PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	Choice of ANesthesia for EndoVAScular Treatment of Acute Ischemic Stroke at Posterior Circulation (CANVAS II): Protocol for an Exploratory Randomized Controlled Study
AUTHORS	Liang, Fa; Zhao, Yan; Yan, Xiang; Wu, Youxuan; Li, Xiuheng; Zhou, Yang; Jian, Minyu; Li, Shu; Miao, Zhongrong; Han, Ruquan; Peng, Yuming

VERSION 1 – REVIEW

REVIEWER	Clarençon Frédéric Pitié-Salpêtrière Hospital. Paris. FRANCE
REVIEW RETURNED	12-Jan-2020

GENERAL COMMENTS	We read with interest the manuscript entitled: “Choice of ANesthesia for EndoVAScular Treatment of Acute Ischemic Stroke at Posterior Circulation (CANVAS II): Protocol for an Exploratory Randomized Controlled Study”. This manuscript presents the research protocol of a randomized controlled trial to come comparing general anesthesia (GA) vs. local anesthesia/conscious sedation (LA/CS) for mechanical thrombectomy (MT) in posterior circulation strokes. The manuscript (and the study design) is interesting and well written. I have however some questions and comments: 1. In the introduction section, the authors report from the literature a mortality rate of posterior circulation acute ischemic strokes of 80 to 95%. I guess that the authors report the spontaneous mortality rate (i.e.: without IV thrombolysis and/or MT). This should be specified. 2. P7L48: please correct for “these studies”. 3. P9L32: please correct: “neither be involved” 4. The authors should explain why they chose a cut-off of 2 to distinguish good from poor clinical outcome on the mRS. In numerous studies focused on basilar artery occlusion treated by MT, the cut-off is 3, a mRS > 3 being defined as a poor clinical outcome. 5. The calculation of the sample size is based on a difference of 30% in terms of good clinical outcome. Isn’t it too ambitious? 6. How will be conducted the data analysis? In “Intention to treat” analysis? In “Per protocol” analysis? In “As treated” analysis? Please specify.

REVIEWER	Massimo Lamperti Cleveland Clinic Abu Dhabi United Arab Emirates
REVIEW RETURNED	13-Jan-2020

GENERAL COMMENTS	This is an interesting protocol on the effects of GA vs PS during mechanical thrombectomy in AIS in the posterior circulation. I have some questions before considering the protocol suitable for publication: 1- there is no mentioning the secondary outcomes on hemodynamic parameters: Systolic blood pressure and MAP could have a role in the final outcome of this cohort of patients. 2- how will the penumbra zone will be evaluated? The authors need to be more detailed in this section P7L53-56 3- which sedation score are they going to use? RASS? if so, which level of sedation will be targeted? P9L10 4- why are the authors using TIVA protocols for sedation by non-anesthesiologists and why using propofol associated to remifentanil? the association can clearly cause respiratory events during the intraoperative period? why not using TCI protocols and using one drug only? BIS is very difficult to be used during mechanical thrombectomy as the sensor is not allowing a proper visualisation of the cerebral vessels 4- who is taking care for the PS? an anesthesiologist? 5- the term LA is referred to the local anesthesia done by the interventional radiologist prior to arterial puncture? 6- even in the GA group, the BIS sensor seems to be difficult to be kept during the procedure 7- will the data be collected manually by the researchers or through an EMR system? 8- P10L26 will phenylephrine be started since the beginning of the procedure to keep targeted SBP? 9- norepinephrine cannot be administered through a peripheral vein catheter 10- there is no mention on the intraoperative complications as apnea, hypotension, hypertension, vomiting 11- is a CTA 24hrs post-stroke a routine practice? if not, the authors have to declare that this is standard practice in their Institution only

REVIEWER	Russell Chabanne Department of Perioperative Medicine, Centre Hospitalier Universitaire de Clermont-Ferrand, Clermont-Ferrand, France I am the principal investigator of the ongoing AMETIS (Anesthesia Management in Endovascular Therapy for Ischemic Stroke) trial that was supported by funding from French Ministry of Health (Programme Hospitalier de Recherche Clinique Inter Régional (PHRC IR) 2016) and from the university hospital of Clermont-Ferrand.
REVIEW RETURNED	01-Feb-2020

GENERAL COMMENTS	The authors provide the study protocol of an ongoing monocentre randomized controlled trial exploring the effect on neurological outcome of general anesthesia versus local anesthesia/conscious sedation for emergency endovascular therapy (EVT) in posterior circulation acute ischemic stroke (AIS). As stated by the authors, this is a persistent controversy question in the field. Recent data exist in EVT for anterior circulation AIS.

	Here are some points that I would like the authors to discuss, clarify or correct. In red font, please find my suggested corrections for the wording. My comments are in italic. **Abstract:** • Observational and interventional studies indicate that the type of anesthesia may be associated with the post-procedural neurological function in patients with anterior circulation acute ischemic stroke ~~patients~~ undergoing endovascular treatment. Patients with acute posterior circulation ischemic stroke may experience different physiological changes and result in severe neurological outcome. However, the effect of the type of anesthesia on post-procedure neurological function ~~has~~ remained unclear in this population. • This is an exploratory randomized controlled trial ~~which~~ that will be carried out at Beijing Tiantan Hospital, Capital Medical University. Patients with acute posterior circulation ischemic stroke and deemed suitable for emergency endovascular recanalization will be recruited in this trial. Eighty-four patients will be randomized to receive either general anesthesia or local anesthesia/conscious sedation with 1:1 allocation ratio. The primary endpoint is the 90-day modified Rankin ~~Score postoperatively~~ Scale. • If the results are positive, the study will indicate ~~that~~ whether the type of anesthesia affects neurological outcome after endovascular treatment of posterior stroke. **Strengths and limitations of this study:** • This is the first randomized control study to determine the effect of anesthesia modality on neurological outcome ~~on~~ of patients with posterior circulation acute ~~ischemia~~ ischemic stroke. • The findings of the study would contribute to ~~being~~ serve as a reference for a future ~~multicentric~~ multicentre trial to verify the effects of anesthesia on patients with posterior circulation ~~AIS~~ acute ischemic stroke undergoing ~~EVT~~ endovascular therapy. • One limitation of the study is that it is a single-centered trial. Future multi-~~centric~~ centre trial is ~~need~~ needed to verify the effects of anesthesia on patients with posterior circulation acute ~~ischemia~~ ischemic stroke undergoing endovascular treatment. **Introduction:** • posterior circulation account for 17%-60% of acute ~~ischemiac~~ ischemic stroke • Though endovascular therapy (EVT) has been demonstrated to be an effective and safe treatment ~~for patients' neurological function~~ with around 30% good clinical outcome ~~improvement~~ and 35% mortality decrease at 90 days ~~after interventional procedure~~, there is a

	substantial proportion of patients ~~suffered from~~ with poor clinical outcomes even ~~undergoing~~ after timely successful reperfusion • General anesthesia (GA) or local anesthesia/conscious sedation (LA/CS), is still ~~remain~~ unclear • Benefits of GA with tracheal intubation or laryngeal mask include secured airway to avoid aspiration: *it is difficult to state that laryngeal mask provides secured airway and avoid aspiration since trachea could be contaminated by secretions and vomiting. Please explain.* • body immobility to avoid ~~intracranial~~ vessel perforation: *It concerns intracranial AND also any extracranial vessel perforation*. • Nosocomial infection, delayed procedure initiation, ~~and~~ loss of neurological evaluation and hyperventilation may contribute to poor outcomes, ~~even yielding devastating complications~~.: *LA/CS could also provide devastating complication such as aspiration or vessel perforation.* • LA/CS management permits neurological function assessment, could shortens mean time from door to groin puncture and minimizes hemodynamic changes associate with ~~airway manipulation~~ GA. • Three randomized controlled trials have compared the neurological outcomes after EVT with GA or LA/CS in anterior circulation AIS patients… (SIESTA) trial reported similar National Institute of Health stroke scale (NIHSS) scores at 24 hours between GA and LA/CS, but favorable outcome~~s~~, measured by modified Rankin scale (mRS) ~~score~~ was found in patients with GA 3 months after treatment as a secondary outcome measure • (GOLIATH) trial reported ~~growing~~ similar brain infarct volume ~~decreased~~ and favorable 90-day mRS ~~score increased~~ with GA also as a secondary outcome measure • indicated ~~that~~ significantly different results in favor of the GA group in other 2 trials, it was analyzed as ~~as the~~ a secondary outcome • ~~Therefore, result of above trials is not suitable for posterior circulation AIS, concerning the relationship between neurological outcome and anesthesia modality~~. *This sentence is not necessary to understand the hypothesis of the proposed trial.* • A few studies observed the feasibility of ~~monitoring~~ monitored anesthesia care for elective endovascular procedures either in anterior or posterior circulations • Although ~~theses~~ these studies included a relatively large proportion of posterior circulation interventions and showed promising results, it is unreasonable to employ previous results in emergent setting, with potential presence of severe brain stem ischemia. Moreover, only one study focused purely on the posterior circulation patients and investigated the influence of anesthesia modality and management on clinical and angiographic outcomes: *I don't understand these 2 sentences? Did you mean that for the*

	moment these studies could not be incorporated in clinical practice related to bias? What is the relationship with brain ischemia? • In this retrospective, matched, ~~observatory~~ case control study • Furthermore, there is no published randomized controlled trial ~~to study~~ that explored whether GA ~~and~~ or LA/CS ~~own the~~ are associated with different neurological outcome at 90 days in patients undergoing EVT for posterior circulation AIS. • On the basis ~~of the findings~~ of previous studies, we propose to conduct a trial to compare neurological outcome in posterior circulation AIS patients receiving GA with those receiving LA/CS for EVT. **Methods:** • Posterior circulation AIS Patients who deemed suitable for recanalization of the culprit's vessels will be considered for ~~recruiting~~ recruitment in the study • posterior circulation ischemia confirmed by CTA/MRA: *please provide definition of CTA/MRA abbreviations and radiological indication for EVT in posterior circulation AIS in your institution: mismatch, collateral status…* • ~~The~~ Reasons ~~that~~ why eligible patients are not recruited to the trial will be documented. • when patients are ~~sent~~ admitted to the interventional neuroradiology suite • *Could you explain how written consent is obtained from the patient or relative: which patient are deemed able to consent in this situation of acute stroke? What if relatives are not immediately present in order to avoid delay in this emergent procedure?* • A designated staff who will neither be involved in anesthesia management • *Who are the outcome assessors? How many are they? Are they specifically trained and certified for outcomes reporting notably administration of the mRS?* • *Reference 22 is not the reference for Practice Guidelines for Sedation and Analgesia by Non-Anesthesiologists by the American Society of Anesthesiology* (*American Society of Anesthesiologists Task force on S, analgesia by N-A. practice guidelines for sedation and analgesia by non-anesthesiologists.; Anesthesiology 2002;96:1004–17.)* • *In your LA/CS protocol, could you be more stringent about your definition of "still following instruction to verbal stimulation" because it is a key parameter to avoid oversedation but could be difficult to obtain in stroke patient with potential aphasia and sensori/motor palsy. Also, who will monitor this clinical state in the difficult environment of the radiology suite with radiation burden. Is a clinical scale used to monitor this aspect?* • *You mention reference 23 for your LA/CS protocol: do you use cervical collar as mentioned in this publication to avoid head movement in this group? Also, only Remifentanil without Propofol was used in this study. Do you think this is*

	the good reference? Also, your protocol is different from the one used in GOLIATH study that you mentioned in reference 13. • *It is a LA/CS group and sedation is not mandatory but you never talked about Local Anesthesia: is it ever done? how is it done? Which drug? Is there also LA in GA group?* • In GA group, patients will receive rapid sequence induction with endotracheal intubation or laryngeal mask ~~implementation~~ insertion with Propofol: as mentioned before, the use of laryngeal mask in this group is questionable especially when your hypothesis rely about possible aspiration effect on outcome. This aspect should be discussed in the discussion part of your protocol as it could be criticized by some clinicians. • After endotracheal intubation or laryngeal mask ~~implementation~~ insertion, mechanical~~ly~~ ventilation will be initiated to achieve normocapnia with a 40%-60% fraction of inspired oxygen. • In cases of procedural emergency including vessel perforation, intracranial subarachnoid hemorrhage (SAH), seizures, deep coma (GCS decrease to less than 8 *(as mentioned in your table 2)),* respiratory failure (PaCO2 or EtCO2 ≥ 60 mmHg *(as mentioned in your table 2)*, or SpO2<94% without relevant improvement by increasing inhaled oxygen fraction), cardiovascular fluctuation: *could you define cardiovascular fluctuation which is surprisingly not mentioned in table 2? Also, a GCS<8 could not be associated with coma or unconsciousness especially in this type of stroke since patient could be paralyzed with persistent vigilance ("locked in state"). So, the term of coma and unconscious in table 2 could be criticized. The isolated visual component of the GCS ("eyes E") < 3 or 4 could have be a better and easier threshold. Please discuss this aspect in the discussion part.* • *I think it could be more didactic to put "Standard anesthesia management protocols during EVT (Concomitant treatment)" part before "interventions" part of your manuscript* • Including electrocardiography (~~EEG~~ ECG) • *How is invasive arterial pressure obtained: on the radiologist arterial access line or a dedicated catheter? Could you specify?* • *You mention that you monitor PaCO2 and EtCO2 in every patient: for PaCO2, is it a continuous monitoring? Otherwise, are there systematic blood gas analysis? You mentioned EtCO2>60mmHg as a trigger to convert to GA in table 2, what about PaCO2 if you also monitor it? Also, EtCO2 and PaCO2 could be very different especially in spontaneous breathing. It is not clear.* • *How could you monitor FiO2 in spontaneous breathing patients? You mentioned that LA/CS patients will have 3L/min O2 but it appears not possible to monitor FiO2 in this setting because it relies on ventilatory flow which is unknown without specific monitoring.* • *Is blood glucose continuously monitored? Otherwise, what is the timing and frequency of blood glucose assessment? Is it intravenous, arterial or capillary measurement? Is there a protocol for blood glucose management?*

	• *I imagine that EtCO2 objective of 35-45mmHg is only in GA group?* • *What is the frequency of BP measurement? How will blood pressure data be monitored?* • *Could you provide in the supplementary files a glossary with every data monitored and the frequency of monitoring?* • *Concerning complications, could you describe how they will be searched? Are there specific procedures to diagnose these complications? Are they just notified by the study team with the medical documents of the patient? Is there an adjudication committee to define these complications based on a priori diagnostic criteria?* • *Who will define mTICI, brain hemorrhage and infarct volume? Will he/they be blinded to the patient group? Is it done by what you called the "outcomes assessor"?* • *What is your definition of brain hemorrhage and infarct volume as a secondary outcome since it could depend whether the patient is evaluated with an MRI or a CT and as it could depend on the timepoint you take?* • The primary endpoint is the neurological disability at 90-day after EVT measured by mRS ~~and~~ . A favorable neurological outcome is ~~identified~~ defined as mRS≤2. • 1. Change in NIHSS ~~before,~~ from baseline to 24 h, 7 days (or at discharge), 30 days and 3 months after randomization. • 5. The length of stay in the hospital ~~or~~ and in intensive care unit after randomization • 6. The rate of ~~converting~~ conversion from LA/CS to GA. • *I am surprised that you don't monitor timing of each step of the procedure (stroke symptom to angiosuite door, door to puncture, puncture to reperfusion…) since it was a part of your hypothesis of a possible outcome difference between LA/CS and GA. Could you explain?* • *Is there an intermediate safety analysis?* **Statistical analysis plan:** • However, other factors including pre-operative NIHSS score, pre-operative intravenous thrombolysis treatment et al. confound the results: *what do you mean by "et al." in this sentence?* • *It is not clear for me how you will assess crossover patients (LA/CS to GA) without a per-protocol analysis. Could you explain?* • *Will you only explore statistically the mRS as a crude value (mean +/- SD) or also as a dichotomization of what you called "favorable neurological outcome as mRS≤2." And unfavorable outcome (i.e. mRS>2)* **Reporting of adverse events:** • will be recorded and closely monitored until resolution or stabilization or until it has been shown that ~~potential conflicts of interest regarding the~~ study treatment ~~are~~ is not the cause of the event • Once adverse events occur, it should be immediately reported to the research department and informed to the

	principal investigator to determine the severity of the adverse events ~~and their consequence of the injury~~. • *Is the principal investigator that report the adverse event blinded to the study treatment? Is the DMC capable of stopping the study in case of security problem?* **Discussion:** • Anesthetic selection and peri-procedural management ~~appear to be closely~~ could be associated with outcomes in patients with posterior circulation AIS undergoing EVT. • The hemodynamics disturbance and the changes in ~~ETCO2~~ carbon dioxide tension may be associated with the ~~poor~~ outcome. • the anesthetic protocols ~~varies~~ vary among different stroke centers. • especially for posterior circulation AIS patients, largely ~~base~~ rely on local protocols and individual preference of neuro-radiologists or anesthesiologists. • A small number of retrospective studies (~~concluding~~ including patients with posterior circulation AIS) • In contrary, GA groups could suffer from worse neurological function, lower blood pressure, • A recent retrospective, matched, case-control study of patients with posterior circulation AIS is the only study to ~~detect~~ explore the effect of anesthesia management on outcome of patients with posterior AIS, • ~~As to above,~~ Several confounding factors contribute to inconclusive results, including specific information of peri-interventional management, such as blood pressure, partial pressure of carbon dioxide, and strict uniform anesthesia protocol, ~~etc~~ • This trial aims to ~~find~~ explore the effect of anesthesia choice on the post-endovascular procedure outcomes in patients with posterior circulation AIS using a randomized controlled trial design. • The findings of the study would contribute to ~~being~~ serve as a reference for a future multi-~~centric~~ centre trial to verify the effects of anesthesia on patients with posterior circulation AIS undergoing EVT. • The burden of intervention will not be taken by participants themselves: *I don't understand this sentence, please explain.* **Table 2:** • *You forgot « cardiovascular fluctuation » that you should define* • Recognized complications from endovascular therapy, such as vessel ~~puncture~~ perforation leading to intracerebral hemorrhage or subarachnoid hemorrhage.

VERSION 1 – AUTHOR RESPONSE

Reviewer: 1

1. In the introduction section, the authors report from the literature a mortality rate of posterior circulation acute ischemic strokes of 80 to 95%. I guess that the authors report the spontaneous mortality rate (i.e.: without IV thrombolysis and/or MT). This should be specified.

Reply: Thank you for your kind reminder. The rate of death and dependency for posterior circulation AIS with intra-arterial or intravenous thrombolysis treatment is reported to be 80 to 95%. To avoid misunderstanding, we have adjusted the words to avoid misunderstanding. Please see page 5 line 8-9.

2. P7L48: please correct for “these studies”.

Reply：Thank you for your kind reminding. We have changed the words in the paper. Please see page 6 line 38.

3. P9L32: please correct: “neither be involved”

Reply：Thank you for your kind reminding. We have changed the words in the paper. Please see page 8 line 24.

4. The authors should explain why they chose a cut-off of 2 to distinguish good from poor clinical outcome on the mRS. In numerous studies focused on basilar artery occlusion treated by MT, the cut-off is 3, a mRS > 3 being defined as a poor clinical outcome.

Reply：Thank you for your advice. Modified Rankin Scale is a 6-point disability scale ranging from 0 to 5. We want to detect the incidence of favorable clinical outcome （no symptoms and no significant disability）in two group, therefore, mRS ≤ 2 is selected as cut-off value. This relatively strict cut-off value in mRS in CANVAS II is in accordance with previous AIS study as well as our CANVAS I study. We explained the cut-off value in the manuscript. Please see page 11 line 28-30 .

5. The calculation of the sample size is based on a difference of 30% in terms of good clinical outcome. Isn’t it too ambitious?

Reply: Thank you for your question. Our study is an exploratory, single-center, controlled and randomized trial. Only two studies indicated the possible sample size calculation evidence of pure vertebrobasilar stroke patients receiving endovascular treatment (reference 19, reference 27). Though patients presented similar mRS score at 90 days in monitored anesthesia care and general anesthesia group in the matched, case-control study of vertebrobasilar occlusion strokes (reference 19), due to the flaw from inappropriate case-control design, the conclusion of the similar mRS score at 90 days is invalid. We choose the result of the retrospective study (reference 27) of our institution as the basis of sample size calculation, which reported a 33.1% differenced of favorable clinical outcome in monitored anesthesia care and general anesthesia group. Therefore, we accept the difference of 30% as the base for sample size calculation.

6. How will be conducted the data analysis? In “Intention to treat” analysis? In “Per protocol” analysis? In “As treated” analysis? Please specify.

Reply: We appreciate the thorough review. We will perform intention-to-treat analysis for the primary outcome. Moreover, due to the conversion between two groups, we will perform per-protocol analysis further. However, the conclusion will be drawn from the intention-to-treat analysis. Please see page 12 line 21-29.

Reviewer: 2

1. There is no mentioning the secondary outcomes on hemodynamic parameters: Systolic blood pressure and MAP could have a role in the final outcome of this cohort of patients.

Reply: Thank you for your question. Intraoperative hemodynamic changes are important factors for clinical outcome of patients. However, hemodynamic parameters are also closely related with the anesthesia method. Therefore, in order to observe the impact of anesthesia method on the clinical outcome, we should control the confounding effect of hemodynamics. In the study, systolic blood pressure, diastolic blood pressure and mean arterial pressure are all maintained according to the SNACC guideline (140-180 mmHg in SBP and >105 mmHg in DBP) in both groups. Therefore, we will record and analyze intraoperative hemodynamic parameters as the confounding, but not as a secondary outcome.

2. How will the penumbra zone be evaluated? The authors need to be more detailed in this section P7L53-56.

Reply: We appreciate your thorough review. Patients will be evaluated by experienced neuro-interventionist as well as neurologists for infarction included penumbra. Post-circulation Alberta Stroke Program Early CT Score (pc-ASPECTS) and pons-midbrain index are used to evaluate the degree of the occlusion and collaterals. Please see page 7 line 56-58.

3. Which sedation score are they going to use? RASS? if so, which level of sedation will be targeted? P9L10

Reply：Thank you for your question. No sedation score will be used in this trial. We apply the bispectral index (BIS) to measure the sedation depth both in conscious sedated group and general anesthesia group. BIS is widely used in anesthesia to assess the sedation depth and calculated from the electroencephalogram through algorithm.

4. Why are the authors using TIVA protocols for sedation by non-anesthesiologists and why using propofol associated to remifentanil? the association can clearly cause respiratory events during the intraoperative period? why not using TCI protocols and using one drug only? BIS is very difficult to be used during mechanical thrombectomy as the sensor is not allowing a proper visualisation of the cerebral vessels

Reply：Thank you for your questions. Maybe we do not make clear, it is anesthesiologist to perform the sedation both in CS patients and GA patients, which is very important to control the comparability between groups. We only apply the *Practice Guidelines for Sedation and Analgesia by Non-anesthesiologists* to guide our anesthesiologist to perform sedation in CS patients. For the question of sedation regime, we tried the TCI protocols of propofol in pilot study and it was difficult to provide sufficient sedation as well as light analgesia in the population. Moreover, there is evidence that the pharmacokinetic set developed in a European population for the TCI of propofol does not apply in Chinese patients, especially for the emergent, critically ill patients. Meanwhile, low dose remifentanil could afford analgesia without respiratory depression with intensive monitoring. Therefore, remifentanil and propofol are selected for CS patients. For the question of BIS monitoring, only the transducer connecting of BIS sensor strip will be visualized on DSA. To provide best DSA image for neuro-interventionist, we routinely fix the transducer in the direction of parietal midline, where no intracranial vessels are crossing over, on skull anterior-posterior or lateral plane. Please see attached picture in Question 7 of how we deal with the BIS lines.

5. Who is taking care for the PS? an anesthesiologist?

Reply：Thank you for your question. Our ischemia-stroke squad of anesthesiologist are 7-days-24-hours standby for the ischemic stroke patients and the anesthesiologist in the squad will take care of patients recruited in the trial. To specify this question, we add this information in the paper, please see page 9 line 29.

6. The term LA is referred to the local anesthesia done by the interventional radiologist prior to arterial puncture?

Reply：Thank you for your question. The term LA is referred to local anesthesia. Actually, both the conscious sedative patients and the general anesthesia patients will receive local anesthesia at puncture site, with 3-5 ml of 1% lidocaine hydrochloride prior to arterial puncture. Anesthesiologist will perform conscious sedation and general anesthesia for patients according to their allocation. To avoid misunderstanding, we change the local anesthesia/conscious sedation (LA/CS) group into conscious sedation (CS) group. Please see page 8 line 38-42.

7. Even in the GA group, the BIS sensor seems to be difficult to be kept during the procedure

Reply: We appreciate the thorough review. In both GA and LA/CS group, BIS sensor strip will be placed on forehead fixed by 3M transparent film (3M Tegaderm 1624W Transparent Film Dressing). The transducer will be fixed by tape in parietal midline direction to insure image quality. To insure safety of operation, all lines (ECG, BIS, SpO_2, iv) and corrugated tube are place in fix route to insure C-arm's moving. Please see the attached picture of how we deal with the lines and patients' head immobilization in CS patients. BIS sensor in GA group are dealt in same way.

8. Will the data be collected manually by the researchers or through an EMR system?

Reply：Thank you for your question. Physiologic parameters during procedure will be manually recorded using purposely designed data collection table (case report form). Meanwhile, the electronic medical records system will record all parameters simultaneously. Please see page 9 line 2.

9. P10L26 will phenylephrine be started since the beginning of the procedure to keep targeted SBP?

Reply：Thank you for your question. Vasopressor support will only be initiated when blood pressure is not between the target ranges. page 9 line 19.

10. Norepinephrine cannot be administered through a peripheral vein catheter.

Reply：Thank you for your advice. There are insufficient data to recommend a specific vasopressor to support blood pressure. Vasopressor choice should be based on individual patient characteristics. We only control the target value of hemodynamics but the vasopressor choice is individualized according to the condition of patients. We've changed the words about vasopressor support, please see page 9 line 19.

11. There is no mention on the intraoperative complications as apnea, hypotension, hypertension, vomiting

Reply：Thank you for your kind reminding. Intraoperative complications, including vessel perforation, intracranial hemorrhage, subarachnoid hemorrhage, seizure, deep coma, respiratory failure, refractory hypotension, refractory cardiac arrhythmia and severe disturbance of the treatment procedure (vomiting, substantial movement and uncoordinated dysphoria) will be recorded. Adverse events will be analyzed as secondary endpoints. Please see page 10 line 21-36.

12. Is a CTA 24hrs post-stroke a routine practice? if not, the authors have to declare that this is standard practice in their Institution only

Reply：Thank you for your kind reminding. According to *Guidelines for the Early Management of Patients With Acute Ischemic Stroke: 2019 Update to the 2018 Guidelines for the Early Management of Acute Ischemic Stroke* and *Multisociety Consensus Quality Improvement Revised Consensus Statement for Endovascular Therapy of Acute Ischemic Stroke*, although there is no evidence that postprocedural imaging improves clinical outcomes, there is consensus based on European and American guidelines that postprocedural imaging is required. CT or MR imaging within 36 hours after intervention should be performed in all stroke patients. Therefore, in our institution, we routinely do CTA scan 24 hours after treatment.

Reviewer 3

1. It is difficult to state that laryngeal mask provides secured airway and avoids aspiration since trachea could be contaminated by secretions and vomiting. Please explain.

Reply：Thank you for your question. In recent study, laryngeal mask presented similar incidence of reparatory complications compared to endotracheal tube. Furthermore, we select LMA Supreme (Teleflex, USA) for aspiration drainage. Before insertion, mouth suction would be performed. And if the patients with full stomach when entering the treating room, endotracheal intubation will be the choice.

2. Body immobility to avoid intracranial vessel perforation: It concerns intracranial AND also any extracranial vessel perforation.

Reply：Thank you for your advice. We have changed the words in the paper. Please see page 5 line 36.

3. Therefore, result of above trials is not suitable for posterior circulation AIS, concerning the relationship between neurological outcome and anesthesia modality. This sentence is not necessary to understand the hypothesis of the proposed trial.

Reply：Thank you for your advice. We delete this sentence in the manuscript. Please see page 7 line 29.

4. Although these studies included a relatively large proportion of posterior circulation interventions and showed promising results, it is unreasonable to employ previous results in emergent setting, with potential presence of severe brain stem ischemia. Moreover, only one study focused purely on the posterior circulation patients and investigated the influence of anesthesia modality and management on clinical and angiographic outcomes. I don't understand these 2 sentences? Did you mean that for the moment these studies could not be incorporated in clinical practice related to bias? What is the relationship with brain ischemia?

Reply：Thank you for your thorough review. Study of Jadhav AP (reference 21) and Taqi M (reference 22) indicated a promising clinical outcome in ischemic patients underwent endovascular treatment with monitored anesthesia care. However, due to the difference in population (reference 21) and the design (reference 22), it is inappropriate to utilize the result of these studies in posterior circulation ischemia which often leading brain stem ischemia. We adjust the sentence for better understanding. Please see page 6 line 40-44.

5. Posterior circulation ischemia confirmed by CTA/MRA: please provide definition of CTA/MRA abbreviations and radiological indication for EVT in posterior circulation AIS in your institution: mismatch, collateral status.

Reply：Thank you for your kind reminding. We've provided the abbreviations of CTA/MRA in the manuscript. Neuroradiology indication for EVT treatment in posterior circulation ischemia is CTA/MRA confirmed basilar or vertebral artery occlusion with mTIMI ≤ 1. Patients with pc-ASPECT<6 or pons -

midbrain index ≥3 will be excluded from endovascular treatment. We update this information in the manuscript. Please see page 7 line 56 57

6. Could you explain how written consent is obtained from the patient or relative: which patient are deemed able to consent in this situation of acute stroke? What if relatives are not immediately present in order to avoid delay in this emergent procedure?

Reply：Thank you for your question. Written informed consent is obtained from patients' legal representatives. If relatives are not immediately present or refuse to participate in this trial, this patient will be excluded from the trial but the medical treatment will be initiated as soon as possible. We've revised the above mentioned information at page 8 line 21.

7. Who are the outcome assessors? How many are they? Are they specifically trained and certified for outcomes reporting notably administration of the mRS?

Reply：Thank you for your questions. Two trained researchers will be responsible for outcome assessment. They were trained in our Department of Neurology as well as WedDCU Clinical Trial Data Management Training and certified for mRS scale and NIHSS scale assessment.

8. Reference 22 is not the reference for Practice Guidelines for Sedation and Analgesia by Non-Anesthesiologists by the American Society of Anesthesiology (American Society of Anesthesiologists Task force on S, analgesia by N-A. practice guidelines for sedation and analgesia by non-anesthesiologists.; Anesthesiology 2002;96:1004–17.)

Reply：Thank you for your kind reminding. We've revised the reference. Please see page 9 line 40.

9. In your LA/CS protocol, could you be more stringent about your definition of "still following instruction to verbal stimulation" because it is a key parameter to avoid over-sedation but could be difficult to obtain in stroke patient with potential aphasia and sensory/motor palsy. Also, who will monitor this clinical state in the difficult environment of the radiology suite with radiation burden. Is a clinical scale used to monitor this aspect?

Reply：Thank you for your suggestion. First of all, to avoid misunderstanding, we change the local anesthesia/conscious sedation (LA/CS) into conscious sedation (CS). In CS group, sedation level will be managed according to BIS monitoring. Target sedation level of CS is BIS of 70. We delete the sentence about verbal stimulation to avoid misunderstanding. Pleases see page 9 line 52. For clinical practice in radiology suite, no matter in CS group or GA group, patients will be monitored by the anesthesiologist from the squad. We closely monitor patients during procedure in several ways. Firstly, we do visual observation from a huge radiation-shielding window in control room. Through the window, we can observe patients' status and operating status of the anesthesia machine. Secondly, we perform a split-screen display of vital sign. Thirdly, we've installed two closed-circuit television cameras in each operation suite to monitor procedure progress and overall situation of the room. Moreover, we've installed microphone for communication between operation suite and control room. Above mentioned measurements ensure the feasibility and safety of clinical work in radiological suit. Please see detailed setting of our radiological suite in below picture.

10. You mention reference 23 for your LA/CS protocol: do you use cervical collar as mentioned in this publication to avoid head movement in this group? Also, only Remifentanil without Propofol was used in this study. Do you think this is the good reference? Also, your protocol is different from the one used in GOLIATH study that you mentioned in reference 13.

Reply: Thank you for your question. We do not use the cervical collar，but we understand the importance of head immobilization. To keep head immobilized at neutral position, we place 1-inch cloth medical tape on forehead (avoiding BIS sensor) and attach the tape to bed. We agree with you that the

references cited here is inappropriate. Our sedation regime is different from either of the references we cited, therefore we've deleted the references there.

11. It is a LA/CS group and sedation is not mandatory but you never talked about Local Anesthesia: is it ever done? how is it done? Which drug? Is there also LA in GA group?

Reply: Thank you for your question. Actually, local anesthesia as the standard step in endovascular treatment, will be carried out in both groups by neuro-interventionist with 1% lidocaine 3-5 ml at puncture site. To avoid unnecessary misunderstanding, we've changed LA/CS group in to CS group. We add the information at page 8 line 40.

12. In GA group, patients will receive rapid sequence induction with endotracheal intubation or laryngeal mask implementation insertion with Propofol: as mentioned before, the use of laryngeal mask in this group is questionable especially when your hypothesis rely about possible aspiration effect on outcome. This aspect should be discussed in the discussion part of your protocol as it could be criticized by some clinicians.

Reply：Thank you for your question. In a recent retrospective study, patients with laryngeal mask and with endotracheal intubation under general anesthesia presented similar incidence of respiratory complications (11.5% vs 6.3%, p=0.385) in endovascular therapy (*Kılıç Y, Baş SŞ, Aykaç Ö, Özdemir AÖ. Nonoperating Room Anesthesia for Interventional Neuroangiographic Procedures: Outcomes of 105 Patients. J Stroke Cerebrovasc Dis. 2020;29(2):104495. doi:10.1016/j.jstrokecerebrovasdis.2019.104495*). Furthermore, average procedure duration for EVT treatment for posterior circulation ischemia was approximately 1.5h (reference 21) and 2 hours in our institution. In this study, to further mitigate risk of aspiration, we choose LMA Supreme (Teleflex, USA) for aspiration drainage. Though as a supraglottic airway device, LMA Supreme is considered appropriate for airway management. In addition, whether choosing endotracheal intubation or LMA insertion is based on patient's respiratory condition.

13. In cases of procedural emergency including vessel perforation, intracranial subarachnoid hemorrhage (SAH), seizures, deep coma (GCS decrease to less than 8 (as mentioned in your table 2)), respiratory failure (PaCO2 or EtCO2 ≥ 60 mmHg (as mentioned in your table 2), or SpO2<94% without relevant improvement by increasing inhaled oxygen fraction), cardiovascular fluctuation: could you define cardiovascular fluctuation which is surprisingly not mentioned in table 2? Also, a GCS<8 could not be associated with coma or unconsciousness especially in this type of stroke since patient could be paralyzed with persistent vigilance ("locked in state"). So, the term of coma and unconscious in table 2 could be criticized. The isolated visual component of the GCS ("eyes E") < 3 or 4 could have be a better and easier threshold. Please discuss this aspect in the discussion part.

Reply：Thank you for your suggestions. Cardiovascular fluctuation in our study includes refractory hypotension or hypertension, refractory cardiac arrhythmia caused by vomiting, perforation of vessels, intracranial hemorrhage, subarachnoid hemorrhage, seizure, deep coma, respiratory failure et al. The cardiovascular fluctuation is merely the sign of above-mentioned events, but not the the reason for conversion itself. Therefore, we delete the cardiovascular fluctuation in the text and table 2 to clarify reasons for converting. We use GCS score decreasing to or less than 8 as one of reasons for converting. In previous study, GCS ≤8 is used as indication of intubation in trauma patients (*Gentleman D, Dearden M, Midgley S, Maclean D. Guidelines for resuscitation and transfer of patients with serious head injury. BMJ. 1993 Aug 28;307(6903):547-52. doi: 10.1136/bmj.307.6903.547; American College of Surgeons Committee on Trauma. Advanced Trauma Life Support Program for doctors. 8th ed. Chicago, IL: American College of Surgeons;2008.*.). In emergency department, researchers found decreased GCS score does not mandate endotracheal intubation(*Duncan R, Thakore S Decreased Glasgow Coma Scale Score Does Not Mandate Endotracheal Intubation in the Emergency Department, J Emerg Med. 2009 Nov;37(4):451-5. doi: 10.1016/j.jemermed*). However, GCS score contains valuable

prediction information, regardless of whether dysphasia is present (*Weir CJ, Bradford AP, Lees KR. The prognostic value of the components of the Glasgow Coma Scale following acute stroke. QJM. 2003;96(1):67–74. doi:10.1093/qjmed/hcg008*). Therefore, we use GCS score ≤8 as one of conditions for conversion, but not only the eye component. We adjust the reasons for conversion in table 2 and in the text.

14. I think it could be more didactic to put “Standard anesthesia management protocols during EVT (Concomitant treatment)” part before “interventions” part of your manuscript

Reply：Thank you for your suggestion. We’ve adapted the description sequence. Please see page 8-9.

15. Including electrocardiography (EEG ECG)

Reply：Thank you for your kind reminding. We’ve corrected the misspelling. Please see page 8 line 59.

16. How is invasive arterial pressure obtained: on the radiologist arterial access line or a dedicated catheter? Could you specify?

Reply：Thank you for your question. We monitor invasive arterial pressure on the radiologist arterial access line in all patients. We add this information on page 9 line 5-6.

17. You mention that you monitor PaCO2 and EtCO2 in every patient: for PaCO2, is it a continuous monitoring? Otherwise, are there systematic blood gas analysis? You mentioned EtCO2>60mmHg as a trigger to convert to GA in table 2, what about PaCO2 if you also monitor it? Also, EtCO2 and PaCO2 could be very different especially in spontaneous breathing. It is not clear.

Reply: Thank you for your question. We intermittently do blood gas analysis for $PaCO_2$ but we continuously monitor $EtCO_2$. The decision of converting is based on $EtCO_2$, but $PaCO_2$ of each patient will also be tested and recorded. $PaCO_2$ of spontaneous breathing patients will be obtained from the blood gas analysis. We place anesthetic gas sampling line at nasal vestibule to monitor $EtCO_2$ in spontaneous breathing patients. Please see page 9 line 50.

18. How could you monitor FiO2 in spontaneous breathing patients? You mentioned that LA/CS patients will have 3L/min O2 but it appears not possible to monitor FiO2 in this setting because it relies on ventilatory flow which is unknown without specific monitoring.

Reply: Thank you for your question. In spontaneous breathing patients, we will record FiO_2. Anesthetic mask will be placed to cover patients’ mouth and nose with elastic bandage to ensure a complete seal. The delivered oxygen concentration is the same as in the gas mixture supplied to the mask. Patient in CS group will receive 3L/min air/oxygen mixture, with a 40%-60% fraction of inspired oxygen.

19. Is blood glucose continuously monitored? Otherwise, what is the timing and frequency of blood glucose assessment? Is it intravenous, arterial or capillary measurement? Is there a protocol for blood glucose management?

Reply: We appreciate the thorough review. Serum glucose monitor is performed according to recommendation of SNACC statement (reference 25) and *Guidelines for the Early Management of Patients with Acute Ischemic Stroke: 2019 Update to the 2018 Guidelines for the Early Management of Acute Ischemic Stroke*, which recommend glucose test once every hour during endovascular treatment. According to the SNACC statement, there is no preferable method of glucose sampling. We sample arterial blood from arterial access line and test glucose with blood gas analyzer. The target of serum glucose is controlled between 140-180mg/ml.

20. I imagine that EtCO2 objective of 35-45mmHg is only in GA group?

Reply: Thank you for your question. EtCO2 will be maintained between 35 and 45 mmHg in both groups. However, for CS patients, if EtCO2 increased to 60 mmHg, they will be converted into GA group.

21. What is the frequency of BP measurement? How will blood pressure data be monitored?

Reply: Thank you for your question. We use a purposely designed data collection table to collect hemodynamic parameters data every 10 minutes. Meanwhile, BP is measured and recorded ever 5 min in electronic medical recording system.

22. Could you provide in the supplementary files a glossary with every data monitored and the frequency of monitoring?

Reply：Thank you for your kind reminding. Please check the glossary in supplementary file.

23. Concerning complications, could you describe how they will be searched? Are there specific procedures to diagnose these complications? Are they just notified by the study team with the medical documents of the patient? Is there an adjudication committee to define these complications based on a priori diagnostic criteria?

Reply: We appreciate the thorough review. Intraoperative complications will be assessed by neuro-interventionist, anesthesiologist and cardiologist, if necessary. Postoperative complication will be recorded by attending neurological intensive care staff. The Data Monitoring Committee will regularly audit trial procedure and define the diagnostic criteria. The diagnosis procedure for complications are as our routine medical service provided by the research team and the complication will be recorded.

24. Who will define mTICI, brain hemorrhage and infarct volume? Will he/they be blinded to the patient group? Is it done by what you called the “outcomes assessor”?

Reply: Thank you for your question. The neuro-interventionist who performs the procedure will do the pre-operative and intraoperative neurological evaluation, including the secondary outcome of mTICI. Postoperative evaluation will be performed by attending doctors in neurological intensive care unit. Above mentioned responsible neuro-interventionist, the neurological intensive care staff as well as the anesthesiologist will not be blinded to the allocation. Primary outcome (90-day mRS after EVT) will be done by a blinded outcome assessor, who is neither involved in allocation nor intervention.

25. What is your definition of brain hemorrhage and infarct volume as a secondary outcome since it could depend whether the patient is evaluated with an MRI or a CT and as it could depend on the timepoint you take?

Reply: We appreciate the thorough review. Patients in our institution will routinely undergo CT/MRI 24 hours after EVT to provide additional information. Besides this routine image scan, patients with severe symptoms including refractory headache, epileptic seizures, hemiplegia and deteriorating status of consciousness will receive more than one radiological test. Cerebral hemorrhage or infarction would be evaluated based on the 24 hours radiology scan and following scan if performed. Postoperative complication will be recorded according to its timepoint till 90 days after treatment.

26. I am surprised that you don’t monitor the timing of each step of the procedure (stroke symptom to angiosuite door, door to puncture, puncture to reperfusion…) since it was a part of your hypothesis of a possible outcome difference between LA/CS and GA. Could you explain?

Reply: Thank you for your reminding. The work flow of our research will be recorded and we will compare the time of each step as the secondary outcome. We add the the information on page 11 line 56-57..

27. Is there an intermediate safety analysis?

Reply: Thank you for your question. We don't have intermediate analysis as this is an exploratory and the small-size trial. But our Data Monitoring Committee will do regular audit to ensure the process of the research and safety of patients.

28. However, other factors including pre-operative NIHSS score, pre-operative intravenous thrombolysis treatment et al. confound the results: what do you mean by "et al." in this sentence?

et al.

Reply: Thank you for your question. We delete "et al "in manuscript. Please see 13 line 20.

29. It is not clear for me how you will assess crossover patients (LA/CS to GA) without a per-protocol analysis. Could you explain?

Reply: Thank you for your question. We will perform intention-to-treat as well as per-protocol analysis. Please see page 12 line 22-28.

30. Will you only explore statistically the mRS as a crude value (mean +/- SD) or also as a dichotomization of what you called "favorable neurological outcome as mRS≤2." And unfavorable outcome (i.e. mRS>2)

Reply: Thank you for your question. We will analyze the mRS as categorical data with Cochran-Mantel-Haenszel test in primary outcome analysis. However, mRS score will also be analyzed as continuous data to describe patients' characteristics.

31. Is the principal investigator that report the adverse event blinded to the study treatment? Is the DMC capable of stopping the study in case of security problem?

Reply: Thank you for your question. If adverse events occurred, the principal investigator will be notified of patient's allocation. However, the outcome assessor is still blinded to patient's allocation. The DMC are responsible for terminating the research in case of severe adverse events. Please see page 12 line 10-12.

32. The burden of intervention will not be taken by participants themselves: I don't understand this sentence, please explain.

Reply: Thank you for your question. We've delete this sentence on page 15 line 53.

33. You forgot « cardiovascular fluctuation » that you should define

Reply: Thank you for your advice. We delete cardiovascular fluctuation because it is a sign caused by other intraoperative complications.

VERSION 2 – REVIEW

REVIEWER	Clarençon F Pitié-Salpêtrière Hospital. Paris. FRANCE
REVIEW RETURNED	13-Apr-2020

GENERAL COMMENTS	The authors have correctly addressed the comments raised by the Reviewers, in my opinion.

REVIEWER	Chabanne, Russell Centre Hospitalier Universitaire Clermont-Ferrand FRANCE
REVIEW RETURNED	07-Apr-2020

GENERAL COMMENTS	Thank you for your corrections and precisions. Just a few things: • Did you want to mention the "modified Thrombolysis in Cerebral Infarction scale (mTICI)" instead of "modified Thrombolysis in Myocardial Infarction scale (mTIMI)" page 7 line 47? (as you mentioned in Secondary endpoints number 2 “mTICI evaluated before…” page 11 line 45) • Please put in bold font “Standard anesthesia management protocols during EVT (Concomitant treatment)” and follow with a line break, page 8 line 57 Thank you.

VERSION 2 – AUTHOR RESPONSE

Review 2

1. Please revise the Strengths and Limitations section of your manuscript (after the Abstract). This section should contain five short bullet points, no longer than one sentence each, that relate specifically to the methods. the potential impact of the findings should not be discussed here.

Reply: Thank you for your kind reminder. We revised our Strengths and Limitations section of your manuscript and please see page 4 line 13-14.

2. We note that you have included the consent form as a confidential file for editors only. If possible, please can you change this to a standard supplementary file and cite it within the text.

Reply: Thank you for your advice. We have uploaded the consent form as a standard supplementary file. Please check the supplemental file 3.

Reviewer: 3

1. Please state any competing interests or state ‘None declared’:

"none declared"

Reply: Thank you for your kind reminder. We have stated in the manuscript. Please see page 15 line 60.

2. Did you want to mention the "modified Thrombolysis in Cerebral Infarction scale (mTICI)" instead of "modified Thrombolysis in Myocardial Infarction scale (mTIMI)" page 7 line 47? (as you mentioned in Secondary endpoints number 2 “mTICI evaluated before…” page 11 line 45)

Reply: Thank you for your kind reminding. We’ve corrected the mistake on page 7 line 47.

3. Please put in bold font “Standard anesthesia management protocols during EVT (Concomitant treatment)” and follow with a line break, page 8 line 57

Reply: Thank you for your kind reminding. We have put the tile into bold font. Please see page 8 line 57

Reviewer: 1

1. Please state any competing interests or state ‘None declared’

Reply: Thank you for your kind reminder. We have stated in the manuscript. Please see page 15 line 60.