laman et al.[51] (2002) studied the relation between the embolic rate and cerebrovascular complications during different periods (dissection, wound closure and postoperative) and found a significant association of cerebrovascular events with the monitoring of more than 10 emboli (P=.0154). Regarding the possibility of prediction of cerebrovascular events, based on embolic rate, they concluded that the best predictive value was in the postoperative period (p=.001), followed by the dissection period (p=.017). Ackerstaff et al.[52] found a significant association between emboli during dissection (p=.03) and wound closure (P=.002) and the occurrence of perioperative stroke. On the other hand, Kim et al.[49] carried out a retrospective study involving 160 patients and found no statistically significant relation between MES>10 and postoperative neurologic events (P=1.000). Out of 160 patients, four patients had a stroke and only one of those four had MES>10 during CEA.

Ogasawara et al.[53] (2008), regarding TCD monitoring, suggest that MES≥10 together with low flow of the middle cerebral artery (≤28 cm/s) can predict the occurrence of an ischaemic stroke and new postoperative neurological deficits.

Moritz et al.[54] states that when using either NIRS or TCD to detect cerebral ischaemia, the relative changes have higher accuracy and therefore should be considered, instead of the absolute values.

Moritz et al.[54] studied the best cut-off, in MCA-V reduction, to detect cerebral ischemia. They found that using a 50% reduction in MCA-V as a cut-off, had a 100% sensibility and 80% specificity to detect cerebral ischemia. Furthermore, to reduce the percentage of false positive results, they tried a 70% reduction in MCA velocity as a cut-off, thus obtaining a 78% sensibility and 100% specificity. It is important to underline that this study was conducted in patients under RA consequently only being valid in CEAs performed in awake patients. Woo Sung Yun[55], studying patients under GA, defined a 50% reduction in MCA-V as a safe cut-off to prevent cerebral ischaemia. Despite the reduction in the number of false positive results caused by the increasing of the cut-off (from 50% to 70% reduction in MCA-V), this would also lead to an increased risk of missing cerebral ischaemia.

In a meta-analysis[21] from 2017, TCD monitoring (either MCA-V or MES) was found to have a sensitivity of 56.1% and a specificity of 72.7% in predicting perioperative strokes. The same meta-analysis, when analysing MCA-V and MES individually estimated a sensitivity of 49.7% and 61.1% and a specificity of 84.1% and 56.6%, respectively, as shown in Table II. The authors attribute the low sensitivity in part to the shunt placement, which, despite being used in response to the change in the TCD, to prevent stroke occurrence may, sometimes have as a side-effect the very same phenomena it was trying to avoid.

In an attempt to find the best cut-off, based on embolic rate by TCD, Laman et al.[51] obtained a 100% sensitivity, 75% specificity and 20% positive predictive value (PPV) during postoperative period with a cut-off point of >0.9 e/min (emboli per minute). During the wound closure period, with a lower cut-off of >0.04 e/min, it was possible to obtain 100% sensitivity, 65% specificity and 15% PPV.

Transcranial Doppler has been showing a good performance in recent years, although it has certain limitations: patients missing an acoustic temporal window (estimated in 10 to 15%) cannot be monitored with this method and there's also the proximity of the operation field that can lead to doppler probe dislocation.[11,54,55] For instance in a prospective study[54] including 48 patients monitored with SP, NIRS, SSEP and TCD, it was not possible to use TCD in 10 (21%) of the patients, either because of the insufficient quality of the signal or the dislocation of the Doppler probe intraoperatively.

NIRS, SP and TCD record changes in the region of the middle cerebral artery. Although this is the region with higher risk of cerebral ischaemia it is important to remember that changes in the vascular region of the anterior and posterior cerebral artery are missed by these devices.[54]

Electroencephalogram

The American Society of Neurophysiological Monitoring has already recognized EEG as a useful neuromonitoring tool intraoperatively, in particular to guide the depth of anaesthesia avoiding burst suppression and preventing stroke during CEA.[56]

Chang et al.[57] elaborated a meta-analysis with the aim of understanding whether the changes observed in the EEG could predict the occurrence of a stroke in the perioperative period, until 30 days after the CEA. They were faced soon with the difficulty of defining significant EEG changes, since the various studies analysed used different criteria. There are several EEG changes that can indicate ischaemia, such as hemispheric asymmetries, loss of faster frequencies, increase in slower frequencies or loss of amplitude.[56] The most commonly used is a rapid unilateral or bilateral attenuation of background fast anaesthetic-induced EEG activity.[58] This same meta-analysis had a sensitivity of 46% and specificity of 86% for EEG changes in predicting perioperative stroke. Meaning that, of all the patients experiencing a stroke in the perioperative period, only half of them would have had significative intraoperative EEG changes (positive diagnostic test). The low sensitivity can be explained on one hand by the small distal embolic strokes that may not be detected by frontal EEG and on the other hand by the interventions performed during surgery that were motivated by EEG changes, such as shunting.[57] Thirumala et al.[59] estimated similar values for sensitivity and specificity, 52% and 84%, respectively, and advert the lack of uniformity in EEG monitoring (montage and number of channels used) and the changes perceived as significant, as a factor contributing for the low sensitivity. Facing the same sensitivity limitation, Leopardi et al.[17] suggested a combination of EEG and SSEP, instead of EEG or TCD alone, claiming that adding SSEP would increase sensitivity.

Hans and Jareunpoon[60] observed EEG changes in awake patients, comparing directly the considered ischaemic EEG changes with the neurologic status. Slowing of EEG frequency in the alpha and beta frequencies and a 50% reduction in EEG amplitude was adopted as the criteria for a significative change in EEG.

When correlating the SP measurement (threshold of 40 mmHg, the currently most used criterion) with the EEG changes, this resulted in a sensitivity of 86.4% and a specificity of 97%.[60] In addition, there were 32 patients, in whom it was inserted a shunt, showing neurological symptoms, but only 19 (59.4%) showed significative EEG changes. This allowed the calculation of a 40% false negative rate. On the other hand, there were 3 patients with EEG changes but no change in neurologic status (false positive rate 1.1%).[60]

Reuter et al.[45] compared two groups of patients submitted do CEA with different monitoring modalities: stump pressure and EEG. Knowing that SP is widely used to evaluate cerebral perfusion. We should bear in mind that SP is only assessed in the beginning of the procedure, thus not being able to detect ischaemic changes throughout the entire surgery. Even so, the group monitored with EEG had the highest stroke rate (8% vs 2%, p=.041) in the perioperative period. This high rate can be attributed to the EEG's inability to detect subtle ischemic changes that later developed into a cerebral infarct.

In fact, the ideal monitor shouldn't miss any patient in risk of cerebral ischaemia.[60] Although other studies have reported a 0% false negative rate with EEG monitoring,[61] the EEG, with the criteria currently established, cannot be used solely as a predictor of ischaemia. Another confounding factor that is important to remember is that these results were obtained in awake patients, who have different normal EEG patterns than patients under general anaesthesia, hence the applicability of these results to patients under general anaesthesia remaining in doubt.[18,62]

Pinkerton[63] used EEG changes as the sole criteria for detecting cerebral ischaemia and was able to detect four of the five strokes that happened in a population of 1661 patients. The patient that had the missed stroke also had a SP of 45 mmHg (>40mmHg), meaning that either by using the EEG or the SP it wouldn't be possible to predict this case. A weakening feature of this study is the fact that it uses general and regional anaesthesia, not specifying which type of anaesthesia was used in the patients who had a stroke.

Khattar et al.[64] identified the shunt placement as a predictive factor of perioperative stroke, but not the neuromonitoring EEG changes. Regarding shunt placement is it interesting to observe that 19% of the patients received a shunt motivated by a complete loss of signal that was fully restored after shunt placement. On the contrary, Pappadà et al.[65] registered nine cases (2.2%) of major stroke but no EEG changes in 413 CEAs performed in 390 patients. Intolerance to carotid cross-clamping was considered when the reduction of ongoing EEG activity exceeded 50% and a burst suppression pattern or focal slow (delta/theta) waves were detected.

Leopardi el al.[17] established a comparison between TCD and EEG monitoring claiming that although EEG provides good information about brain perfusion, it may present a delay in ischaemia detection. Mergeche et al.[47] added that reductions in 30 to 60% below the baseline, that can be indicative of cerebral ischaemia, are detected by TCD but often missed by EEG monitoring.

In conclusion, the development of significant changes in EEG indicates the development of cerebral ischaemia, which is associated with an increased risk of intraoperative stroke.[63] Although EEG changes may not be predictive, it has been observed a statistically significant increase in stroke rate in patients showing an abnormal EEG.[63,64] EEG has some limitations that should be addressed, starting from its monitoring results that are dependent on the experience of monitoring personnel, which result in a relatively high false positive rate.[11,66] Among with the low sensitivity, these limitations demonstrate that the EEG, although very useful, is not safe as the sole method of monitoring.

Near-infrared spectroscopy

NIRS estimates the cerebral regional oxygen saturation (rSO_2) in real time, continuously and noninvasively.[11] This measure will be able to detect hypoperfusion of the brain tissue, a possible precursor of ischaemia, stroke, and death. Hyperperfusion may be important to detect too due to the cerebral hyperperfusion syndrome already described in literature as a perioperative complication of CEA that can lead to stroke and death.[11,12,67] Although this is not the focus of the present study it allows us to acknowledge another utility of NIRS monitoring during CEA.

NIRS has the advantage of allowing an earlier detection of cerebral ischemia when compared to other methods, such as SSEP and EEG, whose detection limits correspond to a lower NIRS threshold (further 10% decrease in basal rSO_2).[68]

Pugliese et al.[69], comparing NIRS and neurologic examination (in awake patients), suggested that NIRS would be able to predict cerebral ischaemia 5-10s before the clinical observation of neurological complications. Despite being a promising method, already used in cardiac surgery, there is no consensus on the best cut-off points of brain oxygen supply parameter for the presence of ischaemia.[68]

Wang et al.[11] selected two specific moments for analysis, where notable hemodynamic changes occur: the moment of clamping and declamping of the carotid artery. It has been observed a significant decrease of mean rSO_2 value ($P < 0.0001$) after clamping, that comes back to normal after declamping and increases after one minute ($P < 0.002$).[68,70]

Similarly to TCD, the best way to use NIRS, whether with absolute or relative values, has not been established. Although some authors state that relative values should be used as patients have different baseline values[54,71], it's not consensual. This disagreement makes it difficult to compare results from different studies and to define a consistent cut-off. Based on a comparison between NIRS and TCD, a 12.3% decrease of rSO_2 was considered a reliable threshold for intraoperative cerebral hypoperfusion by Wang et al..[11] Using this same cut-off and targeting intraoperative hypoperfusion they estimated a sensitivity and specificity of 64.3% and 90.0%, respectively.

Pedrini et al.[70] studied 473 patients monitored with NIRS and registered zero strokes and three TIAs in patients with a rSO_2 decrease greater than 25%. They state a 100% sensitivity and a 95.36% specificity, claiming that the absence of false negatives using a cut-off of 25% grants some safety. However, not having registered any stroke in the whole population weakens this assertion.

The main disadvantage of NIRS is that it is influenced by several physiological factors, such as, systemic hemodynamic and oxygen saturation, tissue metabolism and bronchodilatation. Nevertheless, the anaesthesiologist has the power to modify and normalise these values and restore reliability on NIRS measurement.[15,70] Another weakness is that NIRS monitoring is restricted to the territory of the anterior cerebral artery, just like TCD.[15,54] At last, being NIRS an economic, accessible and easy to read method, seems like a good option for CEA monitoring.[11]

Cognitive dysfunction

Cognitive dysfunction after CEA has received more attention from the scientific community in recent years. In spite of this, the rates of patients presenting with cognitive dysfunction remain very heterogeneous, ranging from 2.6% to 28%, 24 hours after surgery.[15,72]

It should be borne in mind that different studies use different methodologies to diagnose cognitive dysfunction, ranging from the use of the MMSE or MoCA to a whole battery of neuropsychometric tests evaluating several cognitive domains (verbal memory, visuo-spatial organisation, motor function, executive function). This lack of standardisation limits the ability to compare these studies. Nevertheless, we verified that the more comprehensive these tests were, the greater the number of cases diagnosed.[15,47,72]

Kamenskaya et al.[15] studied 466 patients undergoing CEA, from which 19 showed neurological complications (7 strokes and 12 with cognitive dysfunction). These patients had a significant decrease in rSO_2 ($p=0.018$) and ΔrSO_2 ($p=0.029$) at carotid clamping, in agreement with other studies.[47] Following that observation, ΔrSO_2 was identified as an independent predictor of stroke outcome and cognitive disorders in patients undergoing CEA. With a cut-off of 20% decrease in ΔrSO_2, during carotid clamping, they achieved a sensitivity and specificity of 86.0% and 57.1%, respectively, for predicting stroke. Regarding cognitive disorders, for the same 20% cut-off, a sensitivity of 88.1% and specificity of 58.3% were obtained.[15]

Based on the systematic review by Nielsen[68] a decline of 20-25% in rSO_2 seems to be predictive of POCD. However, they suggest that a lower threshold of 10% should be adopted as an indicator for therapeutic intervention, in order to avoid this undesired neurological outcome.

Mergeche et al.[47] even stated that each percent of reduction in MCA-V during cross-clamp was significantly associated with increased risk of cognitive dysfunction (95% CI, $p < 0.001$). A threshold of a 28% reduction from baseline strongly associated with the risk of developing cognitive dysfunction after CEA.

In conclusion both TCD and NIRS seem to present good results in predicting cognitive dysfunction, after CEA, and would bring benefit if implemented in routine monitoring to improve the safety of CEA. [15,47,68]

Delirium

There is a significant association between carotid artery stenosis and POD.[73] As a common neurological complication, it is important to study and find a way to prevent it.[30,74]

Morimoto et al.[38] observed a lower intraoperative rSO_2 in patients with POD, compared to patients with no delirium. During CEA the variations in cerebral perfusion and oxygenation are inevitable, together with the vulnerability of cerebral function, even to brief changes, it is understandable that CEA is considered a risk surgery.[41,75]

Pol et al.[76] developed a cohort study including 548 patients submitted to CEA, where 16 (2.9%) patients presented with POD, with a median age of 80 years old. Despite this result, they found a significantly higher incidence of POD among octogenarians after CEA (p=0.0001).

Although we couldn't find any concerning TCD monitoring changes relation with POD, in patients undergoing CEA, cerebral microembolization is a known significant contributor to POD.[77]

Concerning intraoperative EEG monitoring, it is known that POD increases with longer cumulative intraoperative EEG suppression duration.[78] Intraoperative EEG monitoring can be a powerful weapon to reduce burst suppression pattern, by using minimal anaesthetic doses,[56] and therefore reduce POD rate after CEA.[75,79] Putting in practice this premise, Xu et al.[75] got a significantly lower incidence of POD among the group of patients receiving processed EEG-guided anaesthesia management compared with the standard care group [10/127 (7.87%) vs. 37/128 (28.91%), $P < 0.01$].

On the postoperative period its use is also advantageous as the patients show a slowing of background activity, as detected by EEG, during delirium.[43] EEG may provide a consistent diagnostic method of POD in the future, with specific protocols and proper automatic processing.[30]

Limitations

The present systematic review compiles evidence from multiple research syntheses in order to summarise existing evidence. This type of study is useful when the review question is very broad and a number of systematic reviews have already been conducted in the topic area. However, the different inclusion criteria adopted by the reviews here included can make interpretation problematic. There is a considerable number of studies on the topic, but the heterogeneity is substantial: its goes from the different monitoring cut-offs used, different surgery techniques, type of anaesthesia, proportion of symptomatic patients and outcomes studied. This heterogeneity makes a challenge to compare the results and take valid conclusions. It also makes meta-analysis, the qualitative integration of the findings very challenging to execute.

It would be important to create guidelines or consensus between experts of different areas regarding the type and characteristics of the studies needed in the scientific community to support better clinical decisions.

Conclusion

TCD, either using MES OR MCA-V, is able to predict the occurrence of perioperative neurologic events. It has a major limitations due to technical difficulties: not all patients have an adequate temporal window, as well as the proximity to the surgical field or displacement of the device. The EEG is also an excellent option, being able to prevent the occurrence of perioperative stroke and also allowing a guided anaesthesia, to reduce the time of burst suppression and consequently, other neurological and systemic complications. The performance of this method is optimized when used in combination with other neuromonitoring methods. NIRS is affordable, easy to read and also able to predict neurological events. It has the limitation of being influenced by systemic parameters, being this a surmountable limitation, it makes NIRS a good option. Overall, all methos benefit from the combination with others, increasing its sensitivity and specificity.

Focusing on Delirium and Cognitive Dysfunction, although less addressed in the literature, these are outcomes with a considerable incidence and further studies are encouraged. It is also recommended that routine multimodal neuromonitoring be implemented during CEA. This measure will improve the outcomes of patients, their quality of life and the safety of the surgery.

Appendix

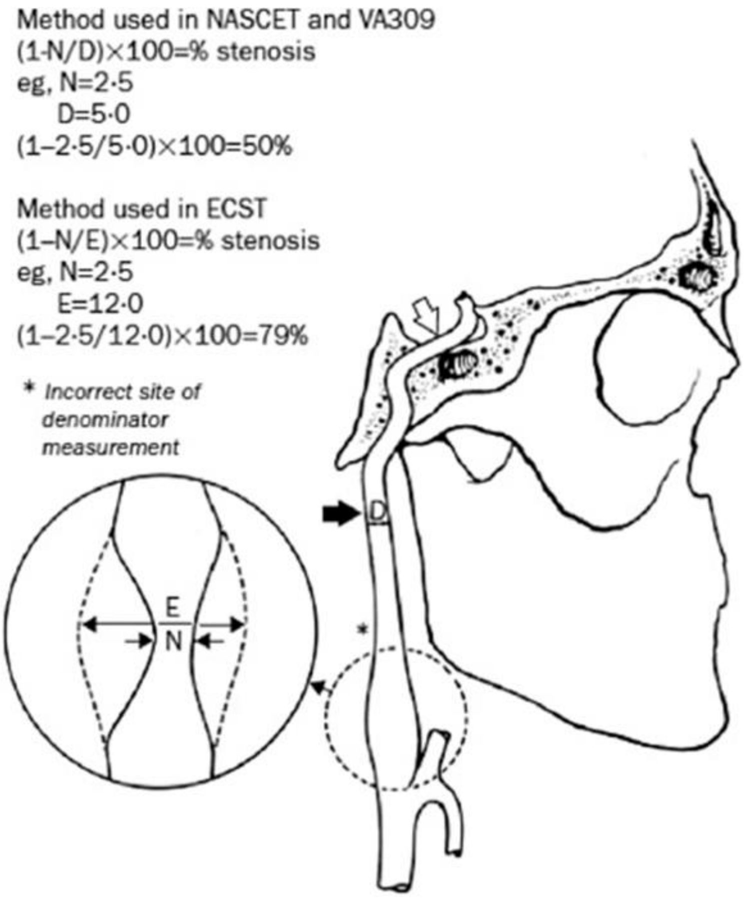

Figure 1: ECST and NASCET methods for measuring stenosis severity (ESVS 2017)[2]

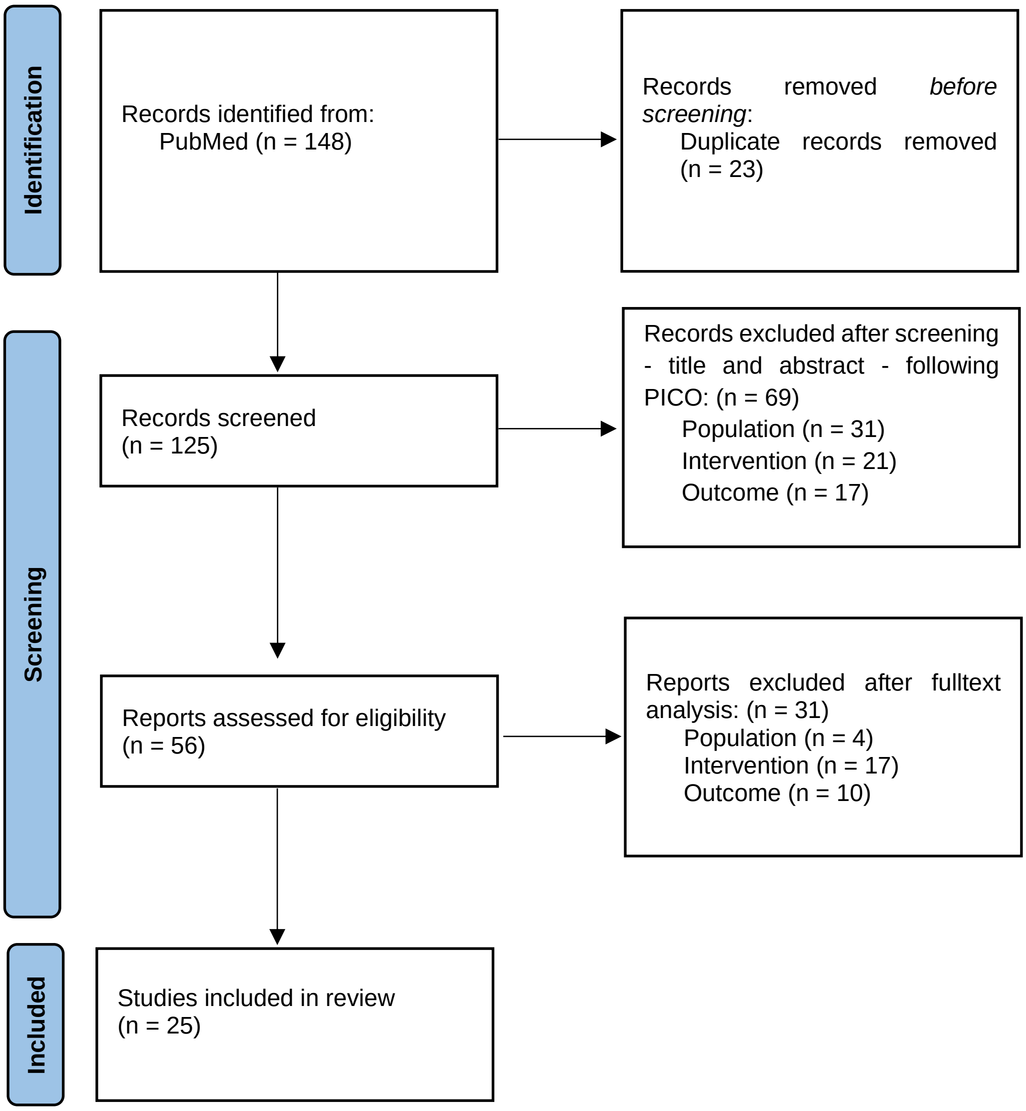

Figure 2: PRISMA 2020 flow diagram for new systematic reviews[1]

Table I: PICO questions developed for query construction

<table>
<tr><th colspan="2" rowspan="2">P: adults undergoing carotid endarterectomy</th><th colspan="3">Outcome</th></tr>
<tr><td>Ischemic stroke</td><td>Cognitive dysfunction</td><td>Delirium</td></tr>
<tr><td rowspan="4">Intervention</td><td>Transcranial Doppler</td><td>h)</td><td>l)</td><td>p)</td></tr>
<tr><td>EEG</td><td>i)</td><td>m)</td><td>q)</td></tr>
<tr><td>NIRS</td><td>j)</td><td>n)</td><td>r)</td></tr>
<tr><td>Intraoperative Neurophysiological Monitoring</td><td>k)</td><td>o)</td><td>s)</td></tr>
</table>

Table II: Characteristic of included studies with TCD monitoring for Stroke

Authors	Study design	Patients	Sx (%)	Stroke rate	Anaesthesia	Monitoring modality	Shunt	Changes in monitoring	Sensibility/ Specificity	Recomendations
Kim et al. (2022)	RCS	160	69%	4/160 (3%)	GA	TCD (MES)	TCD	MES detected in 50/160 (31%) patients, of which 1 stroke;	NA	MES monitoring requires more evidence.
Thirumala et al. (2017)	MA	4705	NA	189/4705 (4.01%)	NA	TCD (MCA-V and MES) + EEG + SSEP	NA	1396 (29.6%) had TCD changes, of which: 110 (7.87%) stroke; 1286 (92.12%) no stroke. 79 patients (2.45%) had a stroke with no TCD changes	**TCD (MCA-V or MES):** 56% sensitivity and 73% specificity; **MCA-V:** 50% sensitivity and 84% specificity; **MES:** 61% sensitivity and 57% specificity.	TCD monitoring during CEA to diagnose perioperative strokes and potentially identify their sources.
Woo-Sung Yun (2017)	RCS	102	75%	2/102 (2%)	GA	TCD (MCA-MV)	TCD	NA	NA	NA
M. Skjelland et al. (2009)	PCS	61	56%	3/61 (4.9%)	GA	TCD (MES)	TCD	Solid and Gaseous microemboli associated with stroke	NA	Solid and gaseous cerebral microemboli numbers should be monitored and reduced to a minimum during CEA
K. OGAsawara et al. (2008)	RCS	163	72%	31/163 (19.02%)	GA	TCD (MCA-V and MES)	0	**TCD**: 8/163 patients with new postoperative neurological deficits, all of them exhibited at least one MES during carotid dissection	**MES ≥ 10**: 63% sensitivity and 80% specificity; **MCA-V≤28 cm/s**: 88% sensitivity and 70% specificity; **MES≥10** and **MCA-V** ≤ 28 cm/s: 50% sensitivity and 98% specificity.	The combination of **MCA MFV ≤ 28 cm/s and number of MES ≥ 10**, to predict the development of new postoperative neurological deficits
S. Moritz et al. (2007)	PCS	48	50%	NA	RA	**TCD** (MCA-V) + SP + NIRS + SSEP	Sx	**TCD**: 9/38 patients with cerebral ischaemia (3 missed due to technical difficulties)	**MCA-V (50%)**: 100% sensitivity and 86% specificity; **MCA-V (70%)**: 78% sensitivity and 100% specificity	Because TCD did not show improved accuracy compared with SP or NIRS, which are both easy to apply, the use of these monitoring systems might be superior in clinical practice.
Laman et al. (2002)	PCS	170	82%	8/170 (4.71%)	GA	TCD (MCA-V)	TCD	ER significantly higher in the CVC group during wound closure and the postoperative period.	**TCD embolic rate** **> 0.9 e/min** during the postoperative period: 100% sensitivity, 75% specifiticy; **> 0.04 e/min** during wound closure had 100% sensitivity and 65% specificity;	TCD monitoring during CEA, starting 40min to 1h after clamp release.
Ackerstaff et al. (2000)	RCS	1058	78%	39/1058 (3.7%)	GA (20 RA)	TCD (MCA-MV and MES)	TCD	≥90% MCA-V decrease at cross-clamping.	NA	TCD as a quality control assessment for early detection of microemboli and MCA-V changes during surgery.
Müller et al. (2000)	PCS	76	49%	4/76 (5.3%)	GA	TCD (MCA-MV and MES)	TCD	NA	NA	NA

Table III: Characteristic of included studies with EEG monitoring for Stroke

Authors	Study design	Patients	Sx (%)	Anaesthesia	Monitoring modality	Shunt	Stroke Rate	Changes in monitoring	Sensitivity/ Specificity	Recomendations
R. Chang, et al. (2020)	MA	10672	64%*	NA	EEG (<8 and >8 channels)	NA	212/10671 (1.99%)	1713 patients (16,1%) had EEG changes, of which 94 (5.49%) had a stroke; 118 (1.32%) patients had a stroke without EEG changes	46% sensitivity and specificity of 86% of EEG changes in predicting stroke	Restoring EEG changes to baseline frequencies and amplitude through reperfusion to reduce the incidence of perioperative stroke.
M. Leopardi et al. (2019)	RCS	152 132	22% 21%	GA	TCD + SP EEG + SP + SSEP	TCD SP EEG SSEP	3 (1.9%) 2 (1.5%)	5 patients had a stroke, of which 3 had no monitoring changes and 2 had changes (1 TCD and 1 SSEP)	NA	EEG with SSEP during carotid surgery demonstrated to be safe and sensitive to predict a cerebral ischemia during carotid clamping.
Thirumala aet al. (2016)	MA	8765	70%*	NA	EEG (<8 and >8 channels)	NA	1.75% (153/8765)	153 patients had a stroke, of which 81 (52.94%) had EEG changes and 72 (47.06%) did not.	52% sensitivity and 84% specificity of EEG changes in predicting stroke	EEG monitoring during CEA can serve as a biomarker of cerebral ischemia.
Khattar et al. (2016)	RCS	584	59%	GA	EEG (8 channels) + SSEP	EEG SSEP	21/584 (3.595%)	6,93% of the patients who had a stroke, had significant changes 38.10% who didn't have stroke, had changes	NA	SSEPs and EEG can function as a biomarker of cerebral hypoperfusion and perioperative strokes during CEA.
G. Pappadà et al. (2010)	RCS	390 (413 CEAs)	81%	GA	EEG	EEG	9/413 (2.2%)	None of the patients 9 patients who had a stroke, showed signs of EEG dysfunction	NA	NA
Hans and Jareunpoon (2007)	PCS	314	23%	RA	EEG (16 channels)	Sx	4/314 (1.2%)	32 patients showing neurological symptoms, of which 19 (59.4%) had EEG changes	NA	NA
Reuter et al. (2004)	RCS	129	50%	GA	EEG (8 channels) + SP	SP EEG	12/129 (9.3%)	NA	NA	When EEG evidence of ischemia is present, shunting is necessary, or a high rate of neurologic events will follow.
Pinkerton (2002)	RCS	1661	57%	GA (132 RA)	EEG (16 channels) + SP	EEG	5/1661 (0.03%)	366 operations had EEG changes, of which 4 (1.1%) patients had a stroke	NA	EEG monitoring as a criterion for determining shunt need during carotid endarterectomy.

*Data pertaining to the number of subjects with symptomatic disease could not be obtained from all the studies analysed

Table IV: Characteristic of included studies with NIRS monitoring for Stroke

Authors	Study design	Patients	Sx (%)	Stroke rate	Anaesthesia	Monitoring modality	Shunt	Changes in monitoring	Sensibility / Specificity	Recomendations
Yu Wang et al (2019)	PCS	84	83%	0	GA	NIRS + TCD (MCA-MV)	TCD	A significant drop of rSO_2 value occurred after carotid clamping.	64% sensitivity and 90% specificity of NIRS monitoring (cut-off of 12.3%) for intraoperative hypoperfusion	NIRS as a substitute for TCD for patients without satisfactory temporal bone windows.
O.V. Kamenskaya et al. (2017)	PCS	466	77%	7/466 (1.5%)	GA	NIRS + SP	0	rSO_2 and ΔrSO_2 significantly decreased at carotid artery clamping.	For ΔrSO2 (cut-off of 20%) during carotid clamping 86% sensitivity and 57% specificity for predicting stroke	NIRS monitoring previously and during CEA to prevent neurological complications, particularly stroke and cognitive dysfunction.
H. B. Nielsen (2014)	SR	NA	NA	NA	NA	NIRS	NA	20–25% decline in rSO_2 appears to predict POCD	NA	A 10% decrease in rSO2 as an indicator for therapeutic intervention to raise cerebral O2 saturation and prevent neurological complications.
Pedrini et al. (2012)	PCS	473	30%	0	GA	NIRS + SP	NIRS	Clamping induced a significant decrease of mean rSO_2.	100% sensitivity and 95% specificity, (cut-off of 25%) for intraoperative hypoperfusion.	NIRS is a reliable method, with a cutoff of 20% or 25% for prolonged hypoperfusion.

Table V: Characteristic of included studies with monitoring for Cognitive Dysfunction

Authors	Study design	Patients	Sx (%)	Stroke rate	Anaesthesia	Monitoring modality	Shunt	POCD incidence	Changes in monitoring	Sensibility/ Specificity	Recomendations
Mergeche et al (2014)	PCS	124	43%	0	GA	**TCD** (MCA–MV) + **EEG** (16 channel)	0	59/124 (47.6%)	Patients with cognitive dysfunction had significantly lower MCA-V during cross-clamp.	NA	TCD assessment of MCA–MV during CEA may be an appropriate approach to reducing the risk of cognitive dysfunction after surgery and further improving the safety of CEA.
O.V. Kamenskaya et al. (2017)	PCS	466	77%	7/466 (1.5%)	GA	NIRS + SP	0	12/466 (2.6%)	20% or more decrease in rSO2 during temporary internal carotid artery clamping	For ΔrSO2 (cut-off 20% decrease) during carotid clamping 88% sensitivity and 58% specificity for predicting POCD	NIRS monitoring previously and during CEA to prevent neurological complications, particularly stroke and cognitive dysfunction.
H. B. Nielsen (2014)	SR	NA	NA	NA	NA	NIRS	NA	NA	20–25% decline in rSO2 appears to predict POCD	NA	A 10% decrease in rSO2 as an indicator for therapeutic intervention to raise cerebral O2 saturation and prevent neurological complications.

Table VI: Characteristic of included studies with monitoring for Delirium

Authors	Study design	Patients	Sx (%)	Stroke rate	Anaesthesia	Monitoring modality	Shunt	POD incidence	Significative findings	Recomendations
Xu et al. (2021)	RCT	255 (127 EEG)	NA	1/127 (0.79%)	GA	**TCD** (MCA-V) + **EEG** (4 channels) + **NIRS**	TCD	10/127 (7.87%)	The incidence of postoperative delirium was significantly lower among patients receiving processed EEG-guided anaesthesia compared with the standard group [10/127 (7.87%) **vs**. 37/128 (28.91%), P < 0.01]	Patients with carotid artery stenosis can benefit from multimodal monitoring during surgery to reduce the onset of EEG suppression.
Pol et al. (2012)	PCS	548	90%	8 (1.5%)	GA	EEG (8 channels) + SP	EEG	16 (2.9%)	We found a significantly higher incidence of POD among octogenarians after CEA (p=0.0001).	Octogenarians should be considered a high-risk population for POD, and by starting preventive treatment or aggressive assessment during hospitalization, perhaps the incidence of POD and ultimately HDOS could be reduced.

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