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Effect of General Anesthesia and Conscious Sedation During Endovascular Therapy on Infarct Growth and Clinical Outcomes in Acute Ischemic Stroke
A Randomized Clinical Trial

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IMPORTANCE Endovascular therapy (EVT) is the standard of care for select patients who had a stroke caused by a large vessel occlusion in the anterior circulation, but there is uncertainty regarding the optimal anesthetic approach during EVT. Observational studies suggest that general anesthesia (GA) is associated with worse outcomes compared with conscious sedation (CS).

OBJECTIVE To examine the effect of type of anesthesia during EVT on infarct growth and clinical outcome.

DESIGN, SETTING, AND PARTICIPANTS The General or Local Anesthesia in Intra Arterial Therapy (GOLIATH) trial was a single-center prospective, randomized, open-label, blinded end-point evaluation that enrolled patients from March 12, 2015, to February 2, 2017. Although the trial screened 1501 patients, it included 128 consecutive patients with acute ischemic stroke caused by large vessel occlusions in the anterior circulation within 6 hours of onset; 1372 patients who did not fulfill inclusion criteria and 1 who did not provide consent were excluded. Primary analysis was unadjusted and according to the intention-to-treat principle.

INTERVENTIONS Patients were randomized to either the GA group or the CS group (1:1 allocation) before EVT.

MAIN OUTCOMES AND MEASURES The primary end point was infarct growth between magnetic resonance imaging scans performed before EVT and 48 to 72 hours after EVT. The hypothesis formulated before data collection was that patients who were under CS would have less infarct growth.

RESULTS Of 128 patients included in the trial, 65 were randomized to GA, and 63 were randomized to CS. For the entire cohort, the mean (SD) age was 71.4 (11.4) years, and 62 (48.4%) were women. Baseline demographic and clinical variables were balanced between the GA and CS treatment arms. The median National Institutes of Health Stroke Scale score was 18 (interquartile range [IQR], 14-21). Four patients (6.3%) in the CS group were converted to the GA group. Successful reperfusion was significantly higher in the GA arm than in the CS arm (76.9% vs 60.3%; $P = .04$). The difference in the volume of infarct growth among patients treated under GA or CS did not reach statistical significance (median [IQR] growth, 8.2 [2.2-38.6] mL vs 19.4 [2.4-79.0] mL; $P = .10$). There were better clinical outcomes in the GA group, with an odds ratio for a shift to a lower modified Rankin Scale score of 1.91 (95% CI, 1.03-3.56).

CONCLUSIONS AND RELEVANCE For patients who underwent thrombectomy for acute ischemic stroke caused by large vessel occlusions in the anterior circulation, GA did not result in worse tissue or clinical outcomes compared with CS.

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Supplemental content

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Endovascular therapy (EVT) is a standard-of-care treatment for selected patients with acute ischemic stroke (AIS) who harbor large vessel occlusions in the anterior circulation and present less than 6 hours from symptom onset.[1-3] However, numerous questions remain regarding best practices for EVT, including which anesthetic strategy results in the best clinical outcomes.[3]

Most observational studies report worse outcomes from general anesthesia (GA) than from conscious sedation (CS) during EVT,[4-7] but these results may be confounded by selection bias given that patients with increased stroke severity are more likely to be treated under GA. In addition, retrospective studies do not report specific anesthesia protocols, and only few report details concerning hemodynamic data. Physiological and procedural considerations may potentially favor one approach over another. Performing GA will likely delay procedure initiation due to intubation. Furthermore, GA is often associated with a drop in blood pressure, with the potential for worsening cerebral ischemia. On the other hand, patient motion during CS might impede revascularization and promote procedural complications.

Two randomized clinical trials comparing GA and CS during EVT have shown conflicting results. The first trial did not show a difference in the primary end point (with a National Institutes of Health Stroke Scale [NIHSS] score improving on day 2), although the proportion of patients achieving functional independence was higher in the GA arm after 90 days.[8] The second trial found no difference in the 90-day modified Rankin Scale (mRS) score.[9] In light of the discrepancy between these trials and the observational studies, further data are warranted. In the present randomized clinical trial—General or Local Anesthesia in Intra Arterial Therapy (GOLIATH)—we aimed to test whether CS or GA reduces infarct growth in patients undergoing EVT for AIS.

Key Points

Question Does infarct growth depend on the type of anesthesia used during endovascular therapy for stroke?

Findings In this randomized, open-label clinical trial including 128 patients, no difference in infarct growth was found between patients randomized to the general anesthesia group and those randomized to the conscious sedation group.

Meaning General anesthesia does not result in more infarct growth compared with conscious sedation during endovascular therapy for stroke.

Methods

Trial Design

The GOLIATH trial was an investigator-initiated, single-center prospective, randomized, open-label, blinded end-point (or PROBE) evaluation that enrolled patients from March 12, 2015, to February 2, 2017. Patients were randomized to GA or CS in a 1:1 fashion; the flowchart (**Figure 1**) displays the number of patients screened and included. The trial protocol has been published previously,[10] and the original version is attached as Supplement 1. The ethics committee of the Central Denmark Region approved the study and accepted a waiver of consent before randomization because eligible patients typically were not able to give informed consent and treatment was time critical. Patients or their next of kin were later required to give written informed consent to remain in the trial, and only 1 patient refused to give postrandomization consent because he did not want to undergo repeated magnetic resonance imaging (MRI) scans. No data monitoring board was involved.

Patients and Randomization

We screened all patients presenting to Aarhus University Hospital with symptoms suggestive of AIS as well as patients referred for EVT to the center by 2 primary stroke centers. We included all adult patients (18 years of age or older) who presented with large vessel occlusions in the anterior circulation and in whom groin puncture could be performed within 6 hours from symptom onset or when last seen well. We excluded patients who were intubated at presentation or with a Glasgow Coma Scale score (score range: 3-15, with a lower score indicating lower levels of consciousness) lower than 9 as well as those who were not living independently and had a premorbid mRS score (score range: 0-6, with a lower score indicating independent living) of more than 2. Because the primary trial end point was infarct growth, we required a diffusion-weighted imaging (DWI) MRI scan to establish a baseline (pre-EVT) infarct volume. Therefore, patients with a contraindication to MRI were excluded. In addition to the DWI scan, the imaging protocol consisted of a T2*—a T2 fluid attenuated inversion recovery—and an angiography sequence. Imaging time was 11 minutes. Patients with baseline infarcts greater than 70 mL were excluded, given their reduced likelihood for achieving good clinical outcomes. Movement or agitation was not a contraindication for the study.

After the qualifying scan, an intravenous tissue plasminogen activator was administered in the absence of a contraindication. Randomization was achieved by a web-based program. Patients were stratified according to age (18-65 years or ≥66 years) and NIHSS score (10-16 or ≥17 points; NIHSS score range: 0-42, with higher scores indicating more severe deficits). Block randomization (with sizes 4, 6, and 8) was performed after stratification. Allocation of block size was also random. The allocation to either GA or CS could not be blinded but was unknown by the imaging core laboratory that evaluated the primary outcome and by the nurse who evaluated the 90-day mRS score.

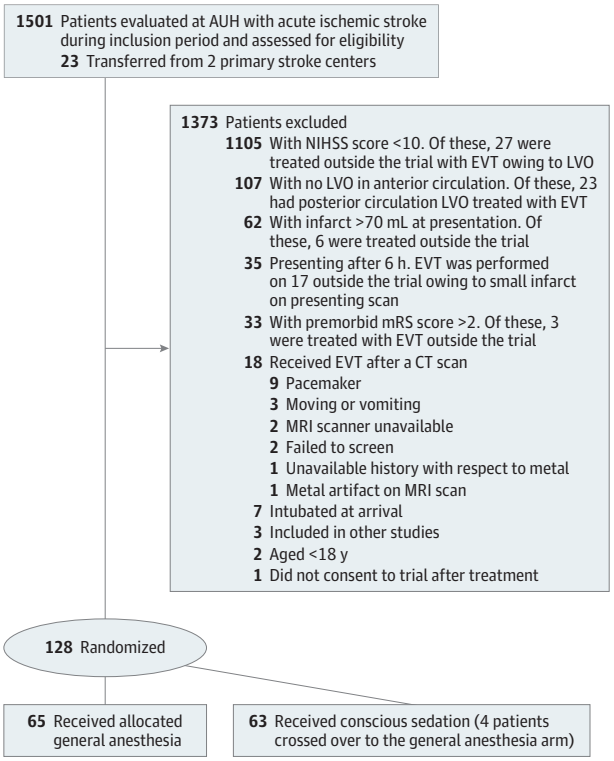
Anesthesia Protocol

The anesthesia protocol is provided in the eAppendix of Supplement 2.[10]

Thrombectomy Procedure

All procedures were performed by 1 of 2 neurointerventionists with 8 and 13 years of experience. Use of stent retriever, direct thrombus aspiration, or intra-arterial thrombolysis alone or in combination was at the discretion of the neurointerventionist. In case of a cervical internal carotid artery stenosis or

Figure 1. Flowchart of Patients Screened



The figure includes all the patients evaluated for acute ischemic stroke, the reasons for not performing endovascular therapy, and the patients who were treated but excluded from the trial. AUH indicates Aarhus University Hospital; CT, computed tomography; EVT, endovascular therapy; LVO, large vessel occlusion; mRS, modified Rankin Scale; MRI, magnetic resonance imaging; and NIHSS, National Institutes of Health Stroke Scale.

occlusion, stenting was performed when possible. Reperfusion was graded by an independent imaging core laboratory according to the modified Thrombolysis in Cerebral Ischemia (mTICI) scale score (range: 0—no flow beyond the occlusion, 1—minimal reperfusion, 2a—less than 50% of the affected vascular territory reperfused, 2b—greater than 50% reperfusion, and 3—complete reperfusion). Successful reperfusion was defined as mTICI 2b or 3.[11]

Outcomes and Imaging Analysis

The primary outcome was infarct growth, measured in milliliters. Secondary outcome measures were mRS scores after 90 days, time and blood pressure levels, and safety end points. The mRS score was evaluated at 90 days (80-100 days) after the stroke over the telephone by a certified study nurse who was blinded to randomization.

Infarct size before and after the procedure, mTICI score, and procedural safety measures (dissection, perforation, and clot migration) were evaluated by an independent core imaging laboratory to ensure the unbiased assessment of the primary outcome. Baseline infarct size was determined on DWI or apparent diffusion coefficient imaging. Follow-up scan (preferably MRI) was obtained 48 to 72 hours after symptom onset to avoid false DWI reversal and to minimize early edema. Final infarct size measurement was performed, using a T2 fluid attenuated inversion recovery sequence with additional reference to the DWI or apparent diffusion coefficient imaging, and included regions of hemorrhagic conversion.

Safety outcomes were symptomatic intracranial hemorrhage, 90-day mortality, vessel injury, and clot migration to a previous unaffected territory; all of these outcomes were evaluated by the independent imaging core laboratory. Intracranial hemorrhage was graded on gradient echo imaging with additional reference to the T2 fluid attenuated inversion recovery scan. Given the increased sensitivity of gradient echo imaging for blood products, symptomatic intracranial hemorrhage was defined as type 2 parenchymal hematoma with an associated NIHSS score worsening of 4 or more points (Safe Implementation of Thrombolysis in Stroke-Monitoring Study classification). Type 2 parenchymal hematoma is larger than 30% of the infarcted area with an associated mass effect. Owing to poor medical condition, 3 patients underwent noncontrast computed tomography scan at 48 to 72 hours for determination of final infarct volume and the presence of intracranial hemorrhage. These infarcts were all large and clearly demarcated.

Statistical Analysis

A difference in infarct growth of 10 mL was deemed clinically meaningful and was used for sample size calculation. Based on the assumption of an SD of 20 mL, the planned sample size at the start of the trial was 128 patients. The protocol, which was published after trial initiation, contained 2 errors. First, the sample size calculation used an SD of 25 mL, which yielded 98 patients per arm. Second, these 98 patients were mistakenly taken as the entire sample size. Thus, to preserve the protocol with the original sample size of 128 patients, a 30% attrition rate was added in the protocol. These 2 errors were identified after trial completion. Nevertheless, the originally planned sample size was attained at the end of the trial. Analyses were performed using Stata, version 12.0 (StataCorp LLC) and MedCalc software, version 14.12.0 (MedCalc).

Primary analysis was unadjusted and according to the intention-to-treat principle. Categorical variables were compared using the χ^2 test or Fisher exact test where appropriate, and continuous variables were compared with either the unpaired, 2-tailed *t* test or Mann-Whitney test, where appropriate. We also evaluated outcomes by patients allocated in a per-protocol (as treated) fashion. Statistical significance was defined as a 2-tailed $P < .05$.

Results

The first patient was enrolled on March 12, 2015, and the last patient was enrolled on February 2, 2017. In that period, 1501 patients were evaluated for suspected AIS, and EVT was performed on 235 patients. A total of 128 patients were included in the trial. For the entire cohort, the mean (SD) age was 71.4 (11.4) years, and 62 (48.4%) were women and 66 (51.6%) were men. The median NIHSS score was 18 (interquartile

Table 1. Baseline Demographic, Clinical, and Treatment Data[a]

Variable	General Anesthesia (n = 65)	Conscious Sedation (n = 63)	*P* Value
Age, mean (SD), y	71.0 (10.0)	71.8 (12.8)	.68
Women, No. (%)	29 (44.6)	33 (52.4)	.38
Premorbid mRS score, No. (%)			
0	50 (76.9)	51 (81.0)	.44
1	9 (13.8)	10 (15.9)	
2	4 (6.2)	2 (3.2)	
3	2 (3.1)	0	
Left-side stroke, No. (%)	39 (60.0)	32 (50.8)	.30
Admission NIHSS score, median (IQR)	18 (13-21)	17 (15-21)	.84
Hypertension, No. (%)	39 (60.0)	32 (50.8)	.34
Atrial fibrillation, No. (%)	24 (36.9)	27 (42.9)	.45
Diabetes, No. (%)	9 (13.8)	9 (14.3)	.91
Smokers, No. (%)	20 (30.8)	20 (31.7)	.81
Time from onset to qualifying MRI, median (IQR), min	118 (77.5-203.8)	112 (68.5-185.0)	.49
Lesion location, No. (%)			
ICA-neck (isolated)	6 (9.2)	2 (3.2)	.10
ICA-T	8 (12.3)	11 (17.4)	
M1	21 (32.3)	32 (50.8)	
M2	12 (18.5)	7 (11.1)	
Tandem	18 (27.7)	11 (17.5)	
IV tPA pretreated, No. (%)	50 (76.9)	46 (73.0)	.61
Spontaneous reperfusion (to mTICI 2b-3), No. (%)	4 (6.2)	5 (7.9)	.69
Thrombectomy approach, No. (%)			
Stent retriever	14 (21.5)	12 (19.0)	.96
Penumbra (ADAPT technique)	25 (38.5)	24 (38.1)	
Both	11 (16.9)	10 (15.9)	
Intra-arterial tPA, No. (%)	9 (13.8)	8 (12.7)	.81
Cervical angioplasty with or without stent, No. (%)	18 (27.7)	12 (19.0)	.27
Systolic BP at induction, mean (SD), mm Hg	164 (24.7)	163 (27.1)	.83
MAP at induction, mean (SD), mm Hg	110 (17.0)	108 (18.4)	.48
Systolic BP at groin puncture, median (IQR), mm Hg	131 (120-147)	156 (136-172)	<.001
MAP at groin puncture, median (IQR), mm Hg	90 (82-99)	102 (88-111)	<.001
Heart rate at groin puncture, median (IQR), beats per min	62 (55-75)	72 (64-82)	<.001
Maximum systolic BP during the procedure, mean (SD), mm Hg	178 (24)	177 (23)	.95
Minimum systolic BP during the procedure, mean (SD), mm Hg	107 (21)	132 (23)	<.001
Maximum MAP during the procedure, mean (SD), mm Hg	120 (16)	117 (19)	.21
Minimum MAP during the procedure, mean (SD), mm Hg	72 (13)	86 (16)	<.001
Referrals, No. (%)	13 (20.0)	10 (15.9)	.54

Abbreviations: ADAPT, A Direct Aspiration First Pass Technique; BP, blood pressure; ICA, internal carotid artery; IQR, interquartile range; IV, intravenous; MAP, mean arterial pressure; MRI, magnetic resonance imaging; mRS, modified Rankin Scale; mTICI, modified Thrombolysis in Cerebral Ischemia; NIHSS, National Institute of Health Stroke Scale; tPA, tissue plasminogen activator.

[a] Age, systolic BP, and MAP at induction and during the procedure were normally distributed. NIHSS scores, time metrics, BPs, and heart rate at groin puncture were not normally distributed.

range [IQR], 14-21). All patients received the intended treatment except for 4 patients of the 63 allocated to CS (6.3%) who crossed over from the CS to the GA arm but remained in the CS group for intention-to-treat analysis. Sixty-five patients (50.8%) were randomized to GA, and 63 (49.2%) were randomized to CS. The 2 groups were balanced regarding age, sex, NIHSS score, stroke risk factors, time to qualifying scan, level of occlusion, rate of intravenous tissue plasminogen activator pretreatment, and EVT technical approach (**Table 1**). Initial infarct size was also comparable between GA and CS (median [IQR], 10.5 [2.4-23.6] mL vs 13.3 [5.2-31.1] mL; *P* = .26) (**Table 2**).

Primary End Point

Final infarct volume was smaller in the GA group (Table 2), but no statistically significant difference in the primary end point of infarct growth was found between the GA and CS arms (median [IQR], 8.2 [2.2-38.6] mL vs 19.4 [2.4-79.0] mL; *P* = .10). Assuming a normal distribution, the mean infarct growth for CS was 57.4 mL and for GA was 34.1 mL (difference, 23.2 mL; 95% CI, −6.4 to 52.9).

Secondary Angiographic and Clinical End Points

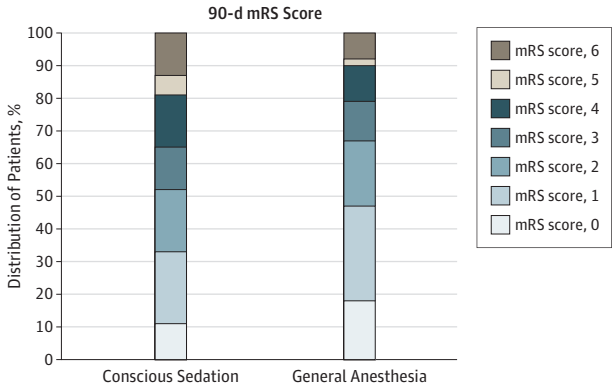
Successful reperfusion was higher in the GA group than in the CS group (76.9% vs 60.3%; *P* = .04). Early neurological out-

Table 2. Primary and Secondary Imaging and Clinical Outcomes

Outcome	General Anesthesia (n = 65)	Conscious Sedation (n = 63)	*P* Value
Successful reperfusion (mTICI 2b-3), No. (%)	50 (76.9)	38 (60.3)	.04
Acute infarct volume, median (IQR), mL	10.5 (2.4-23.6)	13.3 (5.2-31.1)	.26
Final infarct volume, median (IQR), mL	22.3 (8.1-64.5)	38.0 (16.7-128.0)	.04
Infarct volume growth, median (IQR), mL	8.2 (2.2-38.6)	19.4 (2.4-79.0)	.10
90-d mRS score, median (IQR)	2 (1-3)	2 (1-4)	.04
NIHSS score in 24 h, median (IQR)	6 (3-14)	10 (2-19)	.19
Change in NIHSS score after 24 h, median (IQR)	−10 (−14 to −5)	−7 (−13 to 0)	.11

Abbreviations: IQR, interquartile range; mRS, modified Rankin Scale; mTICI, modified Thrombolysis in Cerebral Ischemia; NIHSS, National Institute of Health Stroke Scale.

Figure 2. Modified Rankin Scale (mRS) Score Distribution of Patients Treated Under General Anesthesia and Conscious Sedation



The shift toward better outcome in the general anesthesia group was significant. The odds ratio for a better outcome was 1.91 (95% CI, 1.03-3.56).

comes as measured by the median (IQR) 24-hour NIHSS score (6 [3-14] vs 10 [2-19]; *P* = .19) and 24-hour change in NIHSS score (−10 [−14 to −5] vs −7 [−13 to 0]; *P* = .11) favored GA over CS but were not statistically significant (Table 2).

At 90 days, there was a shift to lower mRS scores in the GA group (**Figure 2**). The odds ratio (OR) for a shift to lower mRS scores was 1.91 (95% CI, 1.03-3.56). Functional independence—90-day mRS score of 0 to 2—was nominally more frequent with GA than with CS (OR, 1.90; 95% CI, 0.93-3.90).

Secondary Time Metrics and Blood Pressure End Points

The only significant difference in time metrics was the median (IQR) time from arrival at the neurointerventional suite to groin puncture (24 [20-27] minutes for the GA group vs 15 [12-20] minutes for the CS group; *P* < .001). There were no differences between the GA and CS groups in the mean (SD) time from symptom onset to groin puncture (202 [70.9] minutes vs 186 [72.2] minutes; *P* = .22) or median (IQR) time from symptom onset to reperfusion (212 [180-288] minutes vs 216 [162-285] minutes; *P* = .63) (**Table 3**).

Significantly more patients in the GA group than in the CS group experienced a decrease of greater than 20% in mean arterial pressure (MAP) (57 patients [87.7%] vs 22 patients [34.9%]; *P* = .001) (Table 3). However, when MAP dropped below 70 mm Hg, the duration was nonsignificantly longer for CS patients than for GA patients (6.5 [2-13] minutes vs 2 [1-5.5] minutes; *P* = .09).

Safety End Points

Four patients (6.3%) in the CS group converted to the GA group due to movement. Two of these patients also vomited, and 1 experienced desaturation due to aspiration.

In the GA group, 4 patients (6.2%) had type 2 parenchymal hematoma hemorrhage and 2 patients (3.1%) were symptomatic. In the CS group, 3 patients (4.8%) had type 2 parenchymal hematoma hemorrhage, of which 1 (1.6%) was associated with clinical deterioration. Mortality rate at 90 days was not significantly different in the GA group than the CS group (7.7% vs 12.7%; *P* = .35) (eTable in Supplement 2).

Supplementary Analyses

In the per-protocol analysis, in which the 4 patients who crossed over from the CS to the GA group were included in the GA group and the 2 patients with mRS scores greater than 2 before inclusion were excluded, successful reperfusion was no longer significantly higher in the GA group than the CS group (73.1% vs 62.7%; *P* = .21). Similarly, the final infarct size (median [IQR], 23.2 [8.3-68.1] mL vs 33.3 [16.0-119.9] mL; *P* = .15) and the 90-day mRS score (OR, 1.54 [95% CI, 0.83-2.87]) were no longer different between the GA and CS groups.

Discussion

In this single-center randomized clinical trial, the primary outcome of infarct growth during EVT was not significantly different between the GA and CS arms. Nevertheless, at 90 days, improved functional outcomes were seen among patients in the GA group. No clinically meaningful differences in safety end points were seen between the 2 arms. These findings support GA as a viable anesthetic approach during EVT.

Contrary to numerous nonrandomized studies that have reported better outcomes with CS, the GOLIATH trial shows signals in favor of GA for multiple end points. In addition to the lower 90-day mRS scores, the GA arm had numerically smaller infarct growth and larger reductions in NIHSS score between baseline and 24 hours. This result is most likely due to the higher rate of successful reperfusion (mTICI 2b to 3) among patients in the GA group. Similarly, in the Sedation vs Intubation for Endovascular Stroke Treatment (SIESTA) study, the GA arm had a higher rate of functional independence at 90 days and a higher, albeit nonsignificant, rate of mTICI 2b to 3 (an absolute difference of 8.5%).[8] These data seem to support the idea that EVT might be performed with greater technical success when patients are under GA and not moving, but no such

Table 3. Secondary Outcomes Associated With Time and Blood Pressure[a]

Time Interval[b]	General Anesthesia (n = 65)	Conscious Sedation (n = 63)	*P* Value
Time from symptom onset to arrival at neurointerventional suite, median (IQR), min	159 (122-230)	145 (113-231)	.55
Time from arrival at neurointerventional suite to groin puncture, median (IQR), min	24 (20-27)	15 (12-20)	<.001
Time from onset to groin puncture, mean (SD), min	202 (71)	186 (72)	.22
Time from imaging to groin puncture, median (IQR), min	61 (48-73)	54 (40-75)	.13
Time from groin puncture to reperfusion, median (IQR), min	34 (21-51)[c]	29 (16-51)[d]	.27
Time from onset to reperfusion, median (IQR), min	212 (180-288)[c]	216 (162-285)[d]	.63
Patients with 20% MAP decrease, No. (%)	57 (87.7)	22 (34.9)	<.001
Patients with MAP <70 mm Hg			
No. (%)	23 (35.4)	10 (15.9)	.01
Median time (IQR), min	2 (1-5.5)	6.5 (2-13)	.09
Phenylephrine hydrochloride, median (IQR), mg	2.2 (1.2-3.0)	0.2 (0.0-1.0)	<.001
Ephedrine sulfate, median (IQR), mg	10 (0-10)	0	<.001

Abbreviations: IQR, interquartile range; MAP, mean arterial pressure.

[a] Decreases in blood pressure levels were treated with vasopressors (ephedrine and phenylephrine) to maintain the levels within recommended limits (systolic blood pressure >140 mm Hg; MAP >70 mm Hg).[11]

[b] Time from onset to groin puncture was normally distributed. Other time intervals were not normally distributed.

[c] For the 50 reperfused patients.

[d] For the 38 reperfused patients.

benefits in terms of reperfusion and functional outcome were seen in the GA arm of the AnStroke trial.[9] In addition, the nonrandomized studies that have reported these data generally found no difference in EVT performance such as procedure duration[12,13] or rate of reperfusion[6,14] under different anesthesia regimens. These variable results may be associated with the differences in institutional or operator experience with performing thrombectomy using CS. At Aarhus University Hospital, prior to the trial, thrombectomy was routinely performed using CS; thus, operator inexperience is unlikely to account for the differences in reperfusion between the trial arms. Taken together, the recent randomized trials of anesthesia for EVT demonstrate that GA does not necessarily lead to worse outcomes after EVT.

The marked discrepancy in findings between the randomized and nonrandomized studies highlights the problem of bias, in particular confounding by indication. Patients with AIS who have very poor presentation (eg, severe stroke, respiratory compromise) are not only more likely to have worse outcomes but also more likely to require GA, and these patients were certainly included in the GA cohort of retrospective studies. This finding is illustrated by comparing the intention-to-treat and per-protocol analyses in the GOLIATH trial. In the intention-to-treat analysis, final infarct volumes were larger and clinical outcomes were worse for the CS group. These differences were no longer significant in the per-protocol analysis. The 4 patients who crossed over from the CS to the GA arm had extensive final infarcts (median final infarct volume, 130 mL), supporting the idea that patients with a medical indication for GA are sicker and simply have worse outcomes. This observation was similarly seen in a post hoc analysis of the Interventional Management of Stroke (IMS) III trial, wherein the worse outcomes in the GA group were driven largely by those who had a medical indication for GA.[15] Previous nonrandomized studies tried to adjust for baseline differences in patients under GA and those under CS,[13,16] but it is difficult to remove residual confounding due to unmeasured sources of bias.

Possible improvements in GA administration in recent randomized clinical trials might also explain the better outcomes achieved with GA compared with outcomes reported in previous literature. Four main factors have been proposed to explain the association between anesthesia and outcomes after EVT: blood pressure, treatment delay, neuroprotection, and ventilation status.

Blood pressure decreases are more frequent with GA and have been associated with worse EVT outcomes, although optimal blood pressure targets remain unknown.[17-19] Small changes (10%) in MAP have been associated with poor outcome,[20] and others have reported that more dramatic MAP changes (>40%) lead to worse outcomes.[19] This association has also been characterized in a post hoc analysis of the Multicenter Randomized Clinical Trial of Endovascular Treatment for Acute Ischemic Stroke in the Netherlands (MR CLEAN) trial.[18] Notably, the blood pressure levels in the MR CLEAN study were generally below recommended values; more than 75% of the patients included in the analysis had a systolic blood pressure lower than 140 mm Hg. All 3 recent anesthesia trials established a goal of intraprocedural systolic blood pressure greater than or equal to 140 mm Hg, which is consistent with recent consensus recommendations.[8,9,21] Blood pressure was lower in the GA arm in both the AnStroke and GOLIATH trials (no difference was seen in the SIESTA trial), but it is conceivable that greater attention to preventing hypotension promoted better neurological outcomes within the trials.

A longer delay for patients in the GA group was observed from arrival at the neurointerventional suite to groin puncture. However, the median difference was only 9 minutes. This time delay for induction and intubation is acceptable in the context of the much longer overall time from stroke onset to treatment and from stroke onset to reperfusion, which was not significantly different between the competing arms. This finding was remarkably consistent across the 3 trials, demonstrating the feasibility of rapid anesthesia workflow for GA.[8,9] Regarding our choice of MRI as a stroke imaging tool, the time delay from hospital admission to vessel puncture in this study was much shorter (median [IQR] for all patients, 68 [55-87] minutes) than in the Solitaire with the Intention for Thrombectomy as Primary Endovascular Treatment (SWIFT PRIME) trial (median [IQR], 90 [69-120] minutes), which largely employed computed tomography imaging.[22]

There are no conclusive data on neuroprotective properties of anesthetic agents to help with recommending one anesthetic agent over another. In this study, propofol was used as both a general anesthetic and a sedative in the CS group to minimize the confounding effect of different drugs. In anesthetic doses, propofol reduces the cerebral metabolic rate of oxygen with the preservation of flow-metabolism coupling and may increase brain tolerance to ischemic insults.[23] Numerous experimental studies have demonstrated the neuroprotective effects of propofol through different molecular pathways.[24] However, this benefit has not been demonstrated in clinical studies. Volatile anesthetic agents have also been suggested as being of benefit.[25]

Finally, the influence of ventilation on stroke outcomes is unknown. To our knowledge, no studies have demonstrated the effect of ventilatory status on outcome after thrombectomy. However, in this group of patients with poor cerebral blood flow, it can be argued that hypercapnia may potentially increase blood flow and oxygenation into critically hypoperfused areas. This matter requires further investigation.

Limitations

The primary limitation of the GOLIATH trial is that it was conducted at a single center, which may limit its generalizability to centers that use different approaches to anesthesia and neurointerventional treatment. However, we standardized as much as possible the anesthesia protocol used in this trial by adhering to the recent consensus recommendations of the Society for Neuroscience in Anesthesiology and Critical Care regarding respiratory and hemodynamic values. In addition, the primary end point was infarct growth, and consequently, no definitive conclusions can be drawn regarding clinical outcomes. As mentioned, the difference in reperfusion in favor of the GA arm may reflect the discomfort of local neurointerventionists with treatment using CS. The literature varies on this point, with most studies reporting reperfusion rates to be similar between GA and CS. However, the neurointerventionists at our center are experienced and had used a standard thrombectomy protocol that incorporated CS before the start of the trial. These factors were expected to maximize treatment success in both arms. Despite this limitation, all 3 single-center randomized anesthesia trials found that GA does not lead to worse outcomes. But it should be emphasized that these studies were performed at institutions with easy access to advanced anesthesia care, which might have contributed to the success of GA use.

Another limitation of the GOLIATH trial, and the other trials, is the relatively small sample size, which may potentially cause important differences between the treatment arms to be missed. Indeed, given the observed numerical difference in infarcts growth in favor of GA, our study may have been underpowered for the primary end point. Pooled individual patient data meta-analysis of the anesthesia trials is planned to address this issue.

Conclusions

Performing EVT under GA, compared with CS, does not result in worse tissue or clinical outcomes when using a GA protocol that limits the time delay for intubation (<10 minutes) and blood pressure level within recommended limits (systolic blood pressure >140 mm Hg and MAP >70 mm Hg).

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