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Abordagem Anestésica no Tratamento Endovascular do Acidente Vascular Cerebral Isquémico: Influências no *Outcome* e Complicações

Anesthetic Management of Endovascular Treatment for Acute Ischemic Stroke: Influences on Outcome and Complications

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Anesthetic Management of Endovascular Treatment for Acute Ischemic Stroke: Influences on Outcome and Complications

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Abordagem Anestésica no Tratamento Endovascular do Acidente Vascular Cerebral Isquémico: Influências no *Outcome* e Complicações

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ABSTRACT

Background and Objectives: The emerging use of endovascular therapies for acute ischemic stroke, the preferred being intra-arterial thrombectomy, requires a better understanding on the anesthetic management needed and its impact in treatment outcomes. This article reviews the available data on the anesthetic approach of endovascular treatment, comparing general anesthesia with conscious sedation, the most used modalities, in terms of time of anesthesia induction and procedure time, patient mobility, location of the occlusion, 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 one randomized study 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 no higher 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 as anesthetic management of patients submitted to endovascular thrombectomy. No anesthetic approach is universally recommended and hopefully the ongoing randomized clinical trials will shed some light on the best method; meanwhile, the choice of anesthetic should be based on the patient's individual characteristics. Regarding neuroprotection, meeting hemodynamic targets is currently the most important strategy, as no pharmacological method has been proven effective in humans.

Keywords: anesthesia; anesthesia, general; conscious sedation; stroke; thrombectomy; endovascular procedures; neuroprotection

INTRODUCTION

Acute ischemic stroke (AIS) is one of the leading causes of mortality and morbidity worldwide[1, 2] and its significant burden has driven the scientific research in its 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. There are two endovascular approaches: intra-arterial fibrinolysis or intra-arterial thrombectomy (with a multitude of devices available); the preferred is the intra-arterial thrombectomy with a stent retriever.[3]

A key factor plays a part 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.[4] In the particular case of endovascular therapy, time to groin puncture should be less than 6 hours.[3] The anesthetic management needed for the endovascular treatment of AIS plays a role 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 permits neurological monitoring but may induce pain and movement, making the procedure longer and more difficult. Some studies also include a monitored anesthesia care approach or even local analgesia alone.

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.[5] However, a substantial number of trials are now ongoing[6-9] and the results from one randomized study have been published.[10] This article reviews the available data on the anesthetic approach of intra-arterial thrombectomy, comparing general anesthesia with conscious sedation in terms of time of anesthesia induction and procedure time, patient mobility, location of the occlusion, 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 up to February 2017 using the following databases: MEDLINE (via Pubmed), Web of Science and clinicaltrials.gov. A combination of the following search terms was used: stroke, anesthesia, thrombectomy, endovascular, conscious sedation, general anesthesia.

Additionally, the references of various articles were examined to find studies which did not appear in the initial search.

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 of intubation (pneumonia and sepsis), more difficult postanesthetic recovery, and a greater need of qualified anesthesiologists, which assumes greater costs.[5, 11-14]

Conscious sedation, on the other hand, permits monitoring during the procedure for new neurological deficits and has less iatrogenic hemodynamic variation and less delay to the start of the intervention, yet it has risks of patient 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.[5, 11-15]

The majority of retrospective studies and also the 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 will be reviewed in more detail. Table I (Enter Table I) contains a summary of most studies' conclusions.

1. Time to groin puncture and procedure time

For every minute a great vessel AIS goes untreated, 1.9million neurons and 13.8 billion synapses are lost.[4] Treatment of AIS is an emergency and the sooner it is initiated, the better the possible outcome; this is why a delay in time from symptom onset to groin puncture is a major concern in patients undergoing endovascular treatment managed with GA. In one study, this delay was found to be of 15 minutes, comparing with CS[15]; in another study, it was of 20 minutes.[12] While some scientists do worry about this delay and found it related to worse outcomes in GA compared to CS[12], others considered that this relatively short delay occurring with GA seems to be tolerable 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 sometimes occurs in awake patients.[15] John *et al*. indeed 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.[16]

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.[17]

Schönenberger *et al*., in the only randomized controlled trial to date, describe a gain of 10 minutes when using CS, although no differences in outcome came from that.[10]

2. Patient mobility

Patient mobility is the major problem regarding CS and one of the main reasons 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.[11]

Patient mobility and agitation can be related to pain, which can be due to the innervation of the blood vessels which are being manipulated[17] or to the transmission of tension to the dura matter[15]. 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.[17] Some researchers, however, report very low rates of wire perforation during percutaneous coronary interventions in which the heart is constantly moving[18], affirming that perforation in endovascular treatments might not be primarily caused by movement.[17]

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.[14]

Janssen *et al*. studied the applicability of a standard cervical collar for head immobilization in order to reduce risks with CS, which seemed to also have a calming effect on patients; the outcomes were favorable.[19]

Patient movement may even be a cause for emergent conversion to GA, being the main cause for the conversion rates ranging between 2,7% to 3,7% in various studies[12, 14, 20]; other motive of conversion was emesis, with greater risk of aspiration. 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.[20]

3. Affected circulation

Endovascular treatment with stent retrievers 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[3].

Posterior circulation occlusion causes 15% to 20% of all AIS; basilar artery occlusion is a subset of posterior AIS, causing only 1% to 4% of all AIS.[21] When the basilar artery is the occluded vessel, patients usually have changes in level of consciousness.[14] SNACC recommends the use of GA in posterior circulation stroke, as they frequently cannot protect the airway (Class IIa, Level of evidence B).[5] There is a lack of studies comparing CS and GA on specific territories and most of them do not focus on posterior circulation AIS, excluding these patients because they are almost exclusively managed with GA.[14, 16, 17]

4. 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.[22, 23] The SNACC consensus recommends a systolic target of 140-180 mmHg (a study associates this range with better outcomes[23]) and a diastolic blood pressure below 105 mmHg; hypotension should be avoided using fluids and vasopressors (Class IIa, Level of evidence B)[5]. Vasopressors commonly used are epinephrine, norepinephrine, phenylephrine or ephedrine[24, 25], but the choice should depend on the patient's individual characteristics.[5]

Hypotension is frequent after the induction of GA[25-27] and may diminish perfusion of the penumbra area by collateral vessels, therefore impairing recovery.[28]

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 administrated during induction of GA, after correcting possible hypovolemia with fluids and heart failure with inotropic agents.[28]

More than a drop in BP, Chung *et al*. indicate BP variability as independently and linearly associated with neurologic deterioration in AIS.[29] 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<100mmHg) requiring vasopressors like norepinephrine.[25]

A study of 190 patients by John *et al*. , nevertheless, found no significant differences in hemodynamic variables between GA and monitored anesthesia care.[16] 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.[10]

Sivasankar *et al*. observe that the diversity of findings concerning blood pressure may be due to differences in dosage of anesthetics or sedatives.[24]

5. 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.[12, 14, 17, 30]

Juma *et al*. study of 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.[14]

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 were a predictor of mortality.[31] 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).[16]

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.[10]

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.[24]

6. 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 intracerebral hemorrhage between 1.5% and 15%, as reported by recent trials.[5]

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.[17] This intraprocedural 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.[31] When grouping the various trials in the area, total complications rates were 0%-20% and 1%-6% when only considering embolization, dissection and perforation.[34]

Abou-Chebl *et al*. found no difference in posttreatment intracranial bleeding.[17] John *et al*. also did not find differences in hemorrhagic transformation of the stroke between GA and monitored anesthesia care, but GA managed patients had a higher rate of parenchymal hematomas.[16]

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 add to a higher risk of pneumonia, like diminished airway reflexes, relaxation of pharyngeal muscles, hypovolemia and dysphagia.[35]

Jumaa *et al*. documented a longer ICU stay, primarily due to difficulties in weaning the patients off the ventilation, and a higher rate of early pneumonia in patients managed with GA. Their main conclusion was that CS was at least as safe as GA for endovascular treatment.[14]

The rate of pneumonia was also higher in GA group in two other studies[31, 35]; Hassan *et al*.[35] 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.

Additionally, intubation is more related to withdrawal of care than CS, accounting for a part of the increased mortality of patients managed with GA.[14] This higher mortality of the deeply sedated patients, related or not to the discontinuation of therapy, is reported by various studies[16, 17, 30, 31, 36-39].

Schönenberger et al. reported no differences in in-hospital and overall mortality between the two groups, but complications like hypothermia, delayed extubation and pneumonia were more frequent in patients managed with GA.[10]

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 prehospital 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 35-37ºC, maintained with antipyretics and cooling devices if needed (Class IIb, Level of evidence B).[5]

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>60mmHg (Class IIa, Level of evidence C).[5]

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.[26] 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.[25] 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).[5]

Glucose values should be maintained between 70 and 140mg/dL (Class IIa, Level of evidence C), with intravenous insulin treatment of hyperglycemia of >140mg/dL (Class IIb, Level of evidence C)[5] and correction of hypoglycemia of <50mg/dL (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[17], limited number of subjects[14, 31] and selection bias[12, 16], with some having major differences in stroke severity between the groups - GA managed patients have higher baseline NIHSS scores in most studies.[14, 17, 31]

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 (Level B-C).[5] This translates the need for well-designed randomized controlled

clinical trials which can produce more reliable data. Although some trials are currently ongoing, only one has published results so far. This study is not without limitations: the fact that it is a single-center study with a sample of only 150 patients, treated by a very specialized staff with vast experience in general anesthesia, might have influenced the results.[10] 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.[11, 12, 17] Some situations, like inability to protect the airway, lack of cooperation and decreased consciousness, will always require GA.[16] 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.[10]

CONCLUSION

The trend towards considering CS as better than GA in terms of outcome might change with recent evidence, as the first randomized trial did not confirm this hypothesis.[10] 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[5] and no method is currently officially recommended. The apparent 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.

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GLOSSARY

AIS – Acute Ischemic Stroke

BP – Blood Pressure

CS – Conscious Sedation

$ETCO_2$ – End Tidal Carbon Dioxide

FiO_2 – Fraction of inspired Oxygen

GA – General Anesthesia

ICU – Intensive Care Unit

IV rtPA – Intravenous recombinant tissue plasminogen activator

NIHSS - National Institutes of Health Stroke Scale

$PaCo_2$ – Partial pressure of Carbon dioxide in the blood

PaO_2 - Partial pressure of Oxygen in the blood

SNACC - Society of Neuroscience in Anesthesiology and Critical Care

SpO_2 - Oxygen Saturation

Table I - Summary of the anesthetic approach in cited studies

Study	Type	N	Affected circulation	Anesthetic approach	Outcomes	Limitations reported by the investigators
Abou-Chebl [17] 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 risk of intracranial hemorrhage	• Retrospective and non-randomized nature • LA - lower NIHSS scores
Jumaa [14] 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 [12] 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)
Davis [30] 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 [31] 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 [16] 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 • GA - older and higher baseline NIHSS scores
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	• 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 [10] 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

[ ], Citation; CS, Conscious Sedation; GA, General Anesthesia; LA, Local Anesthesia; MAC, Monitored Anesthesia Care; NIHSS, National Institutes of Health Stroke Scale

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Ao Fernando Mané e à Maria João Lima, pelo seu domínio excelente da língua inglesa e por descobrirem os erros onde eu já não os via.

Anexo 1

Normas de publicação da Revista Brasileira de Anestesiologia

GUIDES FOR AUTHORS

Articles for publication shall be exclusively forwarded to Brazilian Journal of Anesthesiology through http://ees.elsevier.com/bjan. Articles already published in other journals will not be accepted. Only accept papper submitted in English and Portuguese; and the accepted papers will be published only in the English and Portuguese versions.

Brazilian Journal of Anesthesiology classifies the articles in the following categories:

a) **Scientific Articles:** New clinical or experimental research information.
b) **Reviews:** Summary of well established subjects, with a review of references and conclusions, systematic review.
c) **Clinical Informations:** Case reports, introduction of new techniques, methods and equipments.
d) **Miscellaneous:** Those not matching the above mentioned categories, but relevant for Anesthesiology.
e) **Special Articles:** Subject reviews relevant for Anesthesiology.
f) **Letters to the Editor:** Constructive, objective and educational comments on published matters. Discussions on Anesthesiology-specific subjects will by published on the sole Editor's discretion.
g) **Editorials.**

Publication Approval: All articles proposed for publication will be previously submitted to the analysis of two or more members of the Editorial Council or other Specialized Consultants. When accepted, they will be subjected to minor corrections or changes which do not alter the author's style. Possible modifications in format, style or interpretation will only be carried out after previous consultation. If denied, articles will be returned with a justification of the Editor-in-Chief.

OBS: Author and coauthors shall sign and send during the submission process a Copyright Cession Form to Sociedade Brasileira de Anestesiologia and Elsevier Editora Ltda. These forms shall be sent as separate documents (one form per author), as PDF files, through the submission system.

A template is available for download at: http://ees.elsevier.com/bjan/, under Author Information.

Final Correction: Articles for publication will be forwarded, to the author, for due corrections and shall be returned as soon as possible. If there is a delay in returning the proof, the Editor-in-Chief has the right of publishing regardless of the final correction. The proof will be sent to the author whose address has been indicated for correspondence, remaining the said author responsible for the final appreciation of the subject and the others will agree with such publication.

Articles Presentation: Manuscripts must follow the specifications presented below.

Type of manuscript	Number of words	References
Scientific articles	3000	25
Reviews	5000	50
Letters to the Editor	500	2
Case reports/Clinical informations	1500	5

Title: Article's title shall be short, clear and straightforward to make easy its classification. When needed, a sub-title may be used.

Author(s): Full name(s), their titles and affiliations in Societies or Institutions. Names of other collaborators may be mentioned at the end as acknowledgments. A different paragraph shall be used to indicate the place where the study was carried out.

Structured Abstract: For scientific articles please state: Background and Objectives, Methods, Results and Conclusions. For clinical information please state: Background and Objectives, Case Report and Conclusions. For reviews please state: Background and Objectives, Contents and Conclusions. For all articles, inform Key Words for classification according to Greene NM – Key Words in Anesthesiology, 3rd Ed, New York, Elsevier or newer. Abstract must not exceed 300 words.

Text: without mentioning the author(s) or the place where it has been carried out. Scientific articles should have the following chapters: Introduction, Methods, Results, Discussion, Summary and References.

References: The article shall contain only the references consulted, which shall be numbered as they enter the text. Other quotes of already numbered authors should indicate only the reference number; avoid mentioning the name of the author. The quotation of unpublished articles or presented in Medical Events is not recommended. Text books and congress summaries references older than five years should be limited to those considered fundamental. When an article already accepted for publication is quoted, please include "to be published", indicating the journal and the year. Personal communications will not be accepted. Use the model below:

Journals: Author(s) names, middle name(s) initial(s) – paper's title. Journal's title (abbreviated according to Index Medicus), year of publication; volume: number of first and last pages.

Pereira E, Vieira ZEG – Visita pré-anestésica, responsabilidade intransferível do anestesiologista. Rev Bras Anestesiol, 1977;27:337-353.

Books: Editor(s) name(s), middle name(s) initial(s) – book's title (initials in capital letters), volume and edition, city of publication, Publisher, publication year and number of quoted page(s).

Rigatto M – Fisiopatologia da Circulação Pulmonar, 1ª Ed, São Paulo, Fundo Editorial Procienx, 1973;53-55.

Chapters: Author(s) name(s), middle name(s) initials – chapter title; editor(s) name(s), middle name(s) initials – Book title (initials in capital letters), volume and edition, city of publication, Publisher, publication year and quoted page(s).

Coelho A – Anatomia do Sistema Específico de Condução, em: Germiniani H – Diagnóstico e Terapêutica das Arritmias Cardíacas. São Paulo, Fundo Editorial Procienx, 1972;3-10.

Note: Punctuation should never be used in names or abbreviations of mentioned publications. When there are less than three authors, all of them should be mentioned; when there are more than three, only the first three should be mentioned, followed by the expression “et al.”.

Illustrations: Number illustrations according to text entry order. Number figures in Arabian numerals. Number charts and tables in Roman numerals. Indicate on the text the preferential site for the entry of each illustration (for example: Enter Figure x). Use black and white photos. The same result should not be expressed by more than one illustration.

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Drug Names: The use of commercial drug names (trademarks) is not recommended, but when such use is mandatory, the product name should follow its generic name, in brackets, in lowercase, followed by the trademark symbol (®).

Legal an Ethical Considerations: according with Uniform Requirements for Manuscripts Submitted to Biomedical Journals (International Committee of Medical Journal Editors – February 2006).

Conflict of Interest

Conflict of interest exists when an author (or the author’s institution), reviewer, or editor has financial or personal relationships that inappropriately influence (bias) his or her actions (such relationships are also known as dual commitments, competing interests, or competing loyalties). These relationships vary from those with negligible potential to those with great potential to influence judgment, and not all relationships represent true conflict of interest. The potential for conflict of interest can exist whether or not an individual believes that the relationship affects his or her scientific judgment. Financial relationships (such as employment, consultancies, stock ownership, honoraria, paid expert testimony) are easily identifiable conflicts of interest and the most likely to undermine the credibility of the journal, the authors, and of science itself. However, conflicts can occur for other reasons, such as personal relationships, academic competition, and intellectual passion. For that reason, Author Agreement is a required document signed by all authors.

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Ethical Treatment

When reporting experiments on human subjects, authors should indicate whether the procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1975, as revised in 2000. If doubt exists whether the research was conducted in accordance with the Helsinki Declaration, the authors must explain the rationale for their approach, and demonstrate that the institutional review body explicitly approved the doubtful aspects of the study. When reporting experiments on animals, authors should be asked to indicate whether the institutional and national guide for the care and use of laboratory animals was followed.

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Clinical trial must be register according WHO recommendation at www.who.int/ictrp/en/. The definition of clinical trial include preliminary trials (phase I): any study with prospective recruiting of subjects to undergo any health-related intervention (drugs, surgical procedures, equipment, behavioral therapies, food regimen, changes in health care) to evaluate the effects on clinical outcomes (any biomedical or health-related parameter, including pharmacokinetics measurements and adverse reactions).

The Journal has the right of not publishing trials not complying with these and other legal and ethical standards determined by international guidelines.

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Os artigos para publicação deverão ser encaminhados com exclusividade para a Revista Brasileira de Anestesiologia pelo site http://ees.elsevier.com/bjan. Não serão aceitos artigos já publicados em outros periódicos. São aceitos apenas artigos submetidos em inglês ou português; e os artigos aceitos serão publicados apenas na versão em inglês e na versão em português.

A Revista Brasileira de Anestesiologia classifica os artigos nas seguintes categorias:

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b) **Revisões**: Artigos de síntese, de assuntos bem estabelecidos, com análise crítica das referências bibliográficas consultadas e conclusões, revisões sistemáticas.
c) **Informações Clínicas**: Relatos de casos clínicos, apresentação de novas técnicas, métodos e equipamentos.
d) **Artigos Diversos**: Aqueles que não se enquadram nas categorias anteriores, de interesse para a Anestesiologia.
e) **Artigos Especiais**: Revisões de assuntos de interesse da especialidade.
f) **Cartas ao Editor**: Críticas à matéria publicada, de maneira construtiva, objetiva e educativa. As discussões de assuntos específicos da Anestesiologia serão publicadas a critério do Editor.
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Artigos científicos	3000	25
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Coelho A – Anatomia do Sistema Específico de Condução, em: Germiniani H – Diagnóstico e Terapêutica das Arritmias Cardíacas. São Paulo, Fundo Editorial Procienx, 1972;3-10.

Nota: Não se deve colocar pontuação nos nomes ou abreviaturas dos periódicos citados. Quando houver menos de três autores, cite-os todos e quando houver mais de três, cite somente os três primeiros, seguidos de "et al.".

Ilustrações: Enumerar ilustrações de acordo com a ordem de entrada no texto. Enumerar figuras em algarismos arábicos. Enumerar quadros e tabelas em algarismos romanos. Indicar, no texto, o local preferencial de entrada de cada ilustração (Entra Figura x, por exemplo). Usar fotos em branco e preto. O mesmo resultado não deve ser expresso por mais de uma ilustração.

Uso de Recursos Digitais: Textos obrigatórios em formato DOC (Winword): *Manuscript*, *Title Page* (página com os dados completos do artigo e de seus autores), *Cover Letter* (carta de apresentação do artigo ao Editor), e *Author Agreement* (declaração de ineditismo e não submissão e/ou publicação duplicada); figuras em barras ou linhas XLS (padrão Excel); e fotos e figuras, com resolução mínima de 300 dpi, em formato JPG. Não inserir títulos e legendas nas ilustrações. Não inserir ilustrações no corpo do texto. Cada ilustração deve ter arquivo individual. O nome dos arquivos deve expressar o tipo e a numeração da ilustração (Figura 1, Tabela II, por exemplo). Títulos e legendas das ilustrações, devidamente numerados, devem estar no arquivo de texto. Cópias ou reproduções de outras publicações serão permitidas apenas mediante a anexação de autorização expressa da Editora ou do Autor do artigo de origem.

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Considerações Éticas e Legais: de acordo com Exigências para Manuscritos Submetidos a Revistas da área Biomédica (Comitê Internacional de Editores de Revistas Médicas – Fevereiro de 2006).

Conflito de Interesses

O conflito de interesses existe quando um autor (ou a instituição do autor), revisor, ou editor tem relações de financiamento ou pessoais que influenciem de forma negativa (viés) suas ações. Essas relações variam desde com potencial mínimo até de grande potencial de influência sobre o julgamento, e nem todas representam conflito de interesses verdadeiro. O potencial para conflito de interesses pode existir se um indivíduo acredita ou não que suas relações afetam ou podem influenciar negativamente a credibilidade da revista, dos autores, ou da própria ciência. Entretanto conflitos podem ocorrer por outras razões, como relações pessoais, competição acadêmica e intelectual. Com isso, torna-se obrigatório o Author Agreement assinado por todos os autores.

Consentimento Livre e Esclarecido

Os pacientes têm direito à privacidade que não deve ser infringida sem consentimento livre e esclarecido. A identificação de informação, incluindo iniciais dos nomes dos pacientes, número de registro do hospital, não deve ser publicada através de descrições no texto, fotografias ou qualquer outra modalidade, a menos que ela seja essencial para os propósitos científicos e o paciente (ou responsável) forneça consentimento por escrito para publicação. O consentimento livre e esclarecido para esta finalidade exige que o paciente veja o manuscrito que será publicado. Os autores devem identificar indivíduos que deram assistência na elaboração do texto e declarar a origem dos fundos para essa assistência.

Detalhes que facilitem a identificação devem ser omitidos se não forem essenciais. O anonimato completo é difícil de ser atingido, entretanto consentimento livre e esclarecido deve ser obtido se existir qualquer dúvida. Por exemplo, mascarar a região dos olhos em fotografia de pacientes é uma proteção inadequada para o anonimato. Se características de identificação forem alteradas para garantir o anonimato, os autores devem garantir que essas alterações não provocarão distorção do significado científico.

Quando o consentimento livre e esclarecido for obtido esta informação deve constar da publicação.

Ética

Quando estudos em humanos são publicados, os autores devem indicar se os procedimentos obedeceram aos padrões éticos do comitê de pesquisa em humanos (institucional ou nacional) e a Declaração de Helsinki de 1975, revista em 2000. Se existirem dúvidas quanto à condução de acordo com os padrões da Declaração de Helsinki, os autores devem explicar o racional para o procedimento e demonstrar que a comissão institucional responsável aprovou explicitamente os aspectos duvidosos do estudo. Quando a publicação for relativa à pesquisa com animais os autores devem indicar se foram obedecidas as normas de cuidados institucionais ou nacionais e o uso de animais de laboratório foi seguido.

Registro de Ensaio Clínico

Ensaios clínicos deverão ser registrados de acordo com orientação da OMS no endereço www.who.int/ictrp/en/. A OMS considera ensaios clínicos inclusive ensaios preliminares (fase I), qualquer estudo que recrute prospectivamente sujeitos de pesquisa para serem submetidos a intervenções relacionadas à saúde (fármacos, procedimentos cirúrgicos, aparelhos, terapias comportamentais, dietas, modificações nos cuidados de saúde) com finalidade de avaliar os efeitos sobre desfechos clínicos (qualquer variável biomédica ou relacionada com a saúde, inclusive medidas farmacocinéticas e efeitos adversos).

A revista tem o direito de não publicar estudos clínicos que não estejam de acordo com estes e outros padrões éticos determinados por diretrizes internacionais.