PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	GASS Trial study protocol: a multicentre, single-blind, randomised clinical trial comparing general anaesthesia and sedation during intra-arterial treatment for stroke.
AUTHORS	Maurice, Axelle; Ferré, Jean-Christophe; Ronzière, Thomas; Devys, Jean-Michel; Subileau, Aurelie; Laffon, Marc; Laviolle, Bruno; beloeil, helene

VERSION 1 - REVIEW

REVIEWER	Judith Dinsmore St George's Hospital, London UK
REVIEW RETURNED	10-Jun-2018

GENERAL COMMENTS	The authors present the GASS Trial study protocol: a multicentre, single blind, randomised clinical trial comparing general anaesthesia and sedation during intra-arterial treatment for stroke. This is an important and clinically relevant topic. The efficacy of endovascular treatment in patients with anterior circulation stroke due to large artery occlusion is firmly established. Previous studies have suggested that endovascular treatment under general anaesthesia (GA) is associated with a worse outcome. However, as patients with more severe stroke and comorbidities are more likely to receive GA there is potential for confounding by indication. As such there is a need for large scale prospective randomised controlled trials. The protocol is generally well written however I have a few comments: Introduction: On page 5, line 96 the authors state that no study has assessed the clinical outcome 3 months after the stroke treatment comparing GA and conscious sedation (CS) using standardised anaesthetic protocols and tight haemodynamic control. Although smaller studies and monocentric, both the AnStroke and Goliath trial used standardised protocols and tight haemodynamic control. Both also assessed outcome at 90 days, using the mRS, as a primary outcome in the AnStroke trial and secondary outcome in the Goliath trial. In addition, The CANVAS trial is currently ongoing in China. This is a prospective randomised equivalence trial investigating the effects of GA versus CS on outcome using mRS at 90 days. This is aiming to recruit 635 patients. There is no mention of this.

	Methods: In terms of inclusion criteria, the authors do not define the level or site of vessel occlusion beyond stating large vessel occlusion in the anterior circulation. Nor do they specify the time since stroke onset or functional status prior to the stroke onset. These factors will all influence outcome and are important confounders. In terms of interventions, the general anaesthesia group have a standardised protocol with TCI propofol and remifentanil, presumably titrated to effect by the anaesthetist. The maximum target of propofol seems quite high for such an unstimulating procedure? Would it not be helpful to titrate using depth of anaesthesia monitoring to standardise depth of anaesthesia? Although haemodynamic control targets are set, there do not appear to be any targets for control of carbon dioxide or blood glucose or other important physiological targets. These should be standardised and recorded. For sample size estimation, the authors have picked on only one study and used this. There are many other studies using mRS at 90 days that could have been selected – why use only one and why this one study?

REVIEWER	Alexandros Rentzos Sahlgrenska University Hopsital Neuroradiology/Neurointervention Gothenburg Sweden
REVIEW RETURNED	21-Jun-2018

GENERAL COMMENTS	The GASS study will include 350 patients undergoing endovascular treatment (EVT) for acute ischemic stroke (AIS) who will be randomized to general anesthesia (GA) or conscious sedation (CS). The primary outcome is the modified Rankin Scale (mRS) at 3 months and the study has already started (september 2016). ABSTRACT Strenghts and limitations of this study: The authors state that a systemic CT scan after EVT is not included. A CT scan 22-36 hr after EVT is the standard of practice in all stroke centers in patients after iv thrombolysis and/or mechanical embolectomi. A CT scan must be done to evaluate the presence of hemmorhage and the size of infarct as these factors can influence clinical decisions as: anticoagulation/antiplatelet medication, need for craniectomy, ICU stay and so on. This is a major limitation and a CT follow up 22-36 hr after EVT should be mandatory. Is any radiological examination performed after EVT? Moreover, the authors claim that the sizing of the stroke is not part of the study as it is newly implemented technology. By sizing of stroke they should probably mean the size of the infarct. If this is right then it is unclear why sizing of the infarct is a newly implemented technology. Sizing can easily be done in any CT scan after EVT (far better in MRI but CT could suffice) and it is available since CT scanners were introduced. Many studies use sizing of the infarct (in volume) or other scales as infarct in more or less than 1/3 MCA, ASPECTS score etc. The sizing of infarct is also an important secondary outcome but also an important variable to correlate and even adjust other outcomes (difference in

	initial infarct between groups, adjustement for final infarct-infarct growth, etc). Introduction: Sufficient description of the background but some clarifications and corrections are needed: Line 79: “In terms of hemodynamic instability, retrospective studies reported results in favour of CS (8-10)”. Between 2010, when the first restrospective study was published, and 2017, 17 restrospective studies have been published on the subject. Only four of these studies have data on blood pressure but none of the 3 studies (Berkhemer 2016, Abou-Chebl 2015, Bekelis 2017) the authors are refferring to as support for the claim of hemodynamic instability. Moreover, the four studies that indeed have data on blood pressure show that patients under GA experienced intra-procedural hypotension overwhelmingly. The references should be corrected and clarify instability, as patients with intraprocedural hypotension under GA can be hypotensive but stable after induction. Line 89: A correction is needed in the number of patients, the AnStroke trial included 90 patients. Line 96: It is not true that no study has assessed the clinical outcome 3 months after with a standardized anesthetic protocol and hemodynamic control. AnStroke trial had mRS at 3 months as primary outcome and, as the authors also stated earlier, included a standardized anesthetic protocol and hemodynamic control according to international guidelines. Methods and analysis Criteria: A description of the following is missing: -Contraindications to GA and to anesthetic drugs: It is good to state these contraindications. -Life-threatening comorbities: Which comorbities in a patient with AIS coming for EVT are considered life-threatening? Does the study have a pre-morbid mRS exclusion criteria or all patients, even mRS 4 and 5 can be included? -A major limitation is that all radiological indications/contraindications are missing. Baseline ASPECTS or infarct size? It should be the same between the groups to avoid bias when comparing the effect of GA and CS in the outcome. Occlusion site? Tandem occlusions, ICA, M1, M2, Carotid-T? Is there any perfusion imaging included? Missmatch and ratio then? What is the primary modality for detection of occlusion, CT or MRI? Which protocol? -An NIHSS limit for inclusion/exclusion is missing. Does all patients who present with large vessel occlusion will be included no matter the neurological deficit? This can also lead to bias. The only statement on NIHSS is that a separate analysis will be done for patients with < or > 14 points NIHSS which is a quite old discrimination between severe and moderate stroke but says nothing about which patients will be included. -The mRS at 3 months will be evaluated by research nurses. The most usual and most accepted practice in major randomized studies is that experienced vascular neurologists evaluate the outcome in a personal interview with the patient. Why research nurses? Are they certified? Personal interview? Is this a common practice in France?

	Interventions Line 170: Glascow coma scale<8 and/or deglutition disorders are given as situations where CS can be converted into GA. Both of these situations are exclusion criteria in this study, why would such patients be included in the study and then converted to GA? Clarification or correction is needed. Outcome measures Line 200: “Time between arrival of the patient...” Arrival where? At the hospital or att the angiosuite? Please clarify. The authors give as secondary outcomes time from stroke onset to last angiography and time from arrival of patient (where?) to groin puncture. They should explain why they choose these intervals and why they exclude all others. Especially time from stroke onset to last angiography can be influenced by a lot of factors (traffic, time of call, ambulance response, emergency department time, time in CT, transportation etc.) which might not be relevant when GA and CS are compared. The usual time points (stroke onset, arrival at emergency department, arrival CT-first CT image, groin puncture, recanalization) are important to secure that the groups are similar and should be stated. Moreover, there is time points that should be monitored especially when someone is comparing GA and CS, as arrival att angiosuite, start of GA induction, start of sedation, groin puncture (with these time points the length of anesthesia preparation and induction is measured) and procedural time of course. Are these time points included in the protocol? They are crucial factors in GA vs CS comparison. Line 202: The authors should consider change quality of recanalization to recanalization rate. They give as recanalization rate scale the modified treatment in cerebral ischemia but in parenthesis they write TICI. Which one will be used, mTICI or TICI? Please define. Line 207: Complications: Anesthesiological complications such as aspiration or delayed extubation for example are missing. Are such complications included in the protocol. Also very important to monitor in such a study. Line 213: Why is number of patients who receive norepineprine a secondary outcome? We know for sure that patients under GA will need it more often. Please explain. Statistical analysis Sample size estimation: One previous study with mRS≤2 30% after EVT under GA is given as the ground for the sample size estimation. Ther is also other studies and case series that give in the GA group a variable percentage of mRS≤2, from lower than 20% to more than 40%. Why did the authors choose especially this study for calculation of the sample size? Moreover, they want to show an increase in mRS≤2 up to 45% under CS. Why 45%? Where do the authors base that a 45% is sufficient? As pointed earlier, there is studies (comparing GA vs CS, retrospective, case series) that show mRS≤2 in GA patients more than 40%. If we use the assumption of the authors, meaning 30% mRS≤2 in GA and 45% in CS, then a 15% units difference is the ground for the sample estimation. The difference in mRS≤2 in the retrospective studies varied nontheless from 20% to approx 40% units (lower in GA). Why is 15% the difference that will decide if a method is better? A clarification is needed. Data Registration

	Baseline: Line 263: “time of cerebral angiography or MRI”: Is MRI the image of choice? CT? Cerebral angiography with DSA? Which time is considered here? Time of first image? Intraoperative data: Line 267: “TICI (16)”: See even comment above. Which TICI? Ischemia or Infarction? Modified or non? Please clarify as numerous scales exist. Interventional and anesthesiological complications are missing in data registration. Please define them. If not included it is a major limitation. Postoperative data: Line 275: Please clarify the necessity of noradrenalie during the first 2 hours after EVT. Why? In relation to what this necessity? To unsuccesfull recanalization? Postoperative radiological data are missing and are of paramount importance in such a study.

VERSION 1 – AUTHOR RESPONSE

Reviewer: 1
Introduction:
On page 5, line 96 the authors state that no study has assessed the clinical outcome 3 months after the stroke treatment comparing GA and conscious sedation (CS) using standardised anaesthetic protocols and tight haemodynamic control. Although smaller studies and monocentric, both the AnStroke and Goliath trial used standardised protocols and tight haemodynamic control. Both also assessed outcome at 90 days, using the mRS, as a primary outcome in the AnStroke trial and secondary outcome in the Goliath trial. In addition, The CANVAS trial is currently ongoing in China. This is a prospective randomised equivalence trial investigating the effects of GA versus CS on outcome using mRS at 90 days. This is aiming to recruit 635 patients. There is no mention of this.

=> As described in the table below, the AnStroke and the Goliath study did not assess the clinical outcome 3 months ((as the primary outcome) after the stroke treatment comparing GA and conscious sedation (CS) AND using standardised anaesthetic protocols (providing doses and maximum targets) AND tight haemodynamic control.

	GASS study	AnStroke study (12)	Goliath Study (13)	SIESTA study (11)
Anesthesia protocol	CS: TCI remifentanil (maximum target 2 ng/ml), local anaesthesia with lidocaine 10 mg/ml (maximum 10 ml) GA: Induction: Etomidate (0.25 – 0.4 mg/kg) and succinylcholine (1 mg/kg) and maintenance: TCI propofol (maximum target: 4 microg/ml), TCI remifentanil (0.5-4 ng/ml) and muscle relaxant as needed.	CS: remifentanil GA: Propofol, remifentanil, sevoflurane ⇨ Doses at not given neither in the methods nor in the results section ⇨ Considering the haemodynamic effects of the drugs administered, not showing the doses is a bias ⇨ Moreover, the doses in the CS could have been high and then be close to a GA: another source of bias	Cs: fentanyl + Propofol adjusted as required. GA: suxamathonium, Propofol, alfentanil +/- fentanyl, at the discretion of the neuroradiologist ⇨ Doses at not given neither in the methods nor in the results section ⇨ Considering the haemodynamic effects of the drugs administered, not showing the doses is a bias ⇨ Moreover, the doses in the CS could have been high and then be close to a GA: another source of bias	The anesthesia protocol is not given in detail. The reader (even when reading the e supplement) does not have access to the anesthesia protocol.
Haemodynamic control	SBP between 140 and 185 mmHg; DBP < 110 mmHg. A drop of more than 25% of the MBP will also be avoided. Norepinephrine will be administered in a dedicated intravenous line and diluted at 250 microg/ml.	Objectives: SBP between 140 and 180 mmHg, using dopamine, phenylephrine, norepinephrine, ephedrine ⇨ Control only based on SBP ⇨ Use of different drugs with different effects, which could imply an increase use of vasoactive drugs (i.e dopamine is less efficient than other drugs in increasing blood pressure) ⇨ No standardization of vaso actives drugs	Objectives: SBP > 140 mmHg and MAP < 70 mmHg, using ephedrine or phenylephrine ⇨ Use of different drugs with different effects, which could imply an increase use of vasoactive drugs to obtain the same expected result ⇨ No standardization of vaso actives drugs	Targets for SBP were set at 140 to 160 mmHg in both groups. Results showing no differences in MAP in the 2 groups. However, the anesthesia and the Haemodynamic control protocols are not available. Post hoc analysis (Stroke 2018): no association between the difference in systolic BP, diastolic BP, and mean arterial pressure from baseline to the different phases of intervention and NIHSS change after 24 hours
mRS at 3 months as a primary outcome	yes	yes	no	no
Multicentric	yes	no	no	no

Concerning the ongoing studies, we found 10 of them on Clinicaltrials.gov. We did not mention them because of the absence of published results.

We added the following sentence page 5, line 96, to further explain why the methodology of our study is more rigorous: “ Indeed, in previous studies (12,13), the anaesthesia protocol was either not standardized or the doses not given, the blood pressure was controlled with vasoactives drugs as different as dopamine and norepinephrine in the same study and the clinical outcome 3 months after the stroke was not the primary objective of one study (13).”

Methods:
In terms of inclusion criteria, the authors do not define the level or site of vessel occlusion beyond stating large vessel occlusion in the anterior circulation. Nor do they specify the time since stroke onset or functional status prior to the stroke onset. These factors will all influence outcome and are important confounders.

=>All these data (site of vessel occlusion, time since stroke onset) are collected and will be part of the final analysis. We did not choose to include the patients based on these elements because the aim of the protocol was to study the effect of two anaesthetic modalities in a general population with a stroke.

In terms of interventions, the general anaesthesia group have a standardised protocol with TCI propofol and remifentanil, presumably titrated to effect by the anaesthetist. The maximum target of propofol seems quite high for such an unstimulating procedure? Would it not be helpful to titrate using depth of anaesthesia monitoring to standardise depth of anaesthesia?

=> We agree that monitoring the depth of anaesthesia would be helpful. However, we did not design the protocol with a monitoring of depth of anaesthesia because all centres involved in the study do not have that type of monitoring accessible for anaesthesia in neuroradiology.

Although haemodynamic control targets are set, there do not appear to be any targets for control of carbon dioxide or blood glucose or other important physiological targets. These should be standardised and recorded.

=> We agree. As stated page 8, line 167, capnography is monitored and recorded and will be shown in the results section of the future manuscript. According to our institutional protocol, blood glucose is monitored in diabetic patients only for this type of short procedure. To our knowledge, there are no proof of a benefit of controlling blood glucose during an EVT procedure.

For sample size estimation, the authors have picked on only one study and used this. There are many other studies using mRS at 90 days that could have been selected – why use only one and why this one study?

=> We chose to calculate the sample size based on comparative studies. At the time the protocol was written, only one study was available. Other studies were published since 2016 (after the start of recruitment), and a meta-analysis taking into account the results of these studies was published in 2018 (Campbell et al. Lancet Neurol 2018; 17: 47–53). This meta-analysis showed a benefit of CS vs GA percentages of good functional outcome (mRs≤2) at 3 months of 40% (95% CI [34-46%]) with AG and 50% (95%CI [46-54%]) with CS. Our hypothesis for sample size calculation is close to the 95% CI of these observations.

Reviewer: 2

ABSTRACT
Strenghts and limitations of this study: The authors state that a systemic CT scan after EVT is not included. A CT scan 22-36 hr after EVT is the standard of practice in all stroke centers in patients after iv thrombolysis and/or mechanical embolectomi. A CT scan must be done to evaluate the presence of hemmorhage and the size of infarct as these factors can influence clinical decisions as: anticoagulation/antiplatelet medication, need for craniectomy, ICU stay and so on. This is a major limitation and a CT follow up 22-36 hr after EVT should be mandatory. Is any radiological examination performed after EVT?

⇨ A systematic immediate post-EVT Cone-beal CT scan is performed for all patients. However, we did not include a mandatory CT scan 22-36 hours after EVT as it is not always performed specially when patients return to their primary hospital. We agree it would have been better if it was part of the study. We added the following sentence line 184:" A systematic immediate post-EVT Cone-beal CT scan wiil be performed for all patients.

Moreover, the authors claim that the sizing of the stroke is not part of the study as it is newly implemented technology. By sizing of stroke they should probably mean the size of the infarct. If this is right then it is unclear why sizing of the infarct is a newly implemented technology. Sizing can easily be done in any CT scan after EVT (far better in MRI but CT could suffice) and it is available since CT scanners were introduced. Many studies use sizing of the infarct (in volume) or other scales as infarct in more or less than 1/3 MCA, ASPECTS score etc. The sizing of infarct is also an important secondary outcome but also an important variable to correlate and even adjust other outcomes (difference in initial infarct between groups, adjustement for final infarct-infarct growth, etc).

⇨ As stated in the limitations of the study in the manuscript the sizing (and Aspects score) of the stroke is not part of the study as it was a newly implemented technology at the time of the design of the study. The objective of our study is a clinical result (i.e functional outcome).

Introduction:
Sufficient description of the background but some clarifications and corrections are needed:
Line 79: "In terms of hemodynamic instability, retrospective studies reported results in favour of CS (8-10)". Between 2010, when the first restrospective study was published, and 2017, 17 restrospective studies have been published on the subject. Only four of these studies have data on blood pressure but none of the 3 studies (Berkhemer 2016, Abou-Chebl 2015, Bekelis 2017) the authors are refferring to as support for the claim of hemodynamic instability. Moreover, the four studies that indeed have data on blood pressure show that patients under GA experienced intra-procedural hypotension overwhelmingly. The references should be corrected and clarify instability, as patients with intraprocedural hypotension under GA can be hypotensive but stable after induction.

⇨ As anaesthesiologists, it is part of our daily routine to be able to provide GA without BP drops. GA is not a generic term and it is not necessarily associated with hypotension. However, we agree on the need to clarify the references in the manuscript. Three major studies have been recently published with data on blood pressure: the Siesta study (JAMA 2016), the ANstroke study (Stroke 2017) and the Goliath study (JAM Neurol 2018). As shown in the Table above, these studies were not multicentric, the anaesthesia protocol and the haemodynamic control protocol were not always detailed. None of these studies have reported a worst outcome with GA. The post-hoc analysis of the Siesta Study (Stroke 2018) reported no association between the difference in systolic BP, diastolic BP, and mean arterial pressure from baseline to the different phases of intervention and NIHSS change after 24 hours. One could hypothesize that BP drops could be counterbalanced by the benefits of GA (mild hypocapnia, immobility etc..). However, the Siesta study included only 150 patients and BP was not the primary outcome. The Gass study is

the first multicentric RCT including a detailed anaesthesia protocol with a tight haemodynamic control, comparing GA and CS during EVT and evaluating the functional outcome at 3 months. We added the following sentences page 5, line 96, to further explain why the methodology of our study is more rigorous: " Indeed, in previous studies (11,12,13), the anaesthesia protocol was either not standardized or the doses not given, the blood pressure was controlled with vasoactives drugs as different as dopamine and norepinephrine in the same study and the clinical outcome was not the primary objective of one study (13). The recently published post hoc analysis of the Siesta trial (15) reported noassociation between heamodynamic variations and NIHSS change after 24 hours."

And line 106: "The Gass study is the first multicentric RCT including a detailed anaesthesia protocol with a tight haemodynamic control, comparing GA and CS during EVT and evaluating the functional outcome at 3 months.

Line 89: A correction is needed in the number of patients, the AnStroke trial included 90 patients.

=> We apologize for this. The number has been corrected.

Line 96: It is not true that no study has assessed the clinical outcome 3 months after with a standardized anaesthetic protocol and hemodynamic control. AnStroke trial had mRS at 3 months as primary outcome and, as the authors also stated earlier, included a standardized anesthetic protocol and hemodynamic control according to international guidelines.

=> As described in the table below, the AnStroke and the Goliath study did not assess the clinical outcome 3 months ((as the primary outcome) after the stroke treatment comparing GA and conscious sedation (CS) AND using standardised anaesthetic protocols (providing doses and maximum targets) AND tight haemodynamic control.

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Haemodynamic control	SBP between 140 and 185 mmHg; DBP < 110 mmHg. A drop of more than 25% of the MBP will also be avoided. Norepinephrine will be administered in a dedicated intravenous line and diluted at 250 microg/ml.	Objectives: SBP between 140 and 180 mmHg, using dopamine, phenylephrine, norepinephrine, ephedrine ⇨ Control only based on SBP ⇨ Use of different drugs with different effects, which could imply an increase use of vasoactive drugs (i.e dopamine is less efficient than other drugs in increasing blood pressure) ⇨ No standardization of vaso actives drugs	Objectives: SBP > 140 mmHg and MAP < 70 mmHg, using ephedrine or phenylephrine ⇨ Use of different drugs with different effects, which could imply an increase use of vasoactive drugs to obtain the same expected result ⇨ No standardization of vaso actives drugs	Targets for SBP were set at 140 to 160 mmHg in both groups. Results showing no differences in MAP in the 2 groups. However, the anesthesia and the Haemodynamic control protocols are not available. Post hoc analysis (Stroke 2018): no association between the difference in systolic BP, diastolic BP, and mean arterial pressure from baseline to the different phases of intervention and NIHSS change after 24 hours
mRS at 3 months as a primary outcome	yes	yes	no	no
Multicentric	yes	no	no	no

Concerning the ongoing studies, we found 10 of them on Clinicaltrials.gov. We did not mention them because of the absence of published results.

⇨ We added the following sentence page 5, line 96, to further explain why the methodology of our study is more rigorous: " Indeed, in previous studies (11,12,13), the anaesthesia protocol was either not standardized or the doses not given, the blood pressure was controlled with vasoactives drugs as different as dopamine and norepinephrine in the same study and the clinical outcome was not the primary objective of one study (13). The recently published post hoc analysis of the Siesta trial (15) reported no association between heamodynamic variations and NIHSS change after 24 hours."

And line 106: "The Gass study is the first multicentric RCT including a detailed anaesthesia protocol with a tight haemodynamic control, comparing GA and CS during EVT and evaluating the functional outcome at 3 months.

Methods and analysis

Criteria:
A description of the following is missing:

-Contraindications to GA and to anesthetic drugs: It is good to state these contraindications.

=> The National French Drug Agency (Agence Nationale de Securité du Médicament) asked us to add these contraindications. However, there are no contraindications to GA in this context. We erased this line. The only contra-indications to anaesthetic drugs in this context is allergy. We modified line 133: “ Contra-indication Allergy to one of the anaesthetic drugs”

-Life-threatening comorbities: Which comorbities in a patient with AIS coming for EVT are considered life-threatening? Does the study have a pre-morbid mRS exclusion criteria or all patients, even mRS 4 and 5 can be included?

=> For example, patients with an associated trauma with life-threatening conditions (hemorrhagic shock, head trauma…etc…). The choice to include or not the patient is ultimately left to the anaesthesiologist in charge. We did not add mRS as an exclusion criteria. All patients can be included.

-A major limitation is that all radiological indications/contraindications are missing. Baseline ASPECTS or infarct size? It should be the same between the groups to avoid bias when comparing the effect of GA and CS in the outcome. Occlusion site? Tandem occlusions, ICA, M1, M2, Carotid-T? Is there any perfusion imaging included? Missmatch and ratio then? What is the primary modality for detection of occlusion, CT or MRI? Which protocol?

⇨ As stated in the limitations of the study in the manuscript the sizing (and Aspects score) of the stroke is not part of the study as it was a newly implemented technology at the time of the design of the study. The objective of our study is a clinical result (i.e functional outcome).

-An NIHSS limit for inclusion/exclusion is missing. Does all patients who present with large vessel occlusion will be included no matter the neurological deficit? This can also lead to bias. The only statement on NIHSS is that a separate analysis will be done for patients with < or > 14 points NIHSS which is a quite old discrimination between severe and moderate stroke but says nothing about which patients will be included.

⇨ No limit has been predetermined. All patients who could benefit from EVT could potentially be included. It is already stated in the manuscript line 148: “Randomization will be stratified on the centre, the National Institute of Health Stroke Score (NIHSS ≤ or > 14) and the administration or not of IV thrombolysis”.

-The mRS at 3 months will be evaluated by research nurses. The most usual and most accepted practice in major randomized studies is that experienced vascular neurologists evaluate the outcome in a personal interview with the patient. Why research nurses? Are they certified? Personal interview? Is this a common practice in France?

=> in France, all patients are not seen by a vascular neurologist 3 months after the stroke. There are too many patients who sometimes live far away from the stroke centre. Most patients have a consultation with their GP and a neurologist (not always specialized in vascular neurology) 3 to 6 months after the stroke. In order to standardize the evaluation and the answers, the mRS is evaluated by trained certified research nurse as stated line 193.

Interventions
Line 170: Glascow coma scale<8 and/or deglutition disorders are given as situations where CS can be converted into GA. Both of these situations are exclusion criteria in this study, why would such patients be included in the study and then converted to GA? Clarification or correction is needed.

⇨ A given patient cannot have any contra-indications to conscious sedation (i.e Glascow coma scale<8 and/or deglutition disorders) at the time of inclusion and randomization and present these signs minutes later just before induction of anaesthesia or during the procedure. Even if the patient was randomized in the CS group, the appearance of a Glascow coma scale<8 and/or deglutition disorders are medical reasons to convert CS into a GA.

Outcome measures

Line 200: “Time between arrival of the patient...” Arrival where? At the hospital or att the angiosuite? Please clarify.

⇨ Arrival at the stroke center: the sentence was modified as follows: “Time between the arrival of the patient at the stroke center and the beginning of the endovascular therapy (time of punction)”

The authors give as secondary outcomes time from stroke onset to last angiography and time from arrival of patient (where?) to groin puncture. They should explain why they choose these intervals and why they exclude all others. Especially time from stroke onset to last angiography can be influenced by a lot of factors (traffic, time of call, ambulance response, emergency department time, time in CT, transportation etc.) which might not be relevant when GA and CS are compared. The usual time points (stroke onset, arrival at emergency department, arrival CT-first CT image, groin puncture, recanalization) are important to secure that the groups are similar and should be stated. Moreover, there is time points that should be monitored especially when someone is comparing GA and CS, as arrival att angiosuite, start of GA induction, start of sedation, groin puncture (with these time points the length of anesthesia preparation and induction is measured) and procedural time of course. Are these time points included in the protocol? They are crucial factors in GA vs CS comparison.

⇨ As mentioned above, the arrival of the patient means the arrival at stroke center: the line 200 was modified as follows: “Time between the arrival of the patient at the stroke center and the beginning of the endovascular therapy (time of punction)”

⇨ The following times are also recorded:

- The time between the first contact of the patient with the anaesthesiologist and the induction of anaesthesia (GA or CS) (line 263)
- The duration of anaesthesia (line 270-71)
- The duration of the procedure (line 270-71)

Line 202: The authors should consider change quality of recanalization to recanalization rate. They give as recanalization rate scale the modified treatment in cerebral ischemia but in parenthesis they write TICI. Which one will be used, mTICI or TICI? Please define.

⇨ TICI was modified for mTICI throughout the manuscript

Line 207: Complications: Anesthesiological complications such as aspiration or delayed extubation for example are missing. Are such complications included in the protocol. Also very important to monitor in such a study.

⇨ The following complications will be assessed: Hospitalization in intensive care unit, number of hours of invasive ventilation and complications such as pneumonia, bradycardia with atropine,

conversion from CS to GA, all haemodynamic modifications during and after the EVT for 24 hours.

The following items were added line 284: Bradycardie with atropine treatment during first 24 hours, Hospitalization in intensive care unit, Number of hours of invasive ventilation , Pneumonia

Line 213: Why is number of patients who receive norepineprine a secondary outcome? We know for sure that patients under GA will need it more often. Please explain.

⇨ This is part of our hypothesis. We do not know it for sure. Some patients under CS also benefit of norepinephrine. Our anaesthesia protocol for GA (unlike previous studies) was designed to minimize the risk of hypotension. Norepinephrine is not always needed during a GA in general or a GA for thrombectomy.

Statistical analysis

Sample size estimation: One previous study with mRS≤2 30% after EVT under GA is given as the ground for the sample size estimation. Ther is also other studies and case series that give in the GA group a variable percentage of mRS≤2, from lower than 20% to more than 40%. Why did the authors choose especially this study for calculation of the sample size?

=> We invite the reviewer to refer to our response to reviewer 1 who asked a similar question.

Moreover, they want to show an increase in mRS≤2 up to 45% under CS. Why 45%? Where do the authors base that a 45% is sufficient? As pointed earlier, there is studies (comparing GA vs CS, retrospective, case series) that show mRS≤2 in GA patients more than 40%. If we use the assumption of the authors, meaning 30% mRS≤2 in GA and 45% in CS, then a 15% units difference is the ground for the sample estimation. The difference in mRS≤2 in the retrospective studies varied nontheless from 20% to approx 40% units (lower in GA). Why is 15% the difference that will decide if a method is better? A clarification is needed.

=>The study on which the sample size calculation was based found an absolute benefit of CS of 20% compared with GA. We chose to hypothesize a smaller benefit to avoid a lack of power in case of an observed difference smaller than 20% at the end of the study. If the observed effect is higher our sample size will nevertheless allow us to show a statistical significance

Data Registration

Baseline:
Line 263: “time of cerebral angiography or MRI”: Is MRI the image of choice? CT? Cerebral angiography with DSA? Which time is considered here? Time of first image?

=> the sentence was modified as follows: “time of the cerebral angiography or MRI (meaning time of first image for diagnosis)”

Intraoperative data:
Line 267: “TICI (16)”: See even comment above. Which TICI? Ischemia or Infarction? Modified or non? Please clarify as numerous scales exist.

⇨ => TICI was modified for mTICI throughout the manuscript

Interventional and anesthesiological complications are missing in data registration. Please define them. If not included it is a major limitation.

Complications related to anesthesia are already assessed (line 272). Complications related to EVT are also assessed. We added the following sentence line 277: “procedure related complications (distal embolization in a different territory, intramural arterial dissection, arterial perforation, access-site complications leading to surgery). “

Postoperative data:
Line 275: Please clarify the necessity of noradrenaline during the first 2 hours after EVT. Why? In relation to what this necessity? To unsuccesfull recanalization?

⇨ In order to maintain arterial blood pressure high enough to ensure a good cerebral vascularization (objective of mean arterial blood pressure higher than 65 mmHg), some patients may benefit of norepinephrine for few hours after EVT and recanalization.

Postoperative radiological data are missing and are of paramount importance in such a study.

⇨ These data are not part of the primary or the secondary outcome that we predefined. We chose a functional outcome.

VERSION 2 – REVIEW

REVIEWER	Judith Dinsmore St George's Hospital, London, UK
REVIEW RETURNED	02-Dec-2018

GENERAL COMMENTS	The authors present a revised manuscript for the GASS Trial study protocol: a multicentre, single blind, randomised clinical trial comparing general anaesthesia and sedation during intra-arterial treatment for stroke. As stated previously, this is an important and clinically relevant topic. The protocol is generally well written and most of my queries have been addressed however I have a few comments: Introduction: On page 5, line 98 the authors have attempted to justify their statement that no study has assessed the clinical outcome 3 months after the stroke treatment comparing GA and conscious sedation (CS) using standardised anaesthetic protocols and tight haemodynamic control. However, I remain unconvinced by their argument. Although smaller studies and monocentric, both the AnStroke and Goliath trial did use standardised protocols and tight haemodynamic control. Despite the doses of anaesthetic agents not being strictly prescribed in the GOLIATH or Anstroke trial the agents used were protocolised, but the dosage and infusion rates were adjusted at the discretion of the anaesthetist. Although here the authors here have standardised doses these are given as ranges and I imagine the rates will also be adjusted according to

	clinical need. None of the studies have used and neither will these authors use depth of anaesthesia monitoring to titrate exact situation. In terms of blood pressure control and the agents used, I see no reason why the choice of vasopressor will influence outcome especially as there is currently no evidence in favour of any particular agent. The important outcome is the blood pressure. Whilst they mean feel that their methodology is more rigorous, the real differences between GASS and these earlier RCTs are that GASS will be multicentric and recruit more patients. However, both of these will be real benefits. The authors quote the post hoc analysis of the SIESTA trial reporting no association between haemodynamic variables and NIHSS change at 24hrs. It is also worth mentioning the results from Rasmussen et al who also found no influence of blood pressure on outcome in their analysis of data from the GOLIATH trial (Rasmussen, M. et al. British Journal of Anaesthesia, Volume 120, Issue 6, 1287 – 1294) Methods: In terms of inclusion criteria, the authors have persisted with the statement life threatening co-morbidity. Whilst I understand what they mean it is a very dramatic statement. Do they have a premorbid mRS as a cut off as commonly used in thrombectomy studies? Even if not used as inclusion/ exclusion criteria it would be useful to have a starting mRS recorded (I do not see it in the list of data registered at randomisation). Although they now mention capnography there is no target given for control of carbon dioxide. What PaCO2 will be allowable. Blood glucose is important in terms of outcome and is even highlighted in the AHA/ASA 2018 guidelines. Hyperglycaemia is associated with worse outcome and blood glucose should be monitored / treated (Class 11a evidence). How is blood pressure measured – invasively, continuously? Conscious sedation will be converted to general anaesthesia in the event of respiratory depression with respiratory rate >35 / min. What about hypoventilation – much more likely in view of the remifentanil infusions. It would be useful to have time of extubation / delayed extubation recorded. This is not necessarily the end of the procedure as some patients may be taken to critical care still intubated. I am still unsure why the necessity of noradrenaline during the first 2 hrs after treatment is a data set. It would be incredibly unusual to need this unless there were complications, or the patient remained sedated / anaesthetised?

VERSION 2 – AUTHOR RESPONSE

Reviewer(s)' Comments to Author:

Reviewer: 1

The authors present a revised manuscript for the GASS Trial study protocol: a multicentre, single blind, randomised clinical trial comparing general anaesthesia and sedation during intra-arterial treatment for stroke. As stated previously, this is an important and clinically relevant topic. The protocol is generally well written and most of my queries have been addressed however I have a few comments:

=> Thank you for this comment

Introduction:

On page 5, line 98 the authors have attempted to justify their statement that no study has assessed the clinical outcome 3 months after the stroke treatment comparing GA and conscious sedation (CS) using standardised anaesthetic protocols and tight haemodynamic control. However, I remain unconvinced by their argument. Although smaller studies and monocentric, both the AnStroke and Goliath trial did use standardised protocols and tight haemodynamic control. Despite the doses of anaesthetic agents not being strictly prescribed in the GOLIATH or Anstroke trial the agents used were protocolised, but the dosage and infusion rates were adjusted at the discretion of the anaesthetist. Although here the authors here have standardised doses these are given as ranges and I imagine the rates will also be adjusted according to clinical need. None of the studies have used and neither will these authors use depth of anaesthesia monitoring to titrate exact situation. In terms of blood pressure control and the agents used, I see no reason why the choice of vasopressor will influence outcome especially as there is currently no evidence in favour of any particular agent. The important outcome is the blood pressure. Whilst they mean feel that their methodology is more rigorous, the real differences between GASS and these earlier RCTs are that GASS will be multicentric and recruit more patients. However, both of these will be real benefits.

=> We apologized if our protocol was not clear enough or not detailed enough. In both previous studies (AnSTroke and Goliath), the doses are not given in the results section. Doses were neither protocolized nor given in the results section. Doses in the CS groups could have been high and close to GA. In our study, doses are strictly protocolized. They are adjusted according to clinical need, of course but a maximum dose has been defined and the total doses will be presented in the results section. To acknowledge, the reviewer statement we modified the text as follows: lien 102 “So far, no study few studies has assessed the clinical outcome 3 months after the stroke treatment comparing GA and CS using standardized anaesthetic protocols and tight haemodynamic control. Indeed, in previous studies”.

The authors quote the post hoc analysis of the SIESTA trial reporting no association between haemodynamic variables and NIHSS change at 24hrs. It is also worth mentioning the results from Rasmussen et al who also found no influence of blood pressure on outcome in their analysis of data from the GOLIATH trial (Rasmussen, M. et al. British Journal of Anaesthesia, Volume 120, Issue 6, 1287 – 1294)

=> As requested we added the reference: “The recently published post hoc analysis of the Siesta trial (15) and the GOLIATH trial (16) reported no association between heamodynamic variations and NIHSS change after 24 hours.

Methods:

In terms of inclusion criteria, the authors have persisted with the statement life threatening co-morbidity. Whilst I understand what they mean it is a very dramatic statement. Do they have a premorbid mRS as a cut off as commonly used in thrombectomy studies? Even if not used as inclusion/ exclusion criteria it would be useful to have a starting mRS recorded (I do not see it in the list of data registered at randomisation).

=> We do not record a starting mRS in our study. According to the French Health Authority guidelines (www.has-sante.fr), EVT is not proposed to patients who do not walk (mRS higher than 4). We added this sentence in the non- inclusion criteria: “patients who could not walk prior stroke”

Although they now mention capnography there is no target given for control of carbon dioxide. What PaCO2 will be allowable. Blood glucose is important in terms of outcome and is even highlighted in the AHA/ASA 2018 guidelines. Hyperglycaemia is associated with worse outcome and blood glucose should be monitored / treated (Class 11a evidence).

=> PaCO2 is recorded. We did set a target.

Blood glucose is checked when the patient arrives at the hospital and then 3 times a day during the first 72 hours. Hyperglycemia is treated with IV insuline when necessary (target 11 mmol/L). line 198, the following sentence has been added: “Hyperglycemia will be treated with IV insuline when necessary (target 11 mmol/L).”

How is blood pressure measured – invasively, continuously?

=> Blood pressure is measured continuously non-invasively. We added this sentence line 195: “Blood pressure will be continuously non-invasively monitored”.

Conscious sedation will be converted to general anaesthesia in the event of respiratory depression with respiratory rate >35 / min. What about hypoventilation – much more likely in view of the remifentanil infusions.

=> In case of hypoventilation, remifentanil doses will be lowered, as good practice recommend when remifentanil is used for sedation

It would be useful to have time of extubation / delayed extubation recorded. This is not necessarily the end of the procedure as some patients may be taken to critical care still intubated.

 Duration of invasive ventilation is recorded. It was a mistake to not mention it. We apologize for this. We added the following sentence line 292 : “duration of invasive ventilation”

I am still unsure why the necessity of noradrenaline during the first 2 hrs after treatment is a data set. It would be incredibly unusual to need this unless there were complications, or the patient remained sedated / anaesthetised?

=> In our institution, patients are treated with noradrenaline until they need it, meaning until the blood pressure is within the predefine range (SBP < 180 mmHg, DBP< 110 mmHg and MBP > 65 mmHg. In case of TICI 2a or lower, the objective is MBP > 75 mmHg). It can sometimes take a few hours before patients reach the target in terms of blood pressure and this is independent of the type of anaesthesia according to our experience. We added the following sentence line 202: Postoperative blood pressure targets are defined as follows: SBP < 180 mmHg, DBP< 110 mmHg and MBP > 65 mmHg. In case of TICI 2a or lower, the objective is MBP > 75 mmHg. Norepinephrine will be used if necessary.

VERSION 3 - REVIEW

REVIEWER	Judith Dinsmore St Georges University NHS Trust London, UK
REVIEW RETURNED	09-Feb-2019

GENERAL COMMENTS	The authors present their revised manuscript for the GASS Trial study protocol: a multicentre, single blind, randomised clinical trial comparing general anaesthesia and sedation during intra-arterial treatment for stroke. As stated previously, this is an important and clinically relevant topic. The protocol is generally well written and my queries have been largely addressed.