Review

Stroke thrombectomy perioperative anesthetic and hemodynamic management

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SUMMARY
There is an ongoing debate about the optimal anesthetic and hemodynamic management of acute stoke patients with large vessel occlusion undergoing endovascular mechanical thrombectomy. Several prospective and retrospective analyses, and randomized controlled trials, attempted to address the challenges of using different anesthetic modalities in acute stroke patients requiring mechanical thrombectomy. We review the advantages and disadvantages of monitored anesthesia care, local anesthesia, conscious sedation, and general anesthesia, along with the relevance of hemodynamic management and perioperative oxygenation status in these complex patients.

INTRODUCTION
Stroke is a major global health problem with an overall growing incidence. There are approximately 795 000 new strokes every year in the USA, and 15 million worldwide. Timely restoration of cerebral blood flow using endovascular reperfusion therapy (EVT) is the mainstay for the management of acute ischemic stroke (AIS) with large vessel occlusion (LVO). There has been significant controversy about the optimal anesthetic management of this challenging patient population, especially since a significant effect on clinical outcomes has been associated with the choice of anesthesia. Numerous studies in recent years have attempted to provide data in favor of general anesthesia (GA) or monitored anesthesia care (MAC) in the setting of mechanical thrombectomy. However, contradiction between the results of retrospective and observational studies, mostly suggesting the benefit of MAC, and smaller randomized trials (RCTs), demonstrating no marked differences in outcomes with different anesthetic modalities, has continued to fuel the debate about the ideal perioperative anesthetic management during EVT for AIS. The aim of this paper is to present, critically review, and summarize available evidence in this field.

ANESTHETIC MANAGEMENT OPTIONS DURING EVT FOR AIS WITH LVO
Theoretical background
MAC and local anesthesia/conscious sedation (LA/CS) are often considered easier and quicker to administer than GA without potential delays in starting the endovascular procedure, and they carry the promise of faster access to the patient's occluded brain vessel. GA with endotracheal intubation, on the other hand, can provide protection of the upper airway thus avoiding hypoxia and aspiration, but may be associated with fluctuation of periprocedural mean arterial blood pressure (MAP), resulting in impaired perfusion to the penumbral tissue.[1–3] GA has the potential to decrease the risks of intraprocedural complications, including vessel dissection or perforation, which may occur due to patient movement secondary to pain, lack of cooperation, altered mental status (basilar occlusion or thalamic involvement), and/or aphasia during intracranial catheter navigation and clot retrieval.[4] GA, however, potentially could result in delayed time to groin puncture and longer procedure time. Performing thrombectomy may be safer under GA if there is patient agitation and/or discomfort present.[5] The use of certain anesthetic agents may have additional neuroprotective effects.[6 7]

Retrospective and observational data
Several earlier non-randomized studies seemed to suggest that GA during EVT for ischemic stroke might be associated with increased mortality and a lower odds of good functional outcome despite comparable rates of recanalization. The North American SOLITAIRE Acute Stent Retriever Registry enrolled a total of 281 patients from 18 centers.[8] GA was used in 69.8% (196/281) of patients. In a multivariate analysis, history of hypertension, high National Institutes of Health Stroke Scale (NIHSS) score, unsuccessful revascularization, and GA use (OR 3.3, 95% CI 1.6 to 7.1; $p=0.01$) were associated with death. The use of LA was associated with better neurological outcomes. In another retrospective cohort of 980 patients from 12 stroke centers who underwent EVT for anterior circulation stroke due to LVO, a binary logistic regression model showed that the use of GA was associated with poorer neurological outcome at 90 days (OR 2.33, 95% CI 1.63 to 3.44; $p<0.0001$) and higher mortality (1.68, 1.23 to 2.30; $p<0.0001$) than MAC.[2] The major limitation of this study was the inability to collect information on specific types of anesthetic agents used and hemodynamic fluctuations during thrombectomy.

In a New York Statewide Planning and Research Cooperative System database cohort of 1174 patients undergoing EVT for AIS, an instrumental variable analysis was used to simulate the effects of randomization, and investigate the association of anesthetic technique with case fatality and length of stay. GA was associated with increased case fatality by 6.4%, and an 8.4 day longer length of stay was seen in comparison with MAC.[9] John *et al* retrospectively reviewed 190 patients who underwent

EVT for acute ischemic stroke. Higher mortality was seen in the GA group (25.8 vs 13.3; p=0.040). In addition, the use of GA was associated with a higher number of parenchymal hematomas (26.3 vs 10.1%; p=0.003).[3] However, in several of these studies, patients who received GA had higher presenting NIHSS scores, multiple intracerebral occlusions, and a higher incidence of hypotensive periods during GA.

Better outcomes with MAC were also seen in the Endovascular Therapy Following Imaging Evaluation for Ischemic Stroke 3 (DEFUSE 3) trial for mechanical thrombectomy patients in the extended 6–16 hour time window.[10] In this study, MAC patients had a higher likelihood of functional independence at 90 days, a lower NIHSS score at 24 hours, and a shorter time from femoral puncture to reperfusion compared with those who had GA.

As for posterior circulation thrombectomy, a retrospective, matched, case control study of 215 patients with consecutive vertebrobasilar occlusion strokes treated with EVT demonstrated similar rates of successful reperfusion, good clinical outcomes, hemorrhagic complications, and mortality with MAC compared with GA.[11] The type of anesthetic management was not associated with any significant changes in modified Rankin Scale (mRS) score (MAC: OR 1.52, 95% CI 0.80 to 2.90; p=0.19). The authors suggested that, in properly selected patients, MAC appeared to be as safe and effective as GA for posterior circulation interventions.

Large registry analyses

Publications from large prospectively collected registry datasets provided mixed results. A cohort study on prospectively collected data from 4429 patients in the Italian Registry of Endovascular Treatment for AIS has shown that GA was associated with worse 3 month functional outcomes than CS or LA.[12] Feil *et al* compared the effect of anesthetic regimen using data from the German Stroke Registry.[13] In this large study of 6635 patients, the MAC group had better clinical outcomes at 24 hours, at discharge, and at the 3 month follow-up compared with the GA group. A French registry of 1034 patients at four comprehensive stroke centers who received EVT in the early window (within 6 hours), included 762 patients in the MAC group and 272 patients in the LA group. LA was associated with a lower odds of favorable outcome and successful reperfusion, and higher odds of mortality compared with MAC with EVT of LVO.[14] Wagner *et al*[1] recently published a report from the Swiss Stroke Registry showing that patients with anterior circulation stroke receiving EVT with GA had worse mRS scores after 3 months than patients treated without GA. The specific advantage of this analysis was that the authors adjusted for the baseline variables using coarsened exact matching, which provides lower levels of imbalance, model dependence, and bias between the study groups.

The benefit of these large registries was that large number of patients were included, but with significant limitations: patients with GA had higher presenting NIHSS scores at admission, worse prehospital functional status, older age, and more often had acute ischemic strokes involving multiple vascular territories. Patients who received GA also had a higher incidence of hypotensive periods during their procedure. Most of these studies did not adjust for prespecified baseline variables, which might potentially confound allocation to the type of perioperative anesthetic management, and the data were not primarily collected for the purposes of anesthetic method analysis.

Randomized controlled trials

The results of currently available small RCTs appear to contradict some of the earlier studies, because most of them fail to show a significant difference between the outcomes with MAC vs GA in EVT stroke patients.

SIESTA (Sedation vs Intubation for Endovascular Stroke Treatment)[15] was a single center, randomized, open label GA versus MAC treatment trial that included 150 patients with AIS in the anterior circulation, with presenting NIHSS scores >10. Patients in the MAC group received intravenous low dose, short acting analgesics and sedatives, while the GA group received the same medications at higher doses. There was no difference in neurological outcome (NIHSS with a 4 point difference) at 24 hours between the two groups. Numerically more patients were functionally independent after 3 months in the GA group (37.0%) compared with the MAC group (18.2%), but without statistical significance (p=0.1). The ANSTROKE (Anesthesia During Stroke) trial enrolled 90 patients who were randomized to receive GA versus MAC.[16] No significant difference was found in neurological outcomes (mRS 0–2) 3 months after stroke (42.2% GA vs 40.0% CS; p=0.1). In addition, no differences were seen in intraoperative blood pressure decline from baseline (p=0.57); blood glucose (p=0.94); PaCO2 (p=0.68); degree of successful recanalization (p=1.00); infarction volume (p=0.53); and hospital mortality (p=1.00). The GOLIATH (General or Local Anesthesia in Intra Arterial Therapy) was a single center prospective, randomized, open label, blinded trial of MAC versus GA for anterior circulation EVT.[17] There was no significant difference in the primary study outcome: infarct growth volume on MRI before and 48–72 hours after EVT for GA versus MAC (median (IQR) growth 8.2 (2.2–38.6) mL vs 19.4 (2.4–79.0) mL; p=0.10).

Despite the functional outcomes not being significantly different between GA and MAC, in both SIESTA and GOLIATH the recanalization rates were significantly higher in the GA group (89% vs 80.5% and 76.9% vs 60.3%, respectively). While the time to groin puncture was slightly longer in the GA group, the overall time to reperfusion was significantly decreased with GA in the GOLIATH study. Although all three studies adopted very strict hemodynamic protocols to avoid hypotension during EVT, the GA group often experienced a more pronounced decrease in blood pressure at induction of anesthesia.

The recently published GASS (General Anesthesia vs Sedation, both with hemodynamic control, during intra-arterial treatment for Stroke) study from the French Society of Anesthesiologists was a prospective, multicenter, parallel group, single blind RCT.[18] The primary outcome was an mRS score of 0–2 at 3 months after treatment, which was similar with GA (40%) and MAC (36%) (relative risk 0.91, 95% CI 0.69 to 1.19; p=0.474).

Except for GASS, all other RCTs were single center designs with a relatively small sample size and reduced power to detect moderate but clinically relevant differences in outcomes. Every trial had different prespecified primary outcomes, and two studies were limited by the choice of surrogate outcome parameters presented as early neurological improvement and infarct growth. Another potential source of bias was that GA was the preferred anesthetic technique for neurointerventionalists participating in the studies. The heterogeneous and nonstandardized nature of drugs and techniques used for GA and sedation in these trials could have also had significant effect on the observed outcomes.

Meta-analyses

An earlier meta-analysis of 22 studies that included 4716 patients (three randomized controlled trials and 19 observational ones)

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reported higher odds of death and respiratory complications, and lower odds of good functional outcome after thrombectomy for patients who had their procedure under GA.[19] An updated meta-analysis of 16 studies (three RCTs and 13 non-randomized studies) that included 5836 patients demonstrated a higher odds of 3 month functional independence and lower odds of 3 month mortality with non-GA during EVT for AIS.[20]

Contrary to these results, a recent meta-analysis that only included the first three RCTs with a total of 368 patients, reported that GA was associated with less disability at 3 months compared with procedural sedation.[21] In an updated meta-analysis of the three RCTs by Simonsen *et al*, better outcomes after EVT and lower rates of hemorrhagic transformation in the GA group were mainly explained through the direct effect of GA itself, and to a much smaller extent through indirect effects (ie, better reperfusion).[22]

The main reason for the conflicting results of these meta-analyses is the inclusion of different source studies. Those meta-analyses showing potentially better outcomes with GA explored mostly recent RCTs, while the others also incorporated earlier retrospective and observational data that favored the use of MAC.

Guideline recommendations, and ongoing/future trials

The most recent American Heart Association guidelines for anesthetic management of AIS recommend the selection of GA or MAC based on individual patient risk factors and technical aspects of the procedure.[23] Similarly, the French Society of Anesthesiologists recommends that clinicians may use either approach, mostly based on the recent GASS RCT results.[18]

The ongoing randomized multicenter Sedation versus General Anesthesia for Endovascular Therapy in Acute Ischemic Stroke (SEGA) trial (NCT03263117) is evaluating the effect of MAC versus GA on the outcomes of AIS patients after successful EVT. The specified primary outcome is the degree of disability using the mRS. It is worthwhile noting that this study does not specify a particular combination of medications that must be used in either group and leaves the choice to the managing anesthesiologist.

HEMODYNAMIC MANAGEMENT DURING ANESTHESIA FOR AIS

Blood pressure, collateral flow, and cerebral perfusion

Blood pressure is an important modifiable parameter to ensure proper cerebral perfusion during EVT. Hypotension prior to reperfusion may compromise collateral flow and result in permanent brain ischemia in the region of the penumbra. Patients with poor collateral flow are predisposed to larger ischemic core volume, higher peripheral vascular resistance, and decreased ability to washout emboli, and need a greater hypertensive response to maintain perfusion to the ischemic tissue.[24] Following recanalization, there is often a dramatic increase in cerebral blood flow because of loss of autoregulation in the ischemic tissue, as well as release of vasodilatory substances, which can lead to hyperperfusion syndrome, secondary cellular injury, and brain hemorrhage.[25]

Intraoperative blood pressure management

Data for the management of blood pressure during and after EVT for AIS are limited, and much was derived from studies in the early post recombinant tissue plasminogen activator era. The International Stroke Trial has shown a U shaped relationship between blood pressure and outcome in AIS patients, in which both extremes of blood pressure had prognostic significance for death and disability.[26] Patients presenting with a systolic blood pressure of 140–179 mm Hg had the lowest likelihood of death or dependency at 6 months, with a nadir at round 150 mm Hg. For every 10 mm Hg above a systolic blood pressure of 150 mm Hg, patients had a 3.6% increase of death, while a systolic blood pressure >200 mm Hg had more than 50% increased stroke risk. In contrast, there was a 17.9% increased risk of death for every 10 mm Hg drop below 150 mm Hg. Patients with a systolic blood pressure <120 mm Hg had the worst neurologic outcomes, and a higher incidence of coronary events.

In the Multicenter Randomized Clinical Trial of Endovascular Treatment of Acute Ischemic Stroke in the Netherlands (MR CLEAN), a similar U shaped correlation was also observed between systolic blood pressure and poor functional outcome: the most favorable outcomes were seen at a systolic blood pressure of 120 mm Hg, with a 21% increase in the relative risk of hemorrhage for every 10 mm Hg above this value.[27] In a post hoc analysis of the MR CLEAN trial, an association between aggressive blood pressure reduction and unfavorable outcome was also seen among patients undergoing general anesthesia for EVT.[28]

In a retrospective study of 390 AIS patients scheduled for EVT, the relationship between MAP reduction and patient outcomes was demonstrated.[12] The changes in MAP were calculated between admission MAP and lowest MAP during EVT until recanalization. Mean MAP reduction among patients with favorable outcomes (mRS 0–2) was 20±21 mm Hg compared with 30±24 mm Hg among patients with poor outcome.

Postoperative blood pressure management

In the DAWN (Diffusion Weighted Imaging or Computerized Tomography Perfusion Assessment with Clinical Mismatch in the Triage of Wake Up and Late Presenting Strokes Undergoing Neurointervention with Trevo) trial, keeping systolic blood pressure <140 mm Hg and MAP >70 mm Hg after achieving a Thrombolysis in Cerebral Infarction score of 2b/3 was shown to ensure sufficient perfusion while mitigating risks of hemorrhagic transformation and reperfusion injury.[29] High daily maximum systolic blood pressure and rebound systolic blood pressure on the third day following EVT in AIS patients was independently associated with an increased likelihood of functional dependence in other studies.[30] Chang *et al* found detrimental effects of increased blood pressure variability (BPV) after EVT, which was more frequent in patients with poor collateral circulation.[31]

The BP-TARGET (Blood Pressure Target in Acute Stroke to Reduce Hemorrhage After Endovascular Therapy) study has shown no evidence of benefit of intensively lowering systolic blood pressure to 100–129 mm Hg (compared with standard 130–185 mm Hg) after successful EVT to reduce radiographic intraparenchymal hemorrhage rates 24–36 hours postprocedure.[32] In the post hoc analysis of BP-TARGET, BPV was significantly higher in the intensive systolic blood pressure target group, but it was not associated with worse functional outcome or intracerebral hemorrhage.[33] In a meta-analysis of 11 studies comprising 3520 patients who underwent EVT, short term systolic BPV in AIS patients following EVT was strongly associated with poor functional outcome at 3 months.[34] Patients with large AIS volume, more severe ischemia, or patients with persistent venous post-capillary thrombosis (a phenomenon also known as 'no-reflow' state) were suggested to potentially benefit from induced hypertension.[33]

Guideline recommendations, and ongoing/future trials

The most recent American Heart/Stroke Association (AHA/ASA) guideline recommendations do not differentiate based on recanalization status after EVT, suggesting to maintain a target blood pressure of <180/105 mm Hg for 24 hours postprocedure, both for all patients (class II a, level B) and for patients achieving successful reperfusion (class II b, level B).[23] The Society for Neuroscience in Anesthesiology and Critical Care (SNACC) recommends maintaining a periprocedural systolic blood pressure range between 140 and 180 mm Hg, and a diastolic blood pressure <105 mm Hg[35] . European guidelines suggest that systolic blood pressure should not be actively reduced to <130 mm Hg during the first 24 hours after successful EVT.[36]

The currently ongoing BEST-II (NCT 04116112) and OPTIMAL-BP (NCT 04205305) trials will evaluate systolic blood pressure targets of 140–180 mm Hg in AIS patients. The ENCHANTED 2 trial (NCT 04140110) will examine the effect of systolic blood pressure <120 mm Hg in patients with complete reperfusion after EVT.

OXYGENATION STATUS AND POSTOPERATIVE VENTILATION

While the potential harm associated with hypoxia is well known, oxygen therapy in non-hypoxic AIS patients may also have adverse effects.

Hyperoxia and oxidative stress

Hyperoxia may increase the level of reactive oxygen species that inactivate nitric oxide, thereby potentially resulting in systemic, coronary, and cerebral vasoconstriction. In a recent study, 100% inspiratory oxygen was shown to reduce the mean cerebral blood flow by 27% in young healthy adults, and by 16% in an older subgroup on MRI.[37] Hyperoxia has also significantly reduced lung angiotensin converting enzyme 2 expression and enzyme activity, leading to increased lung inflammation and pulmonary tissue damage.[38]

Oxygenation and clinical outcomes

Results of a meta-analysis of 25 RCTs with 16 037 acutely ill patients (including patients with stroke) showed that liberal oxygen therapy increased mortality. The authors of this analysis suggested that supplemental oxygen might become harmful above an SpO_2 range of 94–96%.[39] In another study including 8003 adults with acute stroke, the prophylactic use of low dose oxygen supplementation in non-hypoxic patients did not reduce death or disability at 3 months.[40] Singhal *et al* showed that AIS patients had better outcome after 7 months when receiving room air rather than supplemental oxygen at 100% oxygen during the first 24 hours after stroke.[41] In another recent study, an important U shaped, non-linear relationship was demonstrated between mortality and SpO_2 in the postoperative period after EVT. High SpO_2 values found in AIS patients who received GA during EVT could explain the association between GA and increased mortality.[42]

DISCUSSION

Tailoring anesthesia and hemodynamic management

None of the studies described in this review are able to definitively answer if one anesthetic modality is superior to another for AIS patients undergoing EVT (table 1). Retrospective trials, observational studies, and large registry analyses all had inherent selection bias: patients in the GA group were sicker, had higher presenting NIHSS scores, often had larger ischemic volumes, and worse premorbid status. In addition, there was no adjustment for baseline variables in many cases. Available RCTs did not provide a conclusive answer either, due to one or more of the following: they allowed blood pressure drops with GA, chose one anesthesia over the other based on preference, had a single center setting, non-standardized drug use, or small sample size. Therefore, until larger RCTs become available, perioperative anesthetic management should be tailored to the patient's medical condition and available resources (table 2). Standardized anesthesia care may have significant advantages in the management of severely ill stroke patients in rapidly evolving and high acuity EVT situations. MAC anesthesia may be favorable for uncomplicated, hemodynamically stable LVO patients with milder symptoms and no associated airway compromise. Hemodynamic management is often easier with lower doses of anesthetic medication and less BPV or fluctuations. GA may be better suited for AIS

Table 1 Large published studies related to the anesthetic management of patients with acute ischemic stroke

Study	Summary of results
North American Solitaire Acute Stent Retriever Registry[8]	GA associated with increased mortality and lower odds of functional outcome
John *et al*[3]	GA associated with parenchymal hematoma
Brinjikji *et al*[19]	Meta-analysis of 22 studies that showed higher odds of death, respiratory complications, and lower odds of functional outcomes after GA
Bekelis *et al*[9]	GA was associated with increased mortality and length of stay
DEFUSE 3 trial[10]	GA was associated with lower functional independence at 90 days and higher NIHSS score after 24 hours
Feil *et al*[13]	GA was associated with worse clinical outcomes at 24 hours, at discharge, and at follow-up at 3 months
Goyal *et al*[20]	A meta-analysis of 16 studies showed lower functional independence and higher odds of 3 month mortality with GA.
Cappellari *et al*[12]	A cohort study from the Italian Registry that showed GA was associated with worse 3 month functional outcomes
Farag *et al*[42]	GA was associated with higher mortality rate compared with MAC
SIESTA ANSTROKE GOLIATH[15–17]	Functional outcome was not different between GA vs MAC, but there was potential positive signal in favor of GA
Schonenberger *et al*[21]	In a meta-analysis of RCTs, the use of GA was associated with less disability at 3 months
Simonsen *et al*[22]	In this meta-analysis, the use of GA was associated with better outcomes than MAC
Maurice *et al*[18]	This RCT of 345 patients showed no difference in the functional outcomes 3 months after EVT between GA vs MAC

GA, general anesthesia; MAC, monitored anesthesia care; NIHSS, National Institutes of Health Stroke Scale; RCT, randomized controlled trial.

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Table 2 Considerations for anesthetic management of patients with acute ischemic stroke undergoing endovascular reperfusion therapy (created based on current American Heart Association guidelines[23] and other available scientific evidence listed throughout the text)

	Monitored anesthesia care or local anesthesia	General anesthesia
Stroke location	Anterior circulation LVO	Posterior circulation LVO/severe left MCA syndrome
Stroke severity	Medium to low NIHSS	High NIHSS
Hemodynamic status	Hemodynamically stable	Hemodynamically unstable
Respiratory status	Uncompromised respiratory function with the ability to protect upper airway	Compromised respiratory function and/or inability to protect upper airway
Patient cooperation	Able to cooperate and/or lie still during the procedure	Lack of cooperation and/or inability to lie still
Blood pressure	Continuous blood pressure monitoring Before reperfusion: SBP >140 mm Hg or MAP >70 mm Hg After successful reperfusion: SBP ≤160 mm Hg	
Other considerations	Avoid hypotension, hypoxia, and hyperoxia Maintain normothermia, normocarbia, normoglycemia	

LVO, large vessel occlusion; MAP, mean arterial pressure; MCA, middle cerebral artery; NIHSS, National Institutes of Health Stroke Scale; SBP, systolic blood pressure.

patients with higher disability and baseline NIHSS, unstable vital parameters, hypoventilation or respiratory compromise, loss of consciousness, and aphasia with excessive movement, as seen with basilar ischemia or left hemispheric LVO. Rapid sequence induction and video laryngoscopy for intubation can be helpful in patients with a potentially difficult airway, reducing the incidence of hypoxia and hemodynamic instability. Extubation of GA patients after the procedure should be encouraged as early as safely possible, as is avoiding unnecessary oxygen supplementation unless the patient is hypoxic.[18 42] It should also be kept in mind that the conversion between different anesthesia types during the procedure may be associated with an increased incidence of morbidity and mortality.[43]

The choice of sedative medication varies among providers and institutions, and results of available studies offer no meaningful guidance. Some agents may have further benefits, including preserving cerebral autoregulation, neuroprotective effect, and sympatholytic effect with minimal potential compromise of the upper airway reflexes.[6 7] From a hemodynamic standpoint, continuous blood pressure, systolic and pulse pressure variation, and fluid responsiveness monitoring appear crucial for early detection and management of BPV, and achieving normovolemia in the perioperative period.

CONCLUSIONS

GA, MAC, and LA/CS may all have advantages and disadvantages during EVT for AIS patients with LVO. Until larger RCTs become available, individualized anesthesia selection and delivery, tailored for the patient's neurologic and hemodynamic status, stroke severity, time constraints, baseline disability, airway compromise, and comorbidities may be necessary for the successful management of these complex patients. There should also be careful monitoring and balancing of the patient's hemodynamic and oxygenation status during and after thrombectomy. Further data are needed to better define the most ideal anesthetic and hemodynamic parameters during the perioperative period of AIS patients with LVO who are treated with EVT.

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Contributors EF: conception and design of the work; acquisition, analysis, and interpretation of the data; and drafting and revising the manuscript. MA: analysis and interpretation of the data, and revision of the manuscript. GT: design of the work; analysis and interpretation of the data; and critical revision and editing of the manuscript. All authors have approved the final version of the manuscript.

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