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Choice of ANesthesia for EndoVAScular Treatment of Acute Ischemic Stroke (CANVAS): Results of the CANVAS Pilot Randomized Controlled Trial

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Background: The effect of choice of anesthesia on clinical outcome for endovascular treatment (EVT) in patients with acute ischemic stroke (AIS) remains unclear.

Methods: We conducted a pilot trial of 43 patients with acute anterior circulation ischemic stroke having EVT. Patients were randomly allocated to receive general anesthesia or conscious sedation. We documented the rate of recruitment and rate of conversion from conscious sedation to general anesthesia. In addition, we recorded the change in National Institute of Health stroke scale (NIHSS) on day 7, the rate of successful reperfusion and measured neurological function by certified researchers using modified Rankin Score (mRS 0 to 2) at 90 days.

Results: The recruitment rate was 31.4% and majority of patients were excluded because of delay in hospital presentation and posterior circulation stroke. The rate of conversion from conscious sedation to general anesthesia was 18.2%. This was primarily related to excessive sedation and uncontrolled movement. Change in NIHSS score, rate of successful reperfusion and functional recovery were similar between groups.

Conclusions: It was feasible to randomize AIS patients receiving either general anesthesia or conscious sedation for EVT.

Key Words: anesthesia, acute ischemic stroke, endovascular treatment

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A number of trials has demonstrated outcome benefits with endovascular treatment (EVT) for acute ischemic stroke (AIS).[1] However, it remains unclear whether this procedure should be managed during general anesthesia (GA) or conscious sedation (CS). Prior observational studies suggested GA was associated with worse outcomes compared with CS.[2–11] In this regard, it is commonly believed that GA delays EVT because of additional procedures, such as tracheal intubation, and may result in hemodynamic instability after induction of anesthesia. CS, in contrast, cannot guarantee immobility, nor does it provide a secured airway in patients with severe agitation and respiratory depression. More importantly, results from the observational studies were potentially confounded by selection bias, so that patients with severe AIS were more likely to receive GA, tracheal intubation and may result in poor outcomes.

Recently, 3 randomized controlled trials have compared the outcomes after EVT with GA or CS (Table 1). The Sedation versus Intubation for Endovascular Stroke TreAtment (SIESTA) trial reported similar National Institute of Health stroke scale (NIHSS) scores at 24 hours between GA and CS, but daily performance, measured by modified Rankin scale (mRS) score was better with GA.[12] The Anesthesia during Stroke (AnStroke) trial reported no difference in 90-day mRS.[13] In contrast, the General Or Local anesthesia in Intra-Arterial THerapy (GOLIATH) trial reported growing size of infarct and worsening of 90-day modified Rankin scale (mRS) score with CS.[14] These data suggested that the effect of anesthetic techniques on patient outcomes for EVT remained controversial and may be largely attributed

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M.T.V.C. and R.H. are the members from the Editorial Board of Journal of Neurosurgical Anesthesiology. The remaining authors declare that they have nothing to disclose.
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TABLE 1. The main Outcomes of 3 Randomized Controlled Trials

	Primary Outcomes	Sample Size	90-day mRS	24-hour Change in NIHSS	Successful Reperfusion Rate	Time from Suite to Puncture	Time from Onset to Reperfusion
SIESTA	24-h change in NIHSS	150	$P=0.01$* (GA was better)	$P=0.82$	$P=0.68$	$P=0.03$* (CS was better)	NA
AnStroke	90-day mRS	90	$P=1.00$	$P=0.272$	$P=1.00$	$P=0.055$	$P=0.783$
GOLIATH	Infarct volume growth	128	$P=0.04$* (GA was better)	$P=0.11$	$P=0.04$* (GA was better)	$P<0.001$** (CS was better)	$P=0.63$

*$P<0.05$.
**$P<0.01$.
ANstroke indicates the Anesthesia during Stroke trial; CS, conscious sedation; GA, general anesthesia; GOLIATH, the General Or Local anesthesia in Intra-Arterial THerapy trial; mRS, modified Rankin scale; NIHSS, National Institute of Health stroke scale; SIESTA, the Sedation versus Intubation for Endovascular Stroke TreAtment trial.

to the limited number of patients recruited in these trials.[12–14]

We have designed the Choice of ANesthesia for EndoVAScular Treatment of Acute Ischemic Stroke (CANVAS) trial, a prospective, randomized, equivalence trial to compare the effect of GA and CS on 90-day independent outcome after EVT for AIS.[15] In the present CANVAS pilot trial, we aimed to determine the feasibility of the CANVAS trial. Specifically, we report the proportion of eligible patients randomized for treatment, the adherence to treatment allocation and the completion of follow-up.

METHOD AND MATERIALS

Trial Design

The CANVAS pilot trial is single-center prospective, randomized, open-label, blinded end-point (PROBE) evaluation and enrolled patients with AIS from Beijing Tiantan Hospital, Capital Medical University between April 2016 and June 2017. This trial was approved by the Ethics Committee of Beijing Tiantan Hospital of Capital Medical University (KY2016-001-01). Details of the trial protocol had been previously published[15] and reported in http://www.clincaltrials.gov (NCT02677415). Legal representatives of the patients provided written informed consent before enrollment.

Patients

The patients were screened for eligibility if they were admitted with AIS for emergency EVT. The inclusion criteria included patients with age 18 years or older having stroke because of intracranial occlusion, based on single phase, multiphase or dynamic computer tomography angiogram (CTA) or digital subtraction angiography (DSA), at one or more of the following arteries: internal carotid artery (ICA), middle cerebral artery (MCA) segments (M1, and M2) equivalent affecting at least 50% of MCA territory. Patients were eligible only if stroke occurred no more than 6 hours from the onset of symptoms and who were previously functionally independent (mRS 0 to 2). In all eligible patients, both neuroradiologists and anesthesiologists agreed to proceed with GA or CS before enrollment.

We excluded patients who were moribund with Glasgow coma scale (GCS) score <8, requiring tracheal intubation for airway protection and lung ventilation. Patients with intracerebral hemorrhage on brain imaging, severely agitation, having seizures, current NIHSS score <8 or >35, or known allergy to specific anesthetics (propofol), or analgesics (sufentanil and remifentail) were excluded from the study.

Randomization and Grouping

Randomization occurred when patients were sent to the interventional neuroradiology suite for EVT and was obtained through a purposely built web-based program, stratified by the site of culprit vessels (ICA or MCA) using permuted blocks. Patients were randomly allocated to receive either GA or CS in a 1 to 1 ratio. An elite group of duty anesthesiologists, independent of the trial, were instructed to perform both GA and CS according to the protocol.

In the GA group, anesthesia was induced with sufentanil of 0.2 μg/kg and target-controlled infusion with propofol of 1 to 4 μg/mL. Muscle relaxation was achieved with rocuronium 0.6 mg/kg for laryngeal mask placement or tracheal intubation and mechanical ventilation. Anesthesia was maintained with infusions of propofol at 1 to 4 μg/mL and remifentanil at 0.1 to 0.2 μg/kg/min to keep the anesthesia depth measured as bispectral index (BIS) value between 40 and 60. In the CS group, patients were provided with supplemental oxygen using facemask. Sedation was provided with sufentanil 0.1 μg/kg bolus and propofol 0.5 to 1.0 μg/mL and allowed to keep the BIS more than 70.

Patients in CS group were converted to GA in case of: (1) complications of EVT (intracranial hemorrhage due to blood vessel piercing); (2) respiratory insufficiency with end-tidal carbon dioxide tension >60 mm Hg or hemoglobin oxygen saturation $<92\%$ after increasing oxygen concentration or adjusting depth of sedation to a pre-determined threshold to improve oxygenation; (3) nausea and vomiting; and (4) decreased level of consciousness or unable to cooperate. The decision of conversion was made by both the attending anesthesiologist and the neurointerventional physician.

Outcomes

The primary outcomes for this pilot trial were the recruitment rate and rate of conversion from CS to GA. In addition, we measured mRS at 90 days by the certified

neurologists who were blinded to the group allocation, the change in NIHSS on day 7 (or upon hospital discharge), the rate of successful reperfusion using the modified Thrombolysis in Cerebral Ischemia scale (mTICI) score 2b-3 and all-cause mortality and morbidity up to 3 months after EVT.[16] The time from onset of symptoms to the start of procedure, arterial puncture, and reperfusion were also recorded. Arterial pressure, respiratory parameters, and BIS values were also recorded.

Statistical Analysis

Our modified intention-to-treat population included eligible, consented patients who were randomly assigned to either GA or CS group and have undergone arterial puncture for EVT. All outcome indicators were analyzed based on both the modified intention-to-treat principle (defined as randomization and intervention surgery) and the treatment received (per-protocol analysis). Descriptive statistics were reported as means ± SD and medians (interquartile range, IQR) for normally distributed data and skewed continuous data, respectively. Continuous variables were analyzed using the Student *t* test or Mann-Whitney *U* test, as appropriate. Rate of death, and other complications were compared between groups by χ^2 test. The changes in arterial pressure was analyzed by the analysis of variance with repeated measures. For multiple comparisons between groups, we specified *a priori* that pairwise comparisons would be performed with $P < 0.007$, with Bonferroni corrections used to denote statistical significance. Statistical analysis was performed by IBM SPSS software, version 20 (Armonk, NY). Two-tailed $P < 0.05$ was considered as statistically significant.

RESULTS

A total of 137 patients with AIS were admitted in Beijing Tiantan Hospital, Capital Medical University from April 2016 to June 2017. Ninety-four patients were excluded, leaving a total of 43 patients (31.4%) randomized to receive GA (n = 21) and CS (n = 23). On average, 2.9 patients were enrolled per month (Fig. 1). Four patients (18.2%) in the CS group had to be converted to GA after randomization because of significant agitation (Fig. 1).

The median (IQR) age was 65 (45 to 74) years and 65% were male. The median (IQR) baseline NIHSS score was 13.9 (10.2 to 16.0). The two groups were comparable in age, sex, NIHSS score, stroke risk factor, ischemia site, and use of intra-arterial tissue plasminogen activator (Table 2).

During arterial puncture for EVT and 10 minutes afterwards, systolic arterial pressure (SAP) in the GA group was lower than that in CS group, 125 ± 26 mm Hg versus 159 ± 42 mm Hg, $P = 0.004$, and 123 ± 21 mm Hg versus 148 ± 33 mm Hg, $P = 0.007$, respectively. Similarly, mean arterial pressure (MAP) during arterial puncture was lower in the GA group, 89 ± 18 mm Hg, compared with CS group 108 ± 25 mm Hg, $P = 0.006$, (Fig. 2). In addition, a decrease in MAP > 20% from baseline occurred in 13 patients (65%) in the GA group and was more frequent than in the CS group, 6 patients (30%), $P = 0.027$. However, the frequency of MAP decrease > 40% were similar between groups (GA: 15% vs. CS: 10%; $P = 1.000$). Administration of vasopressors were similar between groups (GA: 35% vs. CS: 10%; $P = 0.130$). The arterial blood gas analyses were similar between groups (Table 2). The baseline BIS values were similar in GA and CS group (90 ± 3 vs. 91 ± 4; $P = 0.873$), the intraoperative BIS values at arterial puncture (54 ± 13 vs.

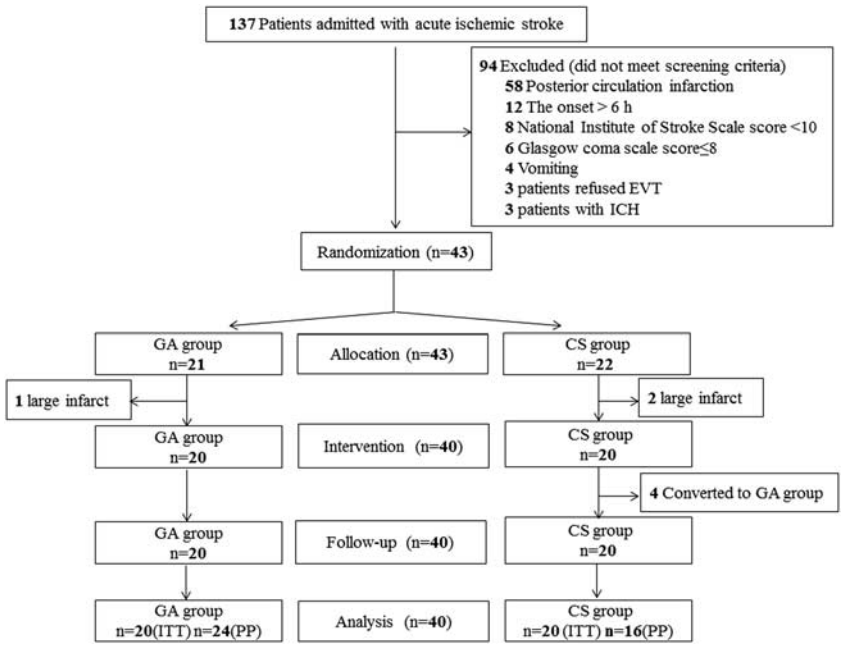

FIGURE 1. Flow chart of recruitment in the CANVAS pilot study. CS indicates conscious sedation; EVT, endovascular treatment; GA, general anesthesia; ICH, intracerebral hemorrhage; ITT, intention to treat; PP, per protocol.

TABLE 2. Demographic, Baseline Characteristics and Vital Signs During the EVT

	n (%)		
	General Anesthesia (n = 20)	Conscious Sedation (n = 20)	*P*
Age [median (IQR)]	67 (57-77)	60 (45-73)	0.067
Male	13 (65)	13 (65)	1.000
Comorbidities			
Hypertension	10 (50)	7 (35)	0.337
Atrial fibrillation	8 (40)	4 (20)	0.168
Coronary artery disease	5 (25)	2 (10)	0.405
Diabetes mellitus	3 (15)	6 (30)	0.449
Peripheral vascular disease	1 (5)	3 (15)	0.598
mRS 0-2	20 (100)	20 (100)	/
NIHSS score [median (IQR)]	14 (11-18)	13 (9-17)	0.417
Intravenous thrombolysis	9 (45)	11 (55)	0.527
Occlusion site			
Middle cerebral artery	12 (60)	13 (65)	0.744
Internal carotid artery	8 (40)	7 (35)	0.744
Types of EVT			
Direct aspiration	8 (40)	9 (45)	0.749
Stent retriever	2 (10)	3 (15)	1.000
Both	10 (50)	8 (40)	0.525
MAP 20% fall	13 (65)	6 (30)	0.027
MAP 40% fall	1 (5)	2 (10)	1.000
Use vasopressors	7 (35)	2 (10)	0.130
PH [mean (SD)]	7.38 (0.59)	7.38 (0.43)	0.933
$PaCO_2$ [mean (SD)] (mm Hg)	41.8 (3.4)	41.7 (5.0)	0.928
PaO_2 [mean (SD)] (mm Hg)	489 (61)	154 (27)	< 0.001
Bispectral index [mean (SD)]			
Pretreatment	90 (3)	91 (4)	0.873
Arterial puncture	54 (13)	75 (12)	< 0.001
Reperfusion	54 (8)	66 (14)	0.002
End of the treatment	68 (11)	78 (12)	0.010

EVT indicates endovascular treatment; IQR, interquartile range; MAP, mean arterial pressure; NIHSS, National Institute of Health stroke scale.

75 ± 12; $P < 0.001$) and reperfusion (54 ± 8 vs. 66 ± 14; $P = 0.002$) were both maintained between the target range and differed between groups.

We found the median (IQR) time from arrival at the interventional suite to groin arterial puncture in the GA group, 29 (25 to 34) minutes was longer than in CS group, 15 (11 to 17) minutes, $P < 0.001$. However, the median (IQR) reperfusion time in minutes did not differ between groups, 428 (350 to 498) in GA group versus 352 (236 to 468) in CS group; $P = 0.064$ (Table 3). Successful reperfusion rate was higher in the GA group compared with CS group (95% vs. 65%; $P = 0.048$). The median (IQR) ICU stay (11.9 [5 to 18] versus 5.9 [2 to 8]; $P = 0.034$) in the GA group were longer than CS group.

At 90 days, the distribution of mRS score in the GA group was similar as the CS group (Fig. 3). The rate of independence (mRS 0-2) at 90 days was also similar in GA group (55%) and CS group (50%). There was no difference in the NIHSS score at 7 days or mRS score at 30 days. Two patients in the CS group had intracranial hemorrhage during treatment and a total of 16 patients (40%) had postoperative pulmonary infection; however, no difference between groups was observed. The mortality at 90 days (GA: 5% vs. CS: 30%) did not differ between groups (Table 3).

On the basis of per-protocol analysis, for which the 4 patients converted to the GA group received GA. Successful reperfusion rate, GA: 88% versus CS: 69%, $P = 0.294$ and ICU stay, GA: 10.1 (6 to 14) versus 7.0 (3 to 10); $P = 0.277$, were similar between groups.

DISCUSSION

In this pilot trial, we demonstrated feasibility to randomize anesthetic techniques in AIS patients with anterior circulation occlusion. The recruitment rate was 31.4%, and the conversion rate from CS to GA was 18.2%. Although we did not intend to infer statistical differences between groups in a pilot trial, rate of arterial reperfusion, NIHSS score at 7 days, functional independence at 30 days or 90 days were similar between groups after EVT.

Although China has a higher incidence of AIS, public awareness of early intervention has been limited, and a delay in hospital arrival precluded EVT.[17] Furthermore, many patients had posterior circulation strokes and were excluded from the CANVAS trial. Finally, many of the participating sites have been providing GA for EVT and hence it is unclear whether it is feasible to conduct a trial comparing GA and CS for EVT at these sites. We therefore believe it is necessary to conduct the pilot trial to test the local feasibility of randomizing choice of anesthesia for AIS patients undergoing EVT.

In the current pilot trial, 137 AIS patients were screened but only 43 (31.4%) were successfully enrolled in 15 months. This was lower than SIESTA (150/247, 60.7%) and GOLIATH trials (128/235, 54.5%), but was similar to the AnStroke trial (106/321, 33%). Among the patients excluded from the pilot study, posterior circulation ischemia and the onset time > 6 hours were the primary reasons for exclusion. Patients with posterior circulation strokes present with significant alteration in level of consciousness and require tracheal intubation for airway protection.[14,18] The only study focused on posterior circulation ischemia indicated no difference in clinical outcomes between choices of anesthesia (OR = 1.60; 95% CI, 0.73-3.53; $P = 0.24$).[18] It is interesting to note that, the meta-analysis involving 22 studies (3 randomized controlled trials and 19 observational studies) including 4716 patients (1819 GA and 2897 non-GA) with anterior circulation ischemia indicated that GA was associated with statistically significant lower odds of good functional outcome (mRS 0 to 2) (OR = 0.59; 95% CI, 0.29-0.94) when adjusting for baseline NIHSS.[19] Saver et al found that the optimal time for endovascular treatment in AIS patients was 7.3 hour.[20] In addition, the DWI or CTP Assessment with Clinical Mismatch in the Triage of Wake-Up and Late Presenting Strokes Undergoing

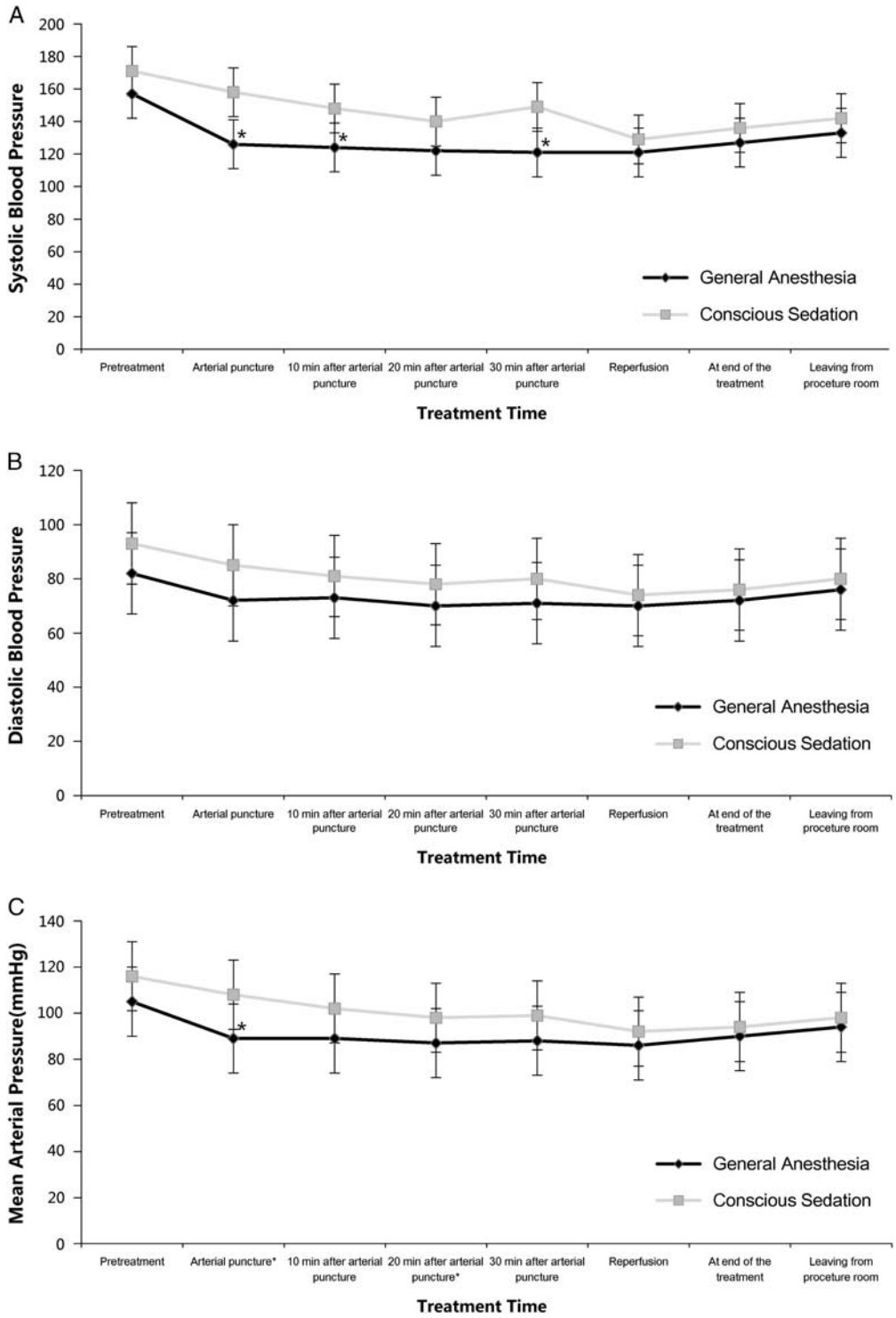

FIGURE 2. Blood pressure (A, systolic blood pressure; B, diastolic blood pressure; C, mean arterial pressure) changed during the endovascular treatment. *The blood pressure differed between general anesthesia group and conscious sedation, with Bonferroni corrections.

Neurointervention with Trevo (DAWN) Trial recently showed that the time window between 6 and 24 hours was still associated with a beneficial effect of thrombectomy.[1] These data suggested that it might be beneficial to extend the time for EVT treatment. We therefore amended the inclusion criteria to include patients with onset time up to 24 hours after stroke. This should improve the recruitment rate to more than 40%.

TABLE 3. Primary and Secondary Outcomes

	n (%)			
	Perprotocol Analysis		Intention-to-treat Analysis	
	GA (n = 24)	CS (n = 16)	GA (n = 20)	CS (n = 20)
Primary outcome				
mRS after 90 d [mean (SD)]	2.4 (1.9)	3.4 (2.2)	2.4 (1.8)	3.1 (2.2)
mRS after 90 d [median (IQR)]	2 (1-4)	3 (1-6)	2 (1-4)	3 (1-6)
Favorable outcomes (mRS 0-2)	14 (58)	7 (44)	11 (55)	10 (50)
Secondary outcome				
mRS after 30 d [mean (SD)]	3.1 (1.9)	3.5 (2.0)	3.1 (1.8)	3.3 (2.0)
NIHSS after 24 h [mean (SD)]	11.8 (5.1)	14.0 (7.6)	12.4 (5.1)	12.8 (7.3)
NIHSS after 7 d [mean (SD)]	8.9 (5.3)	11.2 (6.9)	8.9 (5.2)	10.6 (6.7)
Reperfusion rate (mTICI 2b-3)	21 (88)	11 (69)	19 (95)	13 (65)*
Length of ICU stay [median (IQR)] (d)	10.1 (6-14)	7.0 (3-10)	11.9 (5-18)	5.9 (2-8)*
Complications during EVT				
Substantial movement	0	1 (6)	0	5 (25)
Nausea or vomiting	0	0	0	0
Hypoxemia during the EVT	0	0	0	0
Mortality after 90 d	2 (8)	5 (31)	1 (5)	6 (30)
Vessel perforation	0	2 (12)	0	2 (10)
Pulmonary infection	11 (46)	5 (31)	10 (50)	6 (30)
Workflow time in mins [median (IQR)]				
Symptom to the Door	298 (240-350)	293 (234-361)	307 (271-347)	286 (245-333)
Door to arterial puncture	27 (20-35)	15 (10-19)**	29 (25-34)	15 (11-17)**
Arterial puncture to reperfusion	102 (71-127)	78 (49-105)	98 (75-123)	87 (66-101)
Symptom to reperfusion	428 (350-498)	352 (236-468)	434 (352-524)	361 (276-498)

*$P < 0.05$.
**$P < 0.001$.
CS indicates conscious sedation; EVT, endovascular treatment; GA, general anesthesia; IQR, interquartile range; NIHSS, National Institute of Health stroke scale.

It is commonly believed that GA delays treatment and hemodynamic fluctuations. In the GOLIATH, AnStroke and SIESTA trials, the door-to-arterial puncture time were 9, 9, and 10 minutes, respectively. In our pilot trial, we achieved a 12 minutes door-to-arterial puncture time. We anticipated that by including a core group of investigators to provide anesthesia in the interventional suite, we would be able to shorten the time spent on preoperative evaluation, anesthesia and intubation preparation. It was recommended that the goal of intra-procedural SAP was ≥ 140 mm Hg. Löwhagen Hendén et al[21] found that MAP fall > 40% of the base value was an independent risk factor for poor outcomes. For every 10 mm Hg decrease in MAP, Treurniet et al[22] showed that mRS score increased by 1.67-fold. In our pilot trial, we found SAP was significantly lower after induction in the GA group compared with the CS group, but the proportion of patients receiving vasopressors to maintain arterial pressure did not differ between groups. In addition, no difference was observed in the number of patients with MAP reduced > 40% after EVT between groups. Therefore, it was feasible to apply the current protocol for general anesthesia to the large-scale study.

Movement and respiratory depression are the 2 main reasons for conversion to general anesthesia and tracheal intubation.[12] In the pilot trial, the conversion rate was 18.2%, which was higher than the SIESTA (14.3%), AnStroke (15.5%) and GOLIATH trial (6.3%). The only reason for conversion in the pilot trial was unacceptable movement which was because of impaired consciousness and insufficient

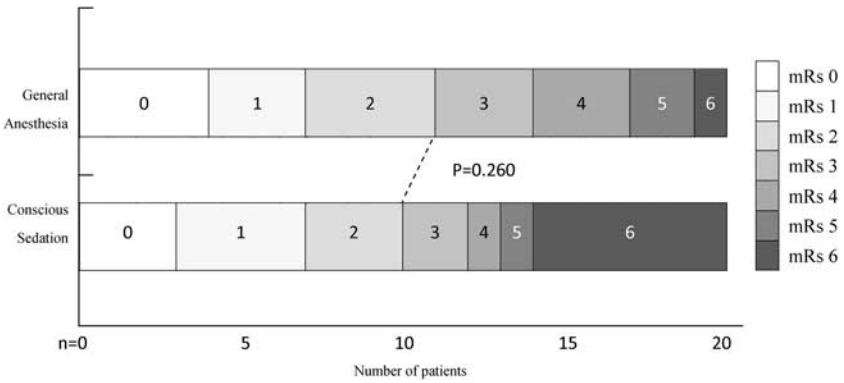

FIGURE 3. Modified Rankin Scale After 90 days.

analgesia and generally occurred during extrication of thrombus from the vessel. Movement would also interfere with the endovascular procedure which reflected the time from groin puncture to reperfusion. The difference of mean time from groin arterial puncture-to-reperfusion between GA and CS groups was 18 minutes in SIESTA, 19 minutes in AnStroke and 5 minutes in GOLIATH trial. We found a longer time difference (24 mins) by providing GA compared with CS in our pilot trial. The sedation depth (measured as BIS) was first maintained intentionally to keep BIS value more than 70 by intravenously infusion propofol and bolus doses of sufentanil. At this level of sedation, patients maintain normal response for verbal stimulus, patent airway, spontaneous breathing, and cardiovascular stability.[23] Opioid-induced respiratory depression should be carefully avoided in patients receiving CS. Nevertheless, the dosage of opioids administered in this pilot trial was titrated slowly and no patient had respiratory depression (arterial carbon dioxide tension was similar between groups) or requiring tracheal intubation for mechanical lung ventilation in CS group. Nevertheless, a high inspiratory fraction of oxygen has been shown to adversely affect the outcomes in patients after acute stroke.[24] In this pilot trial, arterial oxygen tension in both groups were similar.

There are limitations to the pilot trial. Firstly, the sample size was not prespecified. Given the sample size for the CANVAS trial is 640, and we believed 40 patients (6.3%) would be sufficient to test the feasibility of randomization. Secondly, large number of patients were excluded before randomization may have limited the generalizability of the trial. Nevertheless, recruitment has improved with nation-wide reconstruction of emergency care for AIS patients. After the adjustment of inclusion criteria in onset time from 6 to 24 hour, the enlargement of scale in new Beijing Tiantan Hospital, Capital Medical University and the involvement of multicenters, the enrollment proceeding is largely accelerated.

In summary, the pilot trial demonstrated feasibility of the anesthesia protocol, enrollment and data collection for a prospective randomized trial to investigate the choice of anesthesia for EVT. However, the recruitment rate was lower than expected and should be improved by including patients with onset time from 6 hours to 24 hours. We are currently recruiting patients at more sites with the amended inclusion criterion to investigate the effect of anesthesia on clinical outcome in AIS patients undergoing EVT.

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