Rev Bras Anestesiol. 2018;68(6):613-623

REVISTA BRASILEIRA DE ANESTESIOLOGIA
Publicação Oficial da Sociedade Brasileira de Anestesiologia
www.sba.com.br

REVIEW ARTICLE

Anesthetic management of endovascular treatment for acute ischemic stroke: Influences on outcome and complications

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Received 8 April 2017; accepted 15 June 2018
Available online 24 July 2018

KEYWORDS
Anesthesia;
General anesthesia;
Conscious sedation;
Stroke;
Thrombectomy;
Endovascular procedures;
Neuroprotection

Abstract
Background and objectives: The emerging use of endovascular therapies for acute ischemic stroke, like intra-arterial thrombectomy, compels a better understanding of the anesthetic management required and its impact in global outcomes. This article reviews the available data on the anesthetic management of endovascular treatment, comparing general anesthesia with conscious sedation, the most used modalities, in terms of anesthetic induction and procedure duration, patient mobility, occlusion location, hemodynamic parameters, outcome and safety; it also focuses on the state-of-the-art on physiologic and pharmacologic neuroprotection.
Contents: Most of the evidence on this topic is retrospective and contradictory, with only three small randomized studies to date. Conscious sedation was frequently associated with better outcomes, but the prospective evidence declared that it has no advantage over general anesthesia concerning that issue. Conscious sedation is at least as safe as general anesthesia for the endovascular treatment of acute ischemic stroke, with equivalent mortality and fewer complications like pneumonia, hypotension or extubation difficulties. It has, however, a higher frequency of patient agitation and movement, which is the main cause for conversion to general anesthesia.
Conclusions: General anesthesia and conscious sedation are both safe alternatives for anesthetic management of patients submitted to endovascular thrombectomy.

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https://doi.org/10.1016/j.bjane.2018.06.003

No anesthetic management is universally recommended and hopefully the ongoing randomized clinical trials will shed some light on the best approach; meanwhile, the choice of anesthesia should be based on the patient's individual characteristics. Regarding neuroprotection, hemodynamic stability is currently the most important strategy, as no pharmacological method has been proven effective in humans.

PALAVRAS-CHAVE
Anestesia;
Anestesia geral;
Sedação consciente;
Acidente vascular cerebral;
Trombectomia;
Procedimentos endovasculares;
Neuroproteção

Manejo anestésico do tratamento endovascular para acidente vascular cerebral isquêmico agudo: influências no resultado e complicações

Resumo
Justificativa e objetivos: O uso emergente de terapias endovasculares para acidente vascular cerebral isquêmico agudo, como a trombectomia intra-arterial, nos obriga a uma compreensão melhor do manejo anestésico necessário e seu impacto nos resultados globais. Este artigo revisa os dados disponíveis sobre o manejo anestésico do tratamento endovascular, comparando anestesia geral com sedação consciente, as modalidades mais utilizadas, quanto à indução anestésica e duração do procedimento, mobilidade do paciente, localização da oclusão, parâmetros hemodinâmicos, desfecho e segurança; abordando também o estado da arte da neuroproteção fisiológica e farmacológica.
Conteúdo: A maioria das evidências sobre esse tópico é retrospectiva e contraditória, com apenas três pequenos estudos randômicos realizados até o momento. A sedação consciente foi frequentemente associada a melhores resultados, mas as evidências prospectivas indicaram que não há vantagem sobre a anestesia geral em relação a essa questão. A sedação consciente é no mínimo tão segura como a anestesia geral para o tratamento endovascular do AVC isquêmico agudo, com mortalidade equivalente e menos complicações, como pneumonia, hipotensão ou extubações difíceis. Porém, a sedação consciente apresenta uma frequência maior de agitação e movimento do paciente, sendo a principal causa de conversão para a anestesia geral.
Conclusões: Anestesia geral e sedação consciente são alternativas seguras para o manejo anestésico de pacientes submetidos à trombectomia endovascular. Não há um manejo anestésico que seja universalmente recomendado e esperamos que os ensaios clínicos randomizados em andamento possam lançar alguma luz sobre a melhor abordagem; enquanto isso, a escolha da anestesia deve basear-se nas características individuais do paciente. Em relação à neuroproteção, a estabilidade hemodinâmica é atualmente a estratégia mais importante, uma vez que nenhum método farmacológico se mostrou eficaz em humanos.

Introduction

Acute Ischemic Stroke (AIS) is one of the leading causes of mortality and morbidity worldwide[1] and its significant burden has driven the scientific research towards the study of treatment options.

Intravenous recombinant Tissue Plasminogen Activator (IV rtPA) has been the standard treatment for AIS since 1996, when it was approved by the Food and Drug Administration. Endovascular therapy has recently emerged as a supplement to IV rtPA or eventually as a plausible alternative to the standard treatment for patients not eligible for it; it was included in the 2015 American Heart Association/American Stroke Association updated guidelines for the early management of AIS and is highlighted in the 2018 Guidelines for the Early Management of Patients with Acute Ischemic Stroke. There are two endovascular approaches: intra-arterial fibrinolysis or intra-arterial mechanical thrombectomy (with a multitude of devices available); the preferred technique is the thrombectomy with a stent retriever.[2]

A key factor plays an important role in both treatments: time. The concept of ''time is brain'' – meaning that nervous tissue in the penumbra region of reduced blood flow in the brain is not salvageable after a few hours – has long been known, and a shorter period of time between symptom onset and reperfusion is associated with better clinical outcomes.[3] In the particular case of mechanical thrombectomy, time from symptom onset to groin puncture should ideally be less than 6 h, although mechanical thrombectomy might still improve outcome when performed even up to 16–24 h from symptom onset in some restricted cases, as it is considered in the 2018 stroke guidelines.[2] The anesthetic management considered in the endovascular treatment of AIS is determinant in the timing of initiation of the procedure, hence the need for a better understanding of the impact of the anesthetic choice in treatment outcomes.

General anesthesia (GA) and conscious sedation (CS) are the two most used modalities for patients with AIS undergoing intra-arterial thrombectomy. Each has potential advantages and limitations: general anesthesia is thought to be associated with less agitation and movement but may delay the beginning of the endovascular procedure; conscious sedation allows neurological monitoring but may induce pain and movement, making the procedure longer and technically more difficult. Some studies also include consider monitored anesthesia care approach or even local analgesia alone.[4–6]

The lack of randomized prospective information on this topic dictated that practice was based on retrospective studies, meta-analysis and surveys. The Society of Neuroscience in Anesthesiology and Critical Care (SNACC) consensus gave some general recommendations on anesthetic management and hemodynamic goals, based on the available evidence at the time.[7] However, a substantial number of trials are now ongoing[8–10] and the results from three randomized studies (SIESTA, AnStroke and GOLIATH) have been published.[11–13] This article reviews the available data on the anesthetic approach of intra-arterial thrombectomy, comparing general anesthesia with conscious sedation in terms of anesthetic induction and procedure duration, patient mobility, occlusion location, hemodynamic parameters, outcome and safety; it also focuses on the state of the art on neuroprotective strategies.

Methods

Literature search of articles comparing general anesthesia and conscious sedation on endovascular treatment of acute ischemic stroke was conducted between January 2000 and February 2018 using the following databases: MEDLINE (via Pubmed) and Web of Science. A combination of the following search terms was used: stroke, anesthesia, thrombectomy, endovascular, conscious sedation, general anesthesia, neuroprotection. Additionally, the references of various articles were examined to find studies which did not appear in the initial search.

Identified abstracts from the literature were then further evaluated considering the following inclusion criteria: (1) Being clinical trials, retrospective original studies, reviews (qualitative or systematic), meta-analyses, editorials, consensus or guidelines; (2) Abstract referring to endovascular treatment/mechanical thrombectomy in acute ischemic stroke or neuroprotection; (3) Full text available; (4) Full text in English or Portuguese. The articles with the highest times cited number on the Web of Science was given particular importance, as did the published clinical trials.

According to the inclusion criteria and their relevance, 46 articles were selected (Fig. 1).

Ongoing clinical trials were assessed through a search on clinicaltrials.gov.

General anesthesia versus conscious sedation

General anesthesia is generally regarded as a safe anesthetic approach for the endovascular treatment of AIS, mainly because of patient immobility, absence of pain, airway control (with presumed less risk of intraprocedural aspiration) and optimal control of oxygenation and carbon dioxide levels. The main disadvantages appointed to this method are increased induction time (time from symptom onset to groin puncture), hypotension and greater blood pressure fluctuations, complications associated with airway management (pneumonia and sepsis), more difficult post anesthetic recovery, and a greater need of qualified anesthesiologists, which assumes greater costs.[7,14–17]

Conscious sedation, on the other hand, allows monitoring during the procedure for new neurological deficits and has less iatrogenic hemodynamic variation and less delay to the beginning of the intervention, yet it has risks like pain, agitation and movement with possible vessel perforation, upper airway obstruction, respiratory depression, increased procedure time with increased use of contrast and possible emergency conversion to GA.[7,14–18]

The majority of retrospective studies and also the published and ongoing clinical trials compare these anesthetic modalities not only in terms of outcome but also procedure duration, patient mobility, hemodynamic parameters such as blood pressure and overall safety. These aspects will be reviewed in more detail. Table 1 contains a summary of the studies included in this review.

Time to groin puncture and procedure time

For every minute a great vessel AIS goes untreated, 1.9 million neurons and 13.8 billion synapses are lost.[3] Treatment of AIS is an emergency and the sooner it is initiated, the better the outcome; this is why a delay from symptom onset to groin puncture is a major concern when GA is the option chosen. In one study, this delay was found to be of 15 min, comparing with CS[18]; in another study, it was of 20 min.[15] While some scientists do worry about this delay and found it related to worse outcomes in GA compared to CS[15], others considered that this relatively short delay occurring with GA seems to be tolerable especially considering that GA allows the procedure to be performed under optimal conditions, avoiding delays during the treatment itself, which may be far longer if there is patient movement, as it may occurs in awake patients.[18] John et al. describe a longer time of induction and intubation but a shorter time from incision to target vessels with GA, with a global time from symptom onset to recanalization similar between groups.[6]

One study with 980 patients found no significant differences in time to puncture and time to recanalization between CS and GA, but the authors still consider that a delay in GA not demonstrated by their methods might account for some differences in outcome.[19]

In the SIESTA trial, the first randomized controlled trial published on the subject, Schönenberger et al. describe a gain of 10 min when using CS, although no differences in outcome came from that.[11] In the AnStroke and GOLIATH trials the time from stroke onset to groin puncture or to

Table 1 Summary of the anesthetic approach in cited studies.

Study	Type	*n*	Affected circulation	Anesthetic approach	Outcomes	Limitations reported by the investigators
Abou-Chebl[19] 2010	Retrospective, multicentric (12 centers)	980	Anterior circulation large-vessel occlusion strokes	GA vs. CS	GA associated with: poorer neurological outcome at 90 days; higher mortality. No difference in hemorrhagic complications.	Retrospective and non randomized nature GA – more likely to have carotid terminus occlusions and higher baseline NIHSS scores
Abou-Chebl[38] 2015	Retrospective, multicentric (58 centers; cohort from IMS III trial)	434	Anterior, middle and posterior circulation strokes	GA vs. LA	GA associated with: worse neurological outcomes; increased mortality	Retrospective and non-randomized nature. LA – lower NIHSS scores.
Abou-Chebl[37] 2014	Retrospective, multicentric (18 centers)	281	Anterior and posterior circulation strokes	GA vs. LA	GA associated with: worse neurological outcomes; higher mortality No difference in intracranial hemorrhage risk	Retrospective and non randomized nature LA – lower NIHSS scores
Jumaa[17] 2010	Retrospective, monocentric	126	Occlusion of the M1 segment of the middle cerebral artery	Intubated (IS) vs. Non-intubated (NIS)	IS associated with: greater final infarct volume; worse outcomes; higher in-hospital mortality	Retrospective and non randomized nature Small sample size IS – higher baseline NIHSS scores
van den Berg[15] 2015	Retrospective, multicentric (16 centers; cohort from MR CLEAN trial)	348	Anterior circulation stroke	Ga vs. non-GA	GA associated with worse outcomes	Retrospective and non randomized nature – possible selection bias Inequality in group sizes (non-GA 278 vs. GA 70).

Table 1 (*Continued*)

Study	Type	*n*	Affected circulation	Anesthetic approach	Outcomes	Limitations reported by the investigators
Davis[4] 2012	Retrospective, monocentric	96	Large vessel occlusion	GA vs. LA (with or without CS, as needed)	GA associated with: worse outcomes; higher mortality	Retrospective and non randomized nature GA – more severe strokes
Nichols[5] 2010	Retrospective, multicentric (13 centers; cohort from IMS II Study)	75	Anterior circulation stroke	No sedation, mild sedation, heavy sedation, pharmacological paralysis	Mild or no sedation associated with: higher rate of good outcomes; lower mortality; higher angiographic reperfusion rates	Retrospective and non randomized nature Small sample size Baseline NIHSS varied significantly between different levels of sedation (higher in deeper sedation categories)
John[6] 2014	Retrospective, monocentric	190	Anterior circulation stroke	GA vs. MAC	GA associated with: higher mortality; higher rate of parenchymal hematomas No statistical difference in outcomes between groups	Retrospective and non randomized nature – possible selection bias
Li[36] 2014	Retrospective, monocentric	109	Anterior, middle and posterior circulation strokes	GA vs. CS	GA associated with: higher mortality; longer door-to-recanalization time	Retrospective and non randomized nature Small sample size Lack of long-term clinical follow-up at 90 days
Sugg[32] 2010	Retrospective, monocentric	66	Anterior, middle and posterior circulation strokes	GA vs. non-anesthetized	Nonanesthetized associated with: better outcome; lower complication rate	Retrospective and non randomized nature Small sample size

Table 1 (*Continued*)

Study	Type	*n*	Affected circulation	Anesthetic approach	Outcomes	Limitations reported by the investigators
Just[39] 2016	Retrospective, monocentric	109	Anterior, middle and posterior circulation strokes	GA vs. CS	GA associated with: higher mortality at hospital discharge, 3 months and 6 months poststroke onset; greater morbidity	GA – older and higher baseline NIHSS scores Retrospective and non randomized nature Long duration of the study (2000–2013) – technology and technique have evolved significantly over the course of the study Did not study hypotension
Schonenberger[11] 2016	Prospective, monocentric	150	Anterior circulation stroke	GA vs. CS	No statistical difference in primary outcome (early neurological improvement) No difference in mortality	Single center Anesthesiologists more experienced on GA Small sample size
Hendén[12] 2017	Prospective, monocentric	90		GA vs. CS	No statistical difference in neurological outcome 3 months after stroke or in mTICI 2b/3 recanalization	Single center Small sample size
Simonsen[13] 2018	Prospective, monocentric	128		GA vs. CS	No statistical difference in primary outcome (infarct growth during endovascular treatment) nor in safety endpoints GA associated with lower 90 day mRS scores	Single center The primary endpoint was infarct growth – no definitive conclusions regarding clinical outcomes Small sample size

CS, conscious sedation; GA, general anesthesia; LA, local anesthesia; MAC, monitored anesthesia care; mRS, Modified Rankin Scale; mTICI, modified Treatment in Cerebral Infarction score; NIHSS, National Institutes of Health Stroke Scale.

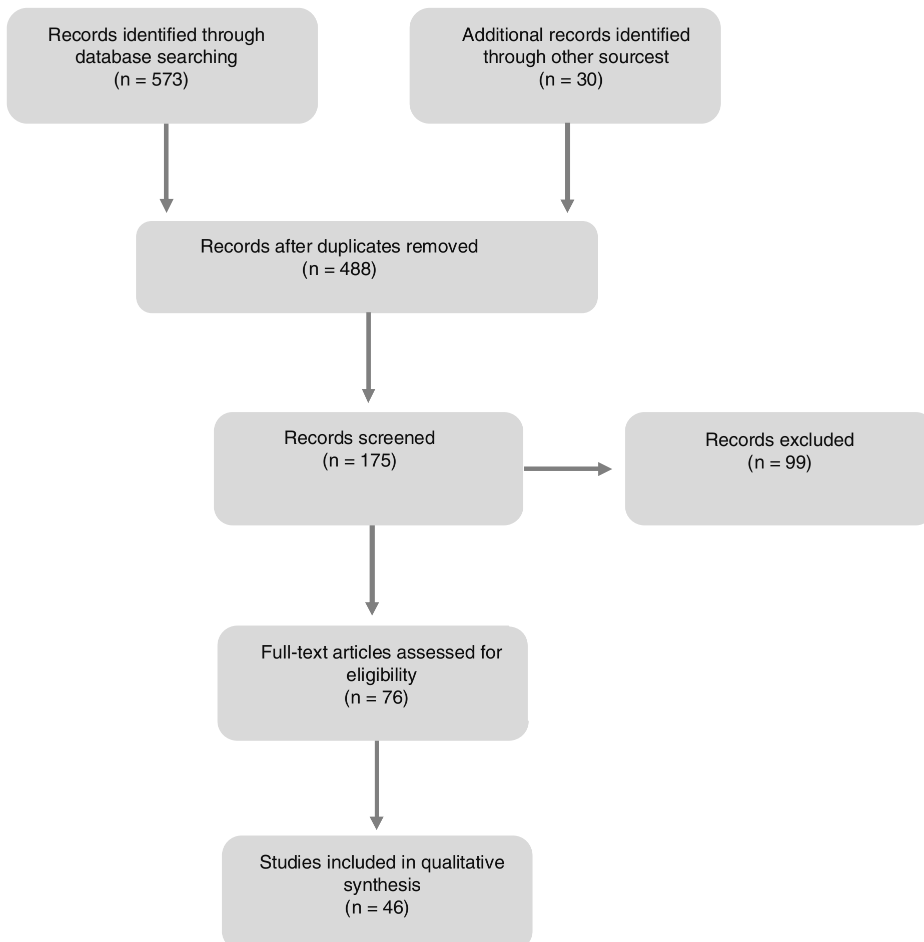

Figure 1 Article selection flowchart.

recanalization was not statistically different in both arms (GA and CS) of the study.[12,13]

Patient mobility

Patient mobility is the major problem regarding CS and one of the main reasons why many physicians prefer GA – a survey conducted in 2010 among 68 members of the Society of Vascular and Interventional Neurology revealed that more than half the respondents preferred GA as their anesthetic method of choice, under the assumption that limited movement correlates with more safety and efficacy.[14]

Patient mobility and agitation can be related to pain, which can be due to the innervation of the blood vessels which are being manipulated[19] or to the transmission of tension to the dura matter.[18] If the patient moves, it can affect fluoroscopy and digital subtraction angiography, increasing the difficulty of the procedure and the risk of complications, such as vessel perforation and brain hemorrhage.[19] Some researchers, however, report very low rates of wire perforation during percutaneous coronary interventions in which the heart is constantly moving,[20] affirming that perforation in endovascular treatments might not be primarily caused by movement.[19]

Nonetheless, perforation and cervical carotid dissection were unexpectedly more frequent in the GA group in Jumaa et al. study, a finding the authors admit could be due to chance.[17]

In the AnStroke trial the rate of procedural complications was similar between the CS and GA groups, despite a higher incidence of patient movement and worse angiographic quality in the CS group.[12]

Janssen et al. studied the applicability of a standard cervical collar for head immobilization in order to reduce the risks of mobility associated with CS, an option which seemed to have a calming effect on patients, and the outcomes were favorable.[21]

Patient movement is a main cause for emergent conversion to GA and other cause for conversion is emesis, with greater risk of aspiration. The conversion rates range from 2.7% to 3.7% in various studies.[15,17,22] Hassan et al. studied conversion in various types of neuroendovascular procedures and reported a global conversion rate from CS to GA of 1.7% (9 in 526 patients), which was not related to worse outcomes than the group managed with GA from the beginning.[22]

Affected circulation

Endovascular treatment with stent retrievers can be used in patients with occlusion of the internal carotid artery or proximal (M1) portion of the middle cerebral artery and might be appropriate for AIS caused by occlusion of the M2 or M3 portion of the middle cerebral arteries, anterior cerebral arteries, vertebral arteries, basilar artery, or posterior cerebral arteries.[2]

Posterior circulation occlusion causes 15–20% of all AIS; basilar artery occlusion is a subset of posterior AIS, causing only 1–4% of all AIS.[23] When the basilar artery is the occluded vessel, patients usually have changes in level of consciousness.[17] SNACC recommends the use of GA in posterior circulation stroke, as they frequently cannot protect the airway (Class IIa, Level of evidence B).[7] There is a lack of studies comparing CS and GA on specific territories and most of them do not focus on posterior circulation AIS, because these patients are almost exclusively managed with GA.[6,17,19] The three clinical trials published focus only on anterior circulation strokes.[11–13]

Hemodynamic parameters – blood pressure

The ischemic penumbra area is highly sensitive to variations in Blood Pressure (BP). As AIS impairs cerebral autoregulation, hypertension and hypotension can cause edema and hemorrhage or infarct extension, respectively, adversely impacting the outcome.[24,25] The SNACC consensus recommends a systolic target of 140–180 mmHg (a study associates this range with better outcomes)[25] and a diastolic blood pressure below 105 mmHg; hypotension should be avoided using fluids and vasopressors (Class IIa, Level of evidence B).[7] Vasopressors commonly used are epinephrine, norepinephrine, phenylephrine or ephedrine,[26,27] but the choice should depend on the patient's individual characteristics.[7] The recently published 2018 Guidelines for the Early Management of Patients With Acute Ischemic Stroke also recommends similar targets (BP $\leq$ 180/105 mmHg) when performing mechanical thrombectomy on stroke patients and during the following 24 hours.[2]

Hypotension is frequent after the induction of GA[27–29] and may diminish perfusion of the penumbra area by collateral vessels, therefore impairing recovery.[30]

Hendén et al. retrospectively studied 108 patients managed with GA for endovascular treatment of AIS, hypothesizing that intraprocedural hypotension was an independent predictor for poor neurological outcomes. In their study, the mean BP was 107 mmHg and almost all patients had a drop in BP during the procedure, with 69 patients (63.8%) falling more than 40% from baseline. It was this mean arterial BP fall of more than 40% from baseline that the authors found to be an independent predictor of poor neurologic outcomes. They also suggest that vasopressors should be administered during induction of GA, after correcting possible hypovolemia with fluids and heart failure with inotropic agents.[30] This team of researchers was also responsible for the AnStroke trial and considered the previous results in this study's protocol, with a more aggressive control of intraprocedural hypotension and consequently a higher use of vasoactive drugs in the GA group.[12]

Chung et al. indicate BP variability – not only BP drops – as independently and linearly associated with neurologic deterioration in AIS.[31] Mundiyanapurath et al. identified a greater BP variability in patients treated under GA, apart from lower mean systolic BP values with episodes of hypotension (systolic BP < 100 mmHg) requiring vasopressors like norepinephrine.[27]

A study of 190 patients by John et al., nevertheless, found no significant differences in hemodynamic variables between GA and monitored anesthesia care.[6] Schönenberger's prospective trial also showed that the mean systolic BP and the variability of systolic BP were not significantly different between GA and CS, which contradicts most of the retrospective evidence.[11]

Sivasankar et al. observe that the diversity of findings concerning blood pressure may be due to differences in dosage of anesthetics or sedatives.[26]

Outcome

Albeit a general preference of GA by practitioners, recent retrospective studies pose CS as an equally safe alternative and even related with better outcomes.[4,15,17,19]

Juma et al. study with 126 patients described an independent association with favorable outcomes of not only age, admission NIHSS score and successful recanalization, but also of CS, which was also related to favorable radiographic outcomes.[17]

Nichols et al. did not compare specifically CS to GA, but also found that lower levels of sedation were independently associated with good clinical outcomes and successful reperfusion and that heavy sedation or pharmacological paralysis was a predictor of mortality.[5] This was also true for a study comparing GA with a non-anesthetized approach.[32]

John et al. revealed similar rates of recanalization, but patients managed with GA had lower associations with good outcomes (not statistically significant).[6]

Contrasting with recent retrospective evidence, the first randomized trial in this area determined that CS was not superior to GA in the management of endovascular treatment of AIS, with early neurological improvement similar in both groups.[11] The other prospective trials also suggested that GA is as safe and effective as CS.[12,13] Interestingly, both the SIESTA and the GOLIATH trial described a tendency for greater functional independence at 90 days in the GA arm;[11,13] however, no difference was found in functional outcome at 3 months in the AnStroke trial.[12]

A study by Sivasankar et al. offered a different perspective on the anesthetic management of endovascular treatment, stating that different methods of general anesthesia (volatile, intravenous or combined) may have different outcomes; in their study, patients with better outcomes were managed with volatile drugs only. The authors criticize the study of non-characterized general anesthesia and sedation, suggesting that future investigation should well-defined anesthetic agents.[26]

Safety/complications

Complications during endovascular treatment of AIS can be divided in two groups: complications of the procedure itself and complications related to the anesthetic management. The most serious complication is cerebral hemorrhage, which can be symptomatic or not. Stent retrievers are related to a frequency of symptomatic intra-cerebral hemorrhage between 1.5% and 15%, as reported by recent trials.[7]

As patients are awake in CS, new or worsening neurological deficits can be assessed during the procedure and the endpoint of treatment can be based on clinical improvement and not only on angiographic recanalization. Deficits may be attributable to decreases in local blood flow due to embolization, thrombus formation, progression of ischemic area or hematoma.[19] This intra-procedural monitoring is one of the advantages of CS, but John et al. point out that a stroke patient frequently has acute neurologic deficits and may be disphasic, which can largely limit the communication with the physician, hampering intra-procedural questioning.[33]

Procedure-related complications are vessel perforation with intracranial hemorrhage (symptomatic or asymptomatic), arterial dissection, distal embolization and problems related to the access site, like groin or retroperitoneal hematomas.[5] When grouping the various trials in the subject, total complications rates were 0–20% and 1–6% when only embolization, dissection and perforation were considered.[34]

Abou-Chebl et al. found no difference in post-treatment intracranial bleeding.[19] John et al. also did not find differences in hemorrhagic transformation of stroke between GA and monitored anesthesia care, but GA managed patients had a higher rate of parenchymal hematomas.[6]

Complications of the anesthetic management are aspiration, pneumonia, blood pressure lability, patient movement and upper airway obstruction. There are some complications specifically attributed to intubation in GA, like pneumonia (aspiration and ventilator-related) and extubation difficulties. AIS patients have certain characteristics that can be associated with a higher risk of pneumonia, like diminished airway reflexes, pharyngeal muscles relaxation, hypovolemia and dysphagia.[35]

Jumaa et al. documented a longer ICU stay in patients managed with GA, primarily due to difficulties in weaning off the ventilation, and a higher rate of early pneumonia in this group of patients. Their main conclusion was that CS was at least as safe as GA for endovascular treatment.[17]

The rate of pneumonia was also higher in GA group in two other studies[5,35]; Hassan et al. hypothesized that the higher rate of pneumonia was responsible for poorer outcomes with GA, but concluded that pneumonia was not the major reason for that.[35]

Additionally, intubation is more related to withdrawal of care than CS, accounting for a part of the increased mortality of patients managed with GA.[17] This higher mortality of the deeply sedated patients, related or not to the discontinuation of therapy, is reported by various studies.[4–6,19,36–39]

No significant differences in mortality between the GA and CS groups were reported in any of the published randomized trials.[11–13] In the SIESTA trial complications like hypothermia, delayed extubation and pneumonia were more frequent in patients managed with GA,[11] but the AnStroke trial did not show differences in complication rates between groups.[12]

Neuroprotection

Cerebral neuroprotection aims to improve the brain's tolerance to ischemia, protecting neurons and other components of the cerebral system.[40] This can be done by maintaining the blood flow in the penumbra area, decreasing metabolic demand or diminishing the deleterious effects of mediators released by cell death.[41] It is regarded as a set of measures complementary to reperfusion in AIS which theoretically can be started in the pre-hospital setting, possibly extending the time window to subsequent treatments.[42]

Some pharmacological agents have shown neuroprotective properties in animal experiments and other preclinical trials, but human studies results have been controversial and unsatisfactory.[43] An example is magnesium sulfate, which was tested in a cardiac and non-cardiac setting, showing neuroprotective effects in both,[43,44] and it was also neuroprotective in animal models of stroke.[42] However, it did not improve disability outcomes at 90 days after stroke in a phase 3 trial.[42]

Currently, there is not a single agent with proven neuroprotective properties in humans. Intravenous anesthetics such as thiopental (a barbiturate), propofol, ketamine, lidocaine and etomidate, and the inhalational anesthetics isoflurane, desflurane, sevoflurane, xenon and argon are some of the agents that have been studied, with inconclusive results so far.[43]

Other methods of neuroprotection aside from pharmacological neuroprotection, such as hypothermia, are being studied. Hypothermia is an established therapy for cardiac arrest and hypoxic ischemic encephalopathy in children, it has been shown to be neuroprotective in laboratory animal models of AIS,[45] and has had promising results in preliminary trials[46]; nonetheless, it has yet to be definitely proven beneficial in human studies.[47,48] The SNACC consensus does not recommend hypothermia, proposing a target temperature of 35–37 °C, maintained with antipyretics and cooling devices if needed (Class IIb, Level of evidence B).[7]

Surely, maintaining the hemodynamic parameters within the normal values is an important component of neuroprotection. Besides body temperature and arterial BP, referred above, oxygenation, ventilation and glycemic values are also considered in the SNACC consensus. Logically, hypoxia should be avoided, and recommendations are that supplemental oxygen should be considered and that FiO_2 should be titrated to keep $SpO_2 > 92\%$ and $PaO_2 > 60$ mmHg (Class IIa, Level of evidence C).[7]

Hyperventilation and hypocapnia can cause cerebral vasoconstriction, therefore reducing the cerebral blood flow and having an adverse impact on the penumbra area. The evidence points towards a correlation between GA and hypocapnia, with lower end tidal carbon dioxide ($ETCO_2$) being associated with worse outcomes.[28] Surprisingly, in Mundiyanapurath et al. study, patients under CS had a lower $ETCO_2$ related to hyperventilation; the investigators admit the possibility of a performance bias or a limitation in the method of measuring end-tidal CO_2 in non-intubated patients.[27] Thus, in patients intubated and managed with GA, ventilation should be regulated to maintain normocapnia ($PaCo_2$ between 35 and 45 mmHg) (Class IIa, Level of evidence C).[7]

Glucose values should be maintained between 70 and 140 mg.dL^{-1} (Class IIa, Level of evidence C), with intravenous insulin treatment of hyperglycemia of >140 mg.dL^{-1} (Class IIb, Level of evidence C)[7] and correction of hypoglycemia of <50 mg.dL^{-1} (Class IIa, Level of evidence C) with intravenous dextrose or infusion of 10% or 20% glucose,[49] this being the only indication for fluids containing dextrose.

Discussion

As the main body of evidence on the anesthetic management of AIS endovascular treatment is retrospective, there is a lot of controversy on the subject. Most studies' limitations are their non-prospective and non-randomized nature,[19] limited number of subjects[5,17] and selection bias,[6,15] with some having major differences in stroke severity between the groups – GA managed patients have higher baseline NIHSS scores in most studies.[5,17,19]

In 2014, the SNACC published a consensus intended to offer some guidance to the clinicians involved in the endovascular treatment of AIS, presenting various targets for variables like BP, oxygenation, ventilation and glucose values. Regarding the anesthetic techniques, the general recommendation was that the choice of agent should be individualized to the clinical setting; more specific recommendations on one agent over the other did not have a strong class of recommendation (Class IIa) or a high level of evidence (Levels B and C).[7] This translates the need for well-designed randomized controlled clinical trials which can produce more reliable data. Although some trials are currently ongoing, only three have published results so far. These studies, although prospective and randomized in nature, are not without limitations: they are single-center studies with small sample sizes (90–150 patients).[11–13] The conclusions of other prospective trials published in the next few years will reinforce or contradict the actual evidence that both approaches are equally safe.

Meanwhile, as the ideal anesthetic approach for the endovascular treatment of AIS remains unknown, the choice of agent should continue to be individualized, weighting the benefits and risks and considering local protocols, personal preferences and experience of the physicians.[2,14,15,19] Some situations, like inability to protect the airway, lack of cooperation and decreased consciousness, will always require GA.[6] On other conditions, the small conversion rate of conscious sedation to general anesthesia might support the use of conscious sedation as the initial anesthetic method.[11]

Conclusion

The trend towards considering CS better than GA in terms of outcome might change with recent evidence, as the first randomized trials did not confirm this hypothesis.[11–13] CS is at least as safe as GA for the endovascular treatment of AIS, with no higher mortality and fewer complications like pneumonia; as the rate of conversion to GA is small, CS might be used as the initial approach in a variety of cases not demanding GA. Essentially, the anesthetic method should always be individualized based on the clinical characteristics of the patient[2,7] and no method is currently officially recommended. The apparently shorter time to initiate the procedure and higher patient mobility with CS, the higher risk of hypotension and BP variability with GA and the affected circulation should be considered.

Regarding neuroprotection, the most important strategy is to maintain the hemodynamic parameters between the recommended targets. As for pharmacological neuroprotection, no agent has been proven effective to date.

Conflicts of interest

The authors declare no conflicts of interest.

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