Original research

Association between anesthesia modality and clinical outcomes following endovascular stroke treatment in the extended time window

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ABSTRACT
Background There is a paucity of data on anesthesia-related outcomes for endovascular treatment (EVT) in the extended window (>6 hours from ischemic stroke onset). We compared functional and safety outcomes between local anesthesia (LA) without sedation, conscious sedation (CS) and general anesthesia (GA).

Methods Patients who underwent EVT in the early (<6 hours) and extended time windows using LA, CS, or GA between October 2015 and March 2020 were included from a UK national stroke registry. Multivariable analyses were performed, adjusted for age, sex, baseline stroke severity, pre-stroke disability, EVT technique, center, procedural time and IV thrombolysis.

Results A total of 4337 patients were included, 3193 in the early window (1135 LA, 446 CS, 1612 GA) and 1144 in the extended window (357 LA, 134 CS, 653 GA). Compared with GA, patients treated under LA alone had increased odds of an improved modified Rankin Scale (mRS) score at discharge (early: adjusted common (ac) OR=1.50, 95% CI 1.29 to 1.74, p=0.001; extended: acOR=1.29, 95% CI 1.01 to 1.66, p=0.043). Similar mRS scores at discharge were found in the LA and CS cohorts in the early and extended windows (p=0.21). Compared with CS, use of GA was associated with a worse mRS score at discharge in the early window (acOR=0.73, 95% CI 0.45 to 0.96, p=0.017) but not in the extended window (p=0.55). There were no significant differences in the rates of symptomatic intracranial hemorrhage or in-hospital mortality across the anesthesia modalities in the extended window.

Conclusion LA without sedation during EVT was associated with improved functional outcomes compared with GA, but not CS, within and beyond 6 hours from stroke onset. Prospective studies assessing anesthesia-related outcomes in the extended time window are warranted.

INTRODUCTION
The optimal anesthetic technique between local anesthesia (LA) without sedation, conscious sedation (CS), or general anesthesia (GA) remains undetermined, with conflicting outcomes reported in previous studies involving patients with acute ischemic stroke (AIS) who underwent endovascular treatment (EVT) predominantly within 6 hours of stroke onset.1-8 Commonly used sedative and hypnotic agents administered during CS and GA are known to disrupt cerebral hemodynamics and cerebral perfusion.9

However, the potential deleterious clinical impact of CS or GA during EVT on the collateral circulation remains uncertain, particularly in the extended time window (>6 hours from stroke onset).10 11 We hypothesized that, due to a larger proportion of ‘slow progressors’ in the extended time window,12 the tenacious collateral supply in these subjects would offset the potential deleterious impact of CS or GA. Hence, we aimed to compare the functional and safety outcomes between LA, CS, and GA in patients undergoing EVT within and beyond 6 hours from stroke onset.

Key messages
What is already known on this topic
► The optimal anesthetic technique during endovascular thrombectomy (EVT) remains undetermined, with paucity of data on the clinical outcome in the extended time window.

What this study adds
► Using a national stroke registry of the UK, this large cohort study (n=4337) provides novel real-world data to suggest that, compared with local anesthesia without sedation, the deleterious impact of general anesthesia on functional outcome may persist in the extended time window cohort, even where there is a higher proportion of ‘slow progressors’ with more robust collateral circulation.

How this study might affect research, practice or policy
► A patient-tailored approach to optimal anesthetic management during EVT should be considered irrespective of the time window while awaiting confirmatory data from randomized controlled studies assessing anesthesia-related outcomes in the extended time window.
METHODS
Data source and study design
We performed a cohort study on prospectively collected data of patients enrolled in a UK national stroke registry (Sentinel Stroke National Audit Programme (SSNAP)), according to STROBE guidelines. SSNAP includes all hospital admissions of patients presenting with acute stroke in England, Wales and Northern Ireland (covering 92% of the population in the UK). Overall case ascertainment of SSNAP is estimated to be over 90% of all acute stroke admissions. Patient data, which include demographic and clinical characteristics, treatments, and outcomes, are submitted prospectively by clinical teams using a secure web-based case report form with real-time data validation checks to ensure data quality, from the time of admission up to 6 months after stroke.

Pseudonymized individual level data of adult patients (≥18 years) presenting with AIS who received EVT between 1 October 2015 and 31 March 2020 in England and Wales were included. Patients were dichotomized according to the time from onset of stroke, or last known well, to arterial puncture: (1) early window (<6 hours) and (2) extended window (>6 hours). Within each time window, patients were further divided into three groups: LA, CS, and GA. Patients with missing discharge modified Rankin Scale (mRS) and anaesthetic modality data were excluded. The choice of anaesthetic technique and agents was at the discretion of the individual practitioners and anesthetists. LA was defined as the use of subcutaneous local anesthetic injection at the site of the arteriotomy (without sedation), GA required endotracheal intubation, and CS required systemic medication for sedation without requiring advanced airway protection.

Data on anesthesia conversion from LA or CS to GA, parenchymal imaging findings and clot location were not available. No specific limits were applied to the clinical inclusion criteria including age, pre-stroke disability and baseline stroke severity (National Institutes of Health Stroke Scale, NIHSS).

Outcome measures
Functional outcome was assessed with the mRS score ranging from 0 (no symptoms) to 5 (severe disability/bedridden) and 6 (death) by ordinal shift and good (mRS ≤2 or equivalent to the pre-stroke mRS) or excellent (mRS ≤1 or equivalent to the pre-stroke mRS) functional outcome at ultimate hospital discharge and at 6 months. Other outcomes were early neurological improvement (NIHSS decrease ≥4 between admission and 24 hours or NIHSS 0–1 at 24 hours), early neurological deterioration (24-hour NIHSS increase ≥4 from baseline), and futile recanalization (mRS 4–6 at hospital discharge or worsening of the pre-stroke disability (mRS 4–5) despite successful reperfusion (modified Thrombolysis in Cerebral Infarction (mTICI) score 2b–3)). Procedural outcomes were successful reperfusion and complete reperfusion (mTICI score 3) at the end of EVT. Safety outcomes were in-hospital mortality, any type of intracranial hemorrhage (ICH) and symptomatic ICH (sICH) (ICH with NIHSS increase ≥4 within 24 hours or death). Workflow time metrics were described.

Statistical analysis
Study characteristics were summarized by the anaesthetic modality using descriptive statistics. Continuous variables were expressed as means and SD and categorical variables were expressed as frequencies or percentages. Comparisons of baseline variables were made using the χ², ANOVA or Student’s t-test, wherever applicable. Analyses of binary and ordinal outcomes were expressed as an OR with 95% CI. Multivariable analysis of the outcome measures used ordinal logistic regression for the full-scale mRS and binary regression analysis for the remaining dichotomized clinical outcomes. Adjustment was made for variables of clinical relevance: age (5-year age bands from 60 to 90 years), sex, baseline stroke severity (NIHSS), pre-stroke functional status (mRS), EVT technique, center, procedural time (min) and prior IV tissue plasminogen activator (IV-tPA). A two-tailed p value of <0.05 was considered statistically significant. All analyses were conducted using StataSE 16.1.

RESULTS
We included 4337 patients who underwent EVT at 25 neuroscience centres: 3193 in the early window (1135 LA, 446 CS, 1612 GA) and 1144 in the extended window (357 LA, 134...
LA was associated with an increased odds of improving the outcomes window, patients treated under LA had higher pre-stroke CS, 653 GA) (online supplemental figure 1). In the extended window, no significant difference in outcome was observed in the LA and CS cohorts in the early and extended windows (table 3). In the GA versus CS analysis, use of GA was associated with worse mRS at discharge in the early window (acOR=0.73, 95% CI 0.45 to 0.96, p=0.017) but not in the extended window (p=0.55) (table 4).

There were lower rates of in-hospital mortality in the LA cohort compared with GA in the early window (table 2: LA (10.7%) vs GA (13.4%) acOR=0.73, 95% CI 0.56 to 0.97, p=0.033) but not in the extended window (p=0.20). No significant differences in the safety outcomes of sICH and in-hospital mortality were identified between the other comparisons of anesthetic modalities in both time windows (tables 2–4). The remaining outcomes are detailed in tables 2–4.

**DISCUSSION**

The findings from this large national stroke registry provide novel real-world data related to the anesthetic modality of choice during EVT for AIS in the early and extended time windows. The use of LA-only was associated with significantly improved functional outcome (mRS) at hospital discharge compared with GA across both early and extended time windows. However, there was no significant difference in functional outcomes between LA and CS across both time windows. Although GA was associated with poorer functional outcome compared with CS in the early window, no significant difference in outcome was observed in the extended window.

A post-hoc analysis of 92 patients in the DEFUSE-3 trial (EVT 6–16 hours from stroke onset) concluded that GA (compared with CS) was associated with poorer functional independence (mRS ≤2) at 90 days. However, in the post-hoc analysis of the DAWN trial (EVT 6–24 hours from stroke onset), GA (compared with CS) was not independently associated with a change in the functional outcome. While the findings between the GA and CS cohorts in our study were in line with the findings of the

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**Table 2** Outcomes dichotomized by the anesthetic modality of local anesthesia versus general anesthesia in the early (<6 hours) and extended (>6 hours) time windows

| Outcome measures | Early window, n/N (%) | Extended window, n/N (%) |
|------------------|-----------------------|--------------------------|
|                   | LA (n=1135)          | GA (n=1612)              | LA (n=357)          | GA (n=653)      |
| Discharge         |                       |                          |                       |                  |
| Median mRS (IQR)  |                       |                          |                       |                  |
| mRS ≤1           | 3 (1–4)               | 4 (2–5)                  | 4 (2–5)               | 4 (3–5)         |
| mRS ≤2           | 285/1135 (25.1)       | 309/1612 (19.1)          | 64/357 (17.9)        | 99/653 (15.1)   |
| TICI 2b–3         | 909/1135 (80.0)       | 1351/1612 (83.8)         | 284/357 (79.5)       | 534/653 (81.7)  |
| TICI 3           | 537/1135 (47.3)       | 819/1612 (50.8)          | 175/357 (49.0)       | 319/653 (48.8)  |
| Futeile recanalization | 359/909 (39.4)    | 699/1351 (51.7)         | 200/357 (56.0)       | 422/653 (64.6)  |
| ENI              | 699/1058 (66.0)       | 966/1569 (61.5)          | 182/338 (53.8)       | 320/629 (50.8)  |
| END              | 122/1135 (10.7)       | 217/1612 (13.4)          | 403/338 (11.8)       | 109/629 (17.3)  |
| In-hospital mortality | 122/1135 (10.7)    | 217/1612 (13.4)          | 39/357 (10.9)        | 90/653 (13.7)   |

| P value |                      |
|--------|-----------------------|
| 0.001* |                       |
| 0.016* |                       |
| 0.033* |                       |
| 0.001  |                       |
| 0.043* |                       |
| 0.007* |                       |
| 0.008* |                       |
| 0.005* |                       |
| 0.009* |                       |
| 0.032  |                       |
| 0.039* |                       |
| 0.043* |                       |
| 0.053† |                       |
| 0.022* |                       |
| 0.005* |                       |
| 0.010* |                       |
| 0.001* |                       |
| 0.010* |                       |
| 0.016* |                       |
| 0.020* |                       |
| 0.001  |                       |
| 0.004  |                       |
| 0.004  |                       |
| 0.017  |                       |
| 1.000  |                       |

*Statistically significant.
†Adjusted odds ratio; END, early neurological deterioration; NIHSS worsening by ≥4; ENI, early neurological improvement (NIHSS improvement by ≥4); GA, general anesthesia; LA, local anesthesia; mRS, modified Rankin Scale; n/N, number of events/total number of patients (%); Futile recanalization, mRS 4–6 despite TICI 2b–3 recanalization; stICH, symptomatic intracranial hemorrhage; TICI, Thrombolysis in Cerebral Infarction.
Table 3  Outcomes dichotomized by the anesthetic modality of local anesthesia versus conscious sedation in the early (<6 hours) and extended (>6 hours) time windows

| Outcome measures | Early window, n/N (%) | Extended window, n/N (%) |
|------------------|-----------------------|--------------------------|
|                  | LA (n=1135)          | CS (n=446)               | aOR (95% CI)* | P value | LA (n=357)          | CS (n=134)               | aOR (95% CI)† | P value |
| Discharge        | 4 (2–5)               | 4 (2–5)                  | 0.73 (0.45 to 0.96) | 0.017* | 4 (2–5)               | 4 (2–5)                  | 1.11 (0.78 to 1.56) | 0.55† |
| mRS ≤1           | 479/1058 (45.4)       | 212/446 (47.5)           | 0.83 (0.65 to 1.08) | 0.18  | 164/653 (25.1)       | 161/146 (25.1)          | 0.91 (0.57 to 1.46) | 0.71  |
| mRS ≤2           | 909/1135 (80.9)       | 341/446 (76.4)           | 0.57 (0.45 to 0.72) | 0.42  | 200/357 (56.0)       | 134/61 (56.0)           | 0.79 (0.47 to 1.35) | 0.40  |
| TICI 2b–3        | 0.96 (0.73 to 1.26)   | 0.76 (0.53 to 1.08)      | 0.20  | 0.12  | 0.07 (0.33 to 1.34) | 1.05 (0.65 to 1.70)     | 0.83  | 0.70  |
| TICI 3           | 72/110 (65.4)         | 2 (1–3)                  | 0.12  | 0.42  | 0.70 (0.44 to 1.10)  | 0.65 (0.41 to 1.02)     | 0.25  | 0.10  |
| ENI              | 0.96 (0.73 to 1.26)   | 0.76 (0.50 to 1.15)      | 0.20  | 0.12  | 0.70 (0.44 to 1.10)  | 0.65 (0.41 to 1.02)     | 0.25  | 0.10  |
| In-hospital mortality | 0.97 (0.73 to 1.26) | 0.76 (0.51 to 1.08)     | 0.20  | 0.12  | 0.70 (0.44 to 1.10)  | 0.65 (0.41 to 1.02)     | 0.25  | 0.10  |

*adjusted multivariate analysis for age, sex, baseline NIHSS, pre-stroke disability, center, EVT technique, procedure time and use of IV thrombolysis. Statistical analysis reference is made to conscious sedation. Analyses performed using binary logistic regression except where ordinal regression was used.
†Analyses performed using ordinal regression.
aOR, adjusted odds ratio; CS, conscious sedation; END, early neurological deterioration (NIHSS worsening by ≥4); ENI, early neurological improvement (NIHSS improvement by ≥4); LA, local anesthesia; mRS, modified Rankin Scale; n/N, number of events/total number of patients (%); Futile recanalization, mRS 4–6 despite TICI 2b–3 recanalization; sICH, symptomatic intracranial hemorrhage; TICI, Thrombolysis in Cerebral Infarction.

Table 4  Outcomes dichotomized by the anesthetic modality of general anesthesia versus conscious sedation in the early (<6 hours) and extended (>6 hours) time windows

| Outcome measures | Early window, n/N (%) | Extended window, n/N (%) |
|------------------|-----------------------|--------------------------|
|                  | GA (n=1612)          | CS (n=446)               | aOR (95% CI)† | P value | GA (n=653)          | CS (n=134)               | aOR (95% CI)† | P value |
| Discharge        | 4 (2–5)               | 4 (2–5)                  | 1.00 (0.67 to 1.49) | 0.97  | 3 (1–4)               | 2 (2–3)                  | 0.96 (0.51 to 1.78) | 0.89† |
| mRS ≤1           | 1351/1612 (83.8)      | 341/446 (76.4)           | 1.77 (1.30 to 2.41) | 0.001* | 534/653 (81.7)       | 134/61 (81.7)           | 1.52 (0.90 to 2.57) | 0.11  |
| mRS ≤2           | 281/495 (56.7)        | 2 (1–3)                  | 2.00 (1.23 to 3.23) | 0.002* | 422/653 (64.6)       | 343/61 (64.6)           | 1.34 (0.84 to 2.16) | 0.21  |
| TICI 2b–3        | 1.00 (0.50 to 1.91)   | 1.09 (0.86 to 1.38)      | 0.45  | 0.011* | 99/653 (15.1)       | 22/134 (16.4)           | 0.72 (0.42 to 1.25) | 0.25  |
| TICI 3           | 1.00 (0.50 to 1.91)   | 1.09 (0.86 to 1.38)      | 0.45  | 0.011* | 99/653 (15.1)       | 22/134 (16.4)           | 0.72 (0.42 to 1.25) | 0.25  |
| ENI              | 966/1569 (61.5)       | 281/427 (65.8)           | 0.80 (0.62 to 1.03) | 0.09  | 320/629 (50.8)       | 60/123 (48.7)           | 0.93 (0.61 to 1.42) | 0.75  |
| END              | 1.00 (0.50 to 1.91)   | 1.09 (0.86 to 1.38)      | 0.45  | 0.011* | 99/653 (15.1)       | 22/134 (16.4)           | 0.72 (0.42 to 1.25) | 0.25  |
| Any ICH          | 1.00 (0.50 to 1.91)   | 1.09 (0.86 to 1.38)      | 0.45  | 0.011* | 99/653 (15.1)       | 22/134 (16.4)           | 0.72 (0.42 to 1.25) | 0.25  |
| sICH             | 45/1187 (3.7)         | 9/257 (3.5)              | 0.12  | 0.52  | 22/487 (4.5)         | 5/82 (6.1)              | 0.68 (0.23 to 1.73) | 0.49  |
| In-hospital mortality | 1.22 (0.85 to 1.76) | 0.50 (0.28 to 2.86)     | 0.26  | 0.26  | 0.12 (0.85 to 1.76) | 0.50 (0.28 to 2.86)     | 0.26  | 0.26  |

*Statistically significant.
†Adjusted multivariate analysis for age, sex, baseline NIHSS, pre-stroke disability, center, EVT technique, procedure time and use of IV thrombolysis. Statistical analysis reference is made to conscious sedation. Analyses performed using binary logistic regression except where ordinal regression was used.
‡Analyses performed using ordinal regression.
aOR, adjusted odds ratio; CS, conscious sedation; END, early neurological deterioration (NIHSS worsening by ≥4); ENI, early neurological improvement (NIHSS improvement by ≥4); LA, local anesthesia; mRS, modified Rankin Scale; n/N, number of events/total number of patients (%); Futile recanalization, mRS 4–6 despite TICI 2b–3 recanalization; sICH, symptomatic intracranial hemorrhage; TICI, Thrombolysis in Cerebral Infarction.

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DAWN trial, direct comparisons are challenging due to the lack of detailed information on the factors that determined the selection of anesthetic approach and the techniques of procedural sedation employed.

During AIS there is loss of the autoregulatory capacity of the pial collaterals in the affected region, which increases its susceptibility to fluctuations in the systemic blood pressure (BP). There is growing evidence that even small decreases in the systemic BP are associated with poor functional outcome due to collateral circulation failure and rapidly progressing large infarct volumes. This would be of particular relevance in ‘fast progressors’ with poor collaterals who may be more susceptible to changes in the cerebral hemodynamics from IV or inhaled anesthetic agents when undergoing CS or GA. However, our results suggest that the deleterious impact of GA may persist in the extended time window cohort, even where there is a higher proportion of ‘slow progressors’ with a more robust collateral circulation. Although not directly evaluated in our study due to the lack of available data on the intraprocedural BP, one study reported that patients treated under CS had a lower average procedural BP and more BP drops compared with patients treated under LA without sedation. This mechanism may, in part, explain the improved functional outcomes observed in the LA cohort in our study. Nevertheless, the neurotoxic or neuroprotective effects of sedative/anesthetic agents and the optimal intra- and peri-procedural BP targets during the acute ischemia-reperfusion injury remain incompletely understood.

The strengths of this study include the large sample size and high quality data within the SSNAP database from standardized case definitions, internal validation and audit trials. There are several limitations. First, due to the observational design, selection bias may have influenced the results. Patient-related factors including the likelihood of compliance during EVT or the clinical stability would influence the anesthetic modality decision. Second, there were missing data for certain outcome measures including the mRS score at 6 months. However, near-complete data (99.3%) were available for the primary outcome measure of mRS at discharge which has a high correlation with disability at 3 months. Third, data on conversion of LA or CS to GA, the techniques of procedural sedation employed and variables such as the Alberta Stroke Program Early CT Score (ASPECTS), collateral status or clot location were not available in the registry. These variables are key criteria in patient selection for EVT and are all strongly associated with clinical outcome. For instance, patients presenting with vertebrobasilar occlusions are more likely to require GA and are likely to have a poorer functional outcome. Hence, it would have been informative to understand the selection criteria used to good effect in this cohort. Last, outcome measures were self-assessed rather than evaluated by a core laboratory.

CONCLUSION

LA without sedation during EVT was associated with improved functional outcomes compared with GA, but not CS, within and beyond 6 hours from stroke onset. Prospective studies assessing anesthesia-related outcomes in the extended time window are warranted.

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