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Disparities among neurointerventionalists suggest further investigation of conscious sedation versus general anesthesia during thrombectomy for acute stroke

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Abstract:

INTRODUCTION: Prior retrospective and case-control studies have shown that the use of general anesthesia (GA) during endovascular therapy (EVT) for acute ischemic stroke with large vessel occlusion (AIS-LVO) was independently associated with poor clinical outcomes compared with cases performed under conscious sedation (CS). Conversely, recent small randomized clinical trials (RCT) demonstrated a trend toward better outcome in cases performed under GA.

METHODS: We submitted an online survey to 193 Society of Vascular Interventional Neurology and 78 American Association of Neurological Surgeons and Congress of Neurological Surgeons – Cerebrovascular Section neuroendovascular practitioners. Questions were aimed at understanding the current state of anesthesia practice during EVT, and to determine if there is clinical equipoise for a large multicenter RCT comparing GA versus CS during EVT.

RESULTS: Between March and May of 2017, we received 116 (43%) responses. Anesthesiologists were responsible for managing 96% of the GA cases as compared to only 51% of the CS cases ($P < 0.0001$). Notable 56% of providers reported performing less than a quarter of their cases under GA. Only 7% performed all cases under GA compared with 17% who used solely CS ($P = 0.048$). More than half of respondents thought a new RCT was necessary, of whom 61% were interested in participating. Among interested responders, 59% were located in centers with 3 or more neurointerventionalists.

CONCLUSION: The significant variation among neuroendovascular providers, added with the lack of consensus among recent trials and meta-analyses, demonstrate clinical equipoise for further studies to explore the effects of anesthesia during EVT in AIS-LVO.

Keywords:

Acute ischemic stroke, anesthesia, cerebrovascular disease, clinical trial, endovascular therapy, equipoise, survey

Introduction

Stroke is the major cause of long-term disability and the second most common cause of death in the world.[1] Endovascular therapy (EVT) has become well established as the treatment modality of choice for Acute Ischemic Stroke due to Large Vessel Occlusion (AIS-LVO), particularly in

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patients not responding to intravenous administration of tissue plasminogen activator. Although up to 20% of all stroke cases are eligible for this therapy, current evidence-based guidelines remain sparse regarding the optimal anesthesia protocol for this frequently performed procedure.[2] Conventionally, EVT had been performed under general anesthesia (GA). As experience and technique evolve, there is a growing number of these cases that are done under conscious sedation (CS).

A retrospective study of a multi-hospital administrative database between 2006 and 2013 found that among 2,515 patients who underwent EVT, 80% received GA, whereas 20% received CS.[3] This suggests that the vast majority of neurointerventionalists during that period may have preferred GA over CS for a variety of reasons, such as a perceived procedural safety with decreased patient movement, and improved procedural outcome.[3] Even though GA is arguably associated with increased procedural time and risk for hemodynamic instability, data are limited due to selection bias.[3,4] In 2018, a systematic review and meta-analysis for CS vs GA determined that AIS-LVO patients who underwent EVT under CS had significantly lower mortality rates and good functional outcomes (modified Rankin score [mRS] ≥2), consistent with a previous systematic review and meta-analysis from 2014.[5,6] In addition, a *post hoc* analysis of thrombectomy patients in Multicenter Randomized Clinical trial of Endovascular Treatment in the Netherlands (MR CLEAN) demonstrated a better 3-month mRS in patients who were managed under CS versus those who underwent GA.[7]

Conversely, two recent single-center randomized clinical trials (RCT) failed to demonstrate such an association and showed a trend toward better functional outcomes in GA versus CS.[4,8] With the evolving interest on this subject, we believe there is a need for a multi-center double-blinded RCT to evaluate the outcome of patients undergoing EVT to compare the type of anesthesia administered (GA vs. CS).

To better understand the current state of practice, determine the level of interest within the neurointerventional community and decide if clinical equipoise exists for the purposes of designing a large RCT for Sedation versus GA, we designed a survey. We then extended this survey to fellow neurologists and neurosurgeons within the Society of Vascular Interventional Neurology (SVIN) and the American Association of Neurological Surgeons and the Congress of Neurological Surgeons – Cerebrovascular Section (AANS/CNS-CV).

Methods

We submitted an online survey using a professional survey software (Survey Monkey) to 193 members of the SVIN and 78 members of the American Association of Neurological Surgeons and Congress of Neurological Surgeons-Cerebrovascular section (AANS-CV) who routinely perform EVTs. In this survey, neurointerventionalists were asked a series of questions to describe their clinical practice. These questions ranged from demographics and provider subspecialties to the number of EVTs performed annually. Specific questions regarding the modality of anesthesia (GA vs CS) were also asked. The questions were aimed at determining if any clinical equipoise existed for designing a large GA versus CS RCT and whether or not there would be enthusiasm for participation in such a trial. There were three reminders sent to the surveyees automated by Survey Monkey to allow maximum participation. Moreover, there was additional attention to randomly pick surveyees from different corners of the nation to decrease geographic bias. Care was also taken to include large stroke centers with the view to eliminate institutional limitations, hence reducing bias with respect to anesthesiology capacity. Our data were analyzed using Fisher's exact tests and Chi-square tests. A $P < 0.05$ was considered statistically significant.

Results

Among 271 neurointerventionalists who were surveyed, we received 116 responses between March and May 2017, corresponding to a 43% response rate to the comprehensive questionnaire. Of the questions included on the questionnaire, there was an average response rate of 84% (95% confidence interval 81%–87%) for each question on the survey [Table 1]. We found that the majority of the surveyees were from centers with 3 or more providers performing EVTs (64%), with almost half (45%) of those having 4 or more neurointerventionalists. Of these providers, 78% were Neurologists and 22% were Neurosurgeons. 49% of centers performed between 50 and 100 EVT cases per year, while 22% performed over 100 cases per year [Table 2].

With respect to the anesthesia subtype, 96% of the GA cases versus only 51% of the CS cases were being managed by anesthesiology ($P < 0.0001$). Almost half of the CS cases (46%) were administered by the neurointerventionalist. In addition, 56% of providers reported performing less than a quarter of their cases under GA with 17% reporting none of their cases were under GA (i.e. entirety of cases under CS). Only 7% reported all of their cases performed under GA ($P = 0.048$) [Figure 1].

Question 10 of the survey asked if there is a need for a randomized study to evaluate the choice of anesthesia (sedation vs. GA) for EVT. Among physicians surveyed, 55% of responders to this question agreed that there is a need for such a study versus the 45% who

Table 1: Survey questions and completion rates

Sample size: 271 193 SVIN members 78 AANS/CNS members	
Survey's success in inducing respondents to return the survey: 116/271=43%	
Survey completion rates	
Question	**Response rate**
Q1: Total IAT performed at your center yearly?	100%
Q2: Who administers and manages moderate sedation and local anesthesia during IAT?	85%
Q3: What percentage of IAT cases are performed under GA?	84%
Q4: Who manages the general anesthetic?	79%
Q5: What type of anesthetic regimen is used for GA?	84%
Q6: Which AIMS is used during a general anesthetic?	78%
Q7: For procedures performed under GA, what percentage of patients are extubated in the IR suite at the end of the IAT procedure?	79%
Q8: Where is post-IAT patient management conducted?	85%
Q9: For patients post-IAT who are taken to the ICU, who manages the patient's ICU care?	85%
Q10: Do you think there is a need for a randomized study to evaluate the choice of anesthesia (sedation vs general anesthesia) for IAT?	84%
Q11: How many interventionalists perform IAT at your institution?	84%
Q12: Do you think you and your center would be interested in participating in trial that randomized IAT patients to conscious sedation or general anesthesia?	85%
Q13: For institutions with more than 1 interventionalist performing IAT, how many of the interventionalists would agree with a new RCT?	81%
Average	84%

RCT: Randomized clinical trial, AIMS: Anesthesia information management system, GA: General anesthesia, IAT: Intraarterial thrombectomies, IR: Interventional neuroradiology, ICU: Intensive care unit

disagreed [Figure 2]. Moreover, 61% of those in favor of a new RCT indicated interest to participate as a center. Finally, 38% of all respondent physicians expressed interest in participating, with 25% expressing no interest and the remaining 35% were undecided [Table 2].

Discussion

EVT has become the standard of care following the reports from major endovascular stroke trials in 2015, namely MR CLEAN, SWIFT PRIME, REVASCAT, ESCAPE, and EXTEND IA.[9-13] In light of this and other further developments, the American Heart Association/American Stroke Association has issued a class IA recommendation for EVT as treatment of AIS-LVO for patients presenting in the early time window within 6 h and the extended time window up until 16 h. They have also issued a class IIA recommendation for patients with AIS-LVO in the late time window at 16–24 h from stroke onset. However, recommendations on the specific modality of anesthesia have remained to be less clear and providers are recommended to select a modality based on patient and case-related factors.[14] While retrospective data and one meta-analysis have favored CS, two prospective single-center studies have attempted to address the issue with mixed results.[4,8] The SIESTA trial failed to show a difference between GA and CS on NIHSS at 24 h (primary outcome) but did demonstrate a trend toward improved mRS at 3 months in the GA group.[8] Similarly, the GOLIATH trial did not show a significant difference in infarct volumes but did show a shift toward improved mRS in the GA group.[4] These studies were limited by small sample size, single-center design and failure to show significant benefit in the primary outcome.

Our survey was designed to assess the current opinion and practices among providers belonging to two of the leading organizations, SVIN and AANS-CV, in the neurointerventional community with respect to the choice of anesthesia type. Our respondents represented a broad spectrum of the neurointerventional practice among academic and nonacademic institutions. The response rate was favorable (43%) and the average response rate for all questions combined was 84%. Around 20% of centers were considered high-volume centers with over 100 cases per year.

Based on the questionnaire results, anesthesia management during EVT varies widely among providers. The majority of providers (56%) do <25% of their cases under GA reflecting a shift in practice from prior 2013.[3] This decision is likely influenced by a variety of factors including training bias, convenience, anesthesia resource availability, and existing retrospective data supporting CS. To further support this, 17% of providers reported none of their cases were performed under GA (i.e. entirely under CS) compared with only 7% reporting performing all of their cases under GA (P = 0.048). There is the disparity in preference of GA versus CS in EVT cases among highly trained professionals even with more

recent prospective studies suggesting potential benefit of GA over CS [Figure 1].

Of importance, among the surveyees, 96% of the GA cases are managed by anesthesiology as compared to only 51% of the CS cases being managed by anesthesiology ($P < 0.0001$). Furthermore, intriguing but yet unclear, the 4% of GA cases were reported to be managed by neurointerventionalists. This number reflects the minority and may suggest variability in the institutional guidelines (i.e. having induction and intubation performed at the Emergency Department), especially in lower volume centers, or in the neurointerventionalists' training background with or without the availability of a nonphysician anesthesia staff (i.e. a trained nurse or a physician assistant). There is retrospective data to suggest that centers favoring CS did not have uniform GA protocols.[5,6] The major criticism for those centers is that without clear protocols, there might have been significant fluctuation in hemodynamic measures, such as blood pressure, during induction and maintenance of anesthesia that would bias the practitioners towards a preference for CS. On the other hand, the fact that 51% of CS cases were managed by anesthesiologists suggests that even where access to anesthesia is available, CS is perceived as being safer, as well as yielding better outcomes and as such, is preferred by many neurointerventionalists.

Moreover, 55% of providers expressed the need for a new RCT to address this question and 38% expressed an interest in participating in such a trial. The centers favoring a new RCT had more than one neurointerventionalist, with almost two-thirds (59%) of these having at least 3 neurointerventionalists. These respondents, therefore, represent moderate to larger centers. When we extrapolate that in those larger centers with more than one neurointerventionalist, there is an even greater inter-provider variability in performing EVT and hence more interest in this proposed trial.

Most recently, two new large systematic reviews and meta-analyses by Schönenberger *et al*. and then by

Table 2: Participant characteristics and new RCT views

Question	Response (%)
Number of physicians that perform EVT	
≤2	36
3	29
4 or more	35
Subspecialty	
Neurosurgery	22
Neurology	78
EVT yearly case volume (*n*)	
≤30	14
31-50	15
51-100	49
>100	22
Physician who manages GA anesthesia	
Anesthesiologist	96
Neurointerventionalist	4
Critical care	0
Physician who manages conscious sedation	
Anesthesiologist	51
Neurointerventionalist	46
Critical care	2
Would your center be interested in participating in a GA versus CS randomized clinical trial?	
Yes	38
Maybe	35
No	25

GA: General anesthesia, CS: Conscious sedation, EVT: Endovascular therapy

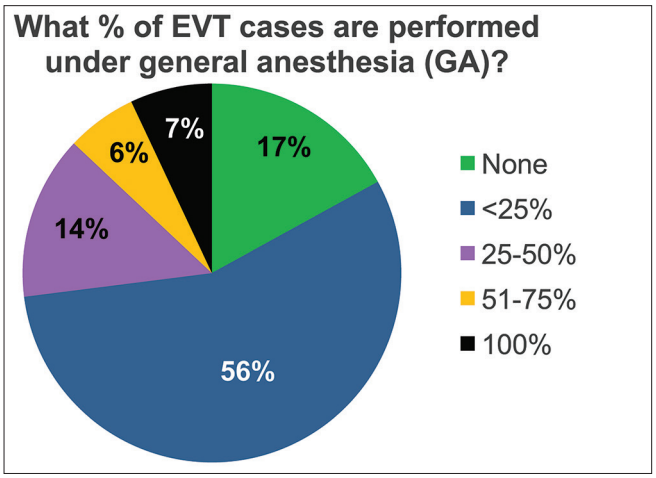

Figure 1: A representative figure for the number of endovascular therapy cases performed under general anesthesia per the participating respondents of AANS, CNS, and Society of Vascular Interventional Neurology. Notable 56% of providers reported performing less than a quarter of their cases under general anesthesia with 17% reporting none of their cases were under general anesthesia. Only 7% reported all of their cases performed under general anesthesia

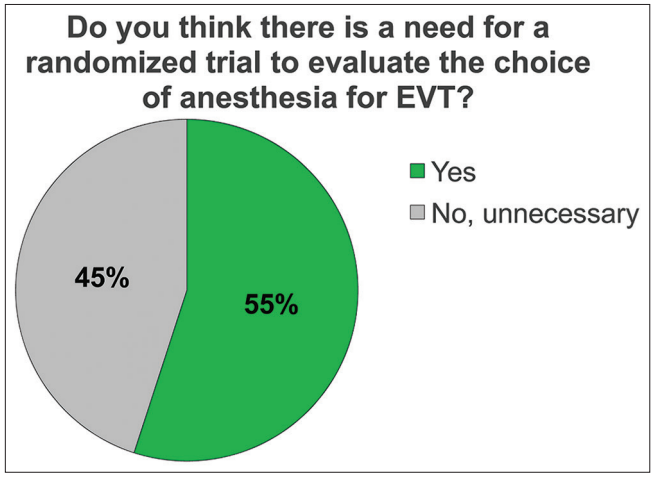

Figure 2: Question 10, which asked if there is a need for a randomized study to evaluate the choice of anesthesia (sedation vs general anesthesia) for endovascular therapy, was completed by 84% of all participating American Association of Neurological Surgeons, CNS, and Society of Vascular Interventional Neurology members that constitute our hypothesis for Sedation versus General Anesthesia Trial initiated on July 2018. Among surveyees, 55% of responders to this question agreed that there is a need for such a study versus the 45% who disagree

Campbell *et al*. showed significance or trends for less disability with the GA arm assessed by mRS at 3 months follow-up, respectively.[15,16] However, as both papers mentioned, in addition to the number of other limitations, the inability to control for patient selection factors in retrospective systematic reviews and meta-analyses likely introduces bias based on premorbid conditions making the patients unsuitable for one anesthesia subtype versus another. Hence, larger RCTs are suggested and warranted to further investigate the effects of GA versus CS.

A perceived limitation of our survey might be that questions detailing particular institutional numbers and neurointerventionalist characteristics may have caught surveyees unprepared for information about their annual treatment trends, or made them uncomfortable, perhaps due to institutional regulations, answering some of our questions. For instance, two questions with the lowest response rates in our survey were Question 6: "Which Anesthesia Information Management System (AIMS) is used during a GA?" and Question 7: "For procedures performed under GA, what percentage of patients are extubated in the neurointerventional (IR) suite at the end of the [EVT] procedure?". Both these questions require anesthesia teams' expertise and their metrics with which the surveyees from SVIN and AANS/CNS are not always involved. Such limitations could have caused several invited SVIN and/or AANS/CNS members to not attempt the survey or this particular question in the survey.

There is also extensive debate about what is considered to be a satisfactory response rate for online surveys. There is evidence that the online surveys yield a lower response rate than the mailed ones.[17-21] Hence, web surveys are encouraged to incorporate mail reminders or follow-ups to encourage increased participation.[19] Moreover, internal versus external surveys were also suggested to impact response rates, and several reports have noted previous studies with anywhere between 30% and 60% response rate while physician surveys are reported at around 50% or as low as 20%.[22-24] Hence, rather than survey response rate, reflecting on why a particular survey or question within a survey was least answered may yield a better understanding.

Finally, we were limited by the inability to extend this questionnaire to neuroradiologists. However, most of our participants were from multi-disciplinary centers including providers from all three subspecialties (neuroradiology, neurology, and neurosurgery), therefore, we believe that the participant demographics had diverse background. Even though our survey captured a substantial number of responses, with an even larger sample size and representation among providers, we may have observed clearer trend in our results.

Conclusion

The results of this survey highlight the need to determine if minimizing disparities in anesthesia preference among neurointerventionalists could result in better patient outcomes for AIS-LVO treated by EVT. The lack of overall consensus, as demonstrated by the result of this survey suggests that there is uncertainty in the best modality of treatment. Further research is not only warranted but could help determine additional universal safety guidelines for the type of anesthesia used to treat AIS-LVO by EVT. In light of these results, to properly evaluate the proposed benefit of GA over CS in AIS-LVO patients undergoing EVT, we designed and begun conducting a multicenter clinical trial: Sedation versus General Anesthesia for EVT in AIS – a Randomized Comparative Effectiveness Trial, Clinicaltrials.gov NCT-03263117.

One of the major remarks in our protocol is to require qualification cases for all the participating neurointerventionalists. Before starting actual enrollments, every participating neurointerventionalist at the approved centers is asked to perform two roll-in cases, one in GA and the other in CS, for thrombectomy and require thrombolysis in cerebral infarction (TICI) score of 2b or higher for the recanalization of the LVO. For those participating neurointerventionalists who have always (>90%) been using either GA or CS, we require the completion of two cases of opposite anesthesia modality against their routine practice. Another important decision in our trial was to try and recruit centers with balanced GA and CS cases. By also implementing pre-qualification roll-in cases and requiring a certain TICI performance as described above, the goal is to eliminate possible dysfluencies throughout the procedure for the actual enrollments.

Moreover, we have treated this trial as much as an anesthesia trial as a stroke trial and had a senior anesthesiologist as the co-principal investigator for the trial, to design and write the anesthesia protocol. In short, CS requires the supervision of an anesthesiologist with a target Richmond Agitation Sedation Scale score of-1 to-3, and those who do not tolerate sedation are converted to inhalational GA. Foreseen adverse events or airway risks already eliminate patient participation in the trial to minimize such cross-over events. In addition, to account for different GA induction methods, two subgroups, inhalational versus intravenous GA, are stratified for secondary outcomes analyses. All these anesthesia measures are taken to ensure replicability of our outcomes with respect to variations between practices among different centers and even different countries like in Europe, where inhalational GA is more common.

If the results of this clinical trial suggest better outcomes with one anesthesia modality over the other, it would guide us to change our practice. Naturally, the future choice of the anesthesia for thrombectomy practice would depend on the individual center and practitioner's discretion if the trial fails to show different outcomes between the two anesthesia groups. We would like to emphasize that our trial initiative does not limit other studies or claim to resolve this disparity alone. With this article and our initiative, we hope to extend our current findings on the existing treatment paradigm and contribute to this discussion in the neurointerventional field.

Acknowledgement

We would like to acknowledge fellow neurologists and neurosurgeons within the Society of Vascular Interventional Neurology (SVIN) and American Association of Neurological Surgeons and Congress of Neurological Surgeons – Cerebrovascular Section (AANS-CV) for their participation in our survey.

Declaration of ethical approval and patient consent

The survey was distributed and only collected from volunteer participants. The survey was not implemented or required from the participants. The survey enacted as a consent on its own. We have acted in accordance with our Institutional Review Board after consulting our Research Compliance, Education, and Support Services at the University of Texas Health Science Center at Houston.

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Stryker Neurovascular has granted research fund for the SEGA trial. The sponsor has had no role in the study design, in the collection, analysis and interpretation of this or any other SEGA trial data, in the writing of the report, or in the decision to submit the article for publication.

Conflicts of interest

There are no conflicts of interest.

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