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BMJ Open GASS Trial study protocol: a multicentre, single-blind, randomised clinical trial comparing general anaesthesia and sedation during intra-arterial treatment for stroke

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ABSTRACT

Introduction Treatment of acute stroke has drastically changed in the last 10 years. Endovascular therapy is now the standard of care for patients with a stroke caused by a large vessel occlusion in the anterior circulation. The impact of the type of anaesthesia (general anaesthesia or conscious sedation) during endovascular therapy on the outcome of the patients is still a matter of debate. Previous studies are mostly retrospective and/or focused on the early postprocedure outcome and/or without blood pressure goals and/or single-centre small size studies. We therefore designed a multicentre study hypothesising that conscious sedation is associated with a better functional outcome 3 months after endovascular therapy for the treatment of stroke compared with general anaesthesia.

Methods/analysis The General Anaesthesia vs Sedation for Stroke (GASS) Trial is a randomised, parallel, single-blind, multicentre study of 350 patients undergoing endovascular therapy for the treatment of stroke. Patients will be randomly allocated to receive either a general anaesthesia or a conscious sedation. The primary outcome measure is the modified Rankin score assessed 3 months after the treatment. Data will be analysed on the intention-to-treat principle.

Ethics/dissemination The GASS Trial has been approved by an independent ethics committee for all study centres. Participant recruitment begins in September 2016. Results will be published in international peer-reviewed medical journals.

Trial registration number NCT02822144.

INTRODUCTION

The treatment of acute stroke has been recently transformed with the publication of randomised controlled trials (RCTs) showing the benefit of endovascular therapy when compared with the medical treatment in terms of functional outcome.^{1–4} Endovascular therapy in addition to the medical treatment is now the standard of care for selected

Strengths and limitations of this study

- GASS Trial is a randomised, parallel, single-blind, multicentre study comparing the effects of general anaesthesia and conscious sedation during endovascular therapy for stroke.
- GASS Trial is focused on the functional outcome of the patients 3 months after the treatment.
- The multicentre design, broad inclusion criteria, large sample size (350 patients) and follow-up will support external validity.
- The study does not include a systemic CT scan after the endovascular treatment.
- The sizing of the stroke is also not part of the study as it is newly implemented technology.

patients who had a stroke caused by a large vessel occlusion in the anterior circulation. All studies have highlighted that the rapidity of the treatment is an essential factor for a good outcome. The other important factor is the haemodynamic conditions during the procedure because instability can worsen the clinical outcome.^{5,6} A retrospective study concluded that a change of even 10% in mean arterial pressure almost quadrupled the risk for poor outcomes.⁷

In this context, the best anaesthetic strategy during the endovascular treatment has not been yet defined. Indeed, the choice between general anaesthesia (GA) and conscious sedation (CS) remains unclear. While allowing immobility, cerebral protection and airway control, GA can delay the endovascular treatment. However, CS is more rapid, allows neurological assessment during the procedure but the thrombectomy can be more difficult for the neuroradiologist because of patients' movements. In terms of haemodynamic stability,

retrospective studies reported results favouring CS.^{8–10} However, these studies did not focus on the anaesthetic protocol and the intraprocedure haemodynamic. Anaesthetic protocols were not standardised. The first RCT on the subject was published in 2016.¹¹ This monocentric study did not find any benefit of CS over GA in terms of outcome 24 hours and 3 months after the treatment. However, functional outcome at 3 months was only a secondary outcome, and the anaesthesia protocol was not detailed. Moreover, the design allowed patients in the CS group to receive analgesics and/or sedatives if necessary, which could then transform a CS into a light GA. Löwhagen Hendén *et al*¹² did also not show any difference between the two anaesthetic techniques using a well-described anaesthesia protocol. However, the study included only 90 patients and was monocentric. The most recent study¹³ using an identical design with infarct growth as the primary endpoint reported no differences between CS and GA. Clinical outcome at 90 days, tested as a secondary endpoint, was better in the GA group. Finally, a meta-analysis analysing the pooled data of seven trials¹⁴ reported that worse outcomes at 3 months were associated with GA. However, the choice to treat a patient with or without GA was not randomised in the trials included in this meta-analysis.¹⁴

So far, few studies have assessed the clinical outcome 3 months after the stroke treatment comparing GA and CS using standardised anaesthetic protocols and tight haemodynamic control. Indeed, in previous studies,^{11–13} the anaesthesia protocol was either not standardised or the doses not given, the blood pressure (BP) was controlled with vasoactive 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 The recently published post hoc analysis of the Sedation vs Intubation for Endovascular Stroke Treatment (SIESTA) trial¹⁵ and the General or Local Anesthesia in Intra-Arterial Therapy (GOLIATH) trial¹⁶ reported no association between haemodynamic variations and National Institute of Health Stroke Score (NIHSS) change after 24 hours.

Therefore, we designed an RCT comparing GA and CS during endovascular treatment for acute stroke. Both GA and CS protocols will be standardised and the control of arterial BP too. We hypothesised that CS will be associated with a better clinical outcome measured with the modified Rankin score (mRS) 3 months after the procedure. The General Anesthesia vs Sedation for Stroke (GASS) study is the first multicentric RCT including a detailed anaesthesia protocol with a tight haemodynamic control, comparing GA and CS during endovascular treatment (EVT) and evaluating the functional outcome at 3 months.

METHODS AND ANALYSIS

Trial design

The GASS study is an investigator-initiated, national, multicentre, randomised, simple-blind, parallel-group clinical trial with concealed allocation of patients scheduled to

undergo endovascular therapy for stroke 1:1 to receive either a GA protocol or a CS protocol. The trial will be conducted in four university and non-university centres. It started in September 2016 and will continue for a total of 36 months.

Participant eligibility and consent

Trial site investigators will identify consecutive eligible patients from the listed criteria. Eligible patients or a family member when appropriate will receive written and oral information and will be included after investigators have obtained informed written consent.

Inclusion criteria

1. Adult (18 years or older) patients admitted to the participating centre.
2. Occlusion of a large vessel in the anterior cerebral circulation.
3. Undergoing endovascular therapy for stroke.
4. Benefiting from the health insurance system.
5. Signed informed consent from the patient or their legally next of kin.

Non-inclusion criteria

1. Pregnant or breastfeeding women.
2. Patients already intubated and mechanical ventilated before inclusion in the study.
3. Intracerebral haemorrhage associated with the ischaemic stroke.
4. Contraindications to CS: Glasgow coma scale inferior to 8, agitation not allowing the patient to stay still during the procedure and deglutition disorders.
5. Contraindications to succinylcholine: hyperkalaemia and allergy.
6. Body mass index superior to 35 kg/m².
7. Allergy to one of the anaesthetic drugs.
8. Uncontrolled hypotension.
9. Life-threatening comorbidity.
10. Adults legally protected (under judicial protection, guardianship or supervision) and persons deprived of their liberty.
11. Patients who could not walk prior stroke.

Allocation and blinding

Patients will be randomised in two groups (GA group and CS group). Randomisation will be done by investigators as close as possible to the endovascular therapy. Each patient will be given a unique randomisation number (patient code). Randomisation will be stratified on the centre, the National Institute of Health Stroke Score (NIHSS ≤ 14 or > 14) and the administration or not of intravenous thrombolysis. The primary evaluation criterion will be assessed blinded to the randomisation group. During the study period, outcome assessors will be kept blind to the randomisation group. Research nurses evaluating the outcomes 3 months after the treatment will not participate to the anaesthesia and will not be aware of the randomisation group. They will be blinded to the treatment. The anaesthesiologist, the nurse anaesthesiologist,

the neuroradiologist and the neurologist will not be blinded. They will not participate in the assessment of the patients at any time.

At each participating centre, data will be collected and entered into the electronic web-based case report form (eCRF) by trial or clinical trained personal (clinical research associate), blinded to the allocation group, under the supervision of the trial site investigators.

Interventions

All included patients will be allocated to one of the following two study groups:

- ▶ GA group: patients will receive a standardised anaesthesia protocol with remifentanyl.
- ▶ CS group: patients will receive a standard CS with remifentanyl.

Standardised GA will include: Induction: etomidate (0.25–0.4 mg/kg) and succinylcholine (1 mg/kg) and maintenance: TCI propofol (maximum target: 4 µg/mL), TCI remifentanyl (0.5–4 ng/mL) and curares as needed.

Standardised CS will include: Target controlled infusion (TCI) remifentanyl (maximum target 2 ng/mL), local anaesthesia with lidocaine 10 mg/mL (maximum 10 mL). Oxygen will be administered only if $\text{SPO}_2 \leq 96\%$. Respiratory rate and capnography will be monitored.

CS can be converted into a GA in the following situations:

- ▶ Agitation or restlessness not allowing the endovascular therapy.
- ▶ Vomiting not allowing the endovascular therapy.
- ▶ Glasgow Coma Scale <8 and/or deglutition disorders.
- ▶ Severe hypoxaemia with $\text{SPO}_2 < 96\%$ with oxygen delivered with a high concentration mask (10 L/min maximum).
- ▶ Respiratory depression with respiratory rate >35/min and/or clinical signs of respiratory exhaustion.

In both groups: intraoperative dose changes will be left to the anaesthesiologist in charge of the patient if necessary, intravenous norepinephrine will be administered in order to maintain BP within the recommended range: systolic blood pressure (SBP) between 140 mm Hg and 185 mm Hg; diastolic blood pressure (DBP) <110 mm Hg. A drop of more than 25% of the mean blood pressure (MBP) will also be avoided. BP will be continuously non-invasively monitored. Norepinephrine will be administered in a dedicated intravenous line and diluted at 250 µg/mL. Hyperglycaemia will be treated with intravenous insulin when necessary (target 11 mmol/L).

A systematic immediate post-EVT Cone-beam CT scan will be performed for all patients.

Decisions about all other aspects of patient care will be performed according to the expertise of the staff at each centre and to routine clinical practice to minimise interference with the trial intervention. Postoperative BP targets are defined as follows: SBP <180 mm Hg, DBP <110 mm Hg and MBP >65 mm Hg. In case of treatment in cerebral ischemia scale (TICI) 2a or lower, the objective is MBP >75 mm Hg. Norepinephrine will be

used if necessary. Three months after the thrombectomy, patients will consult with a neurologist.

Outcome measures

Primary outcome measure

The primary outcome measure will be the neurological outcome assessed with the mRS 3 months¹⁷ after the endovascular therapy. Success will be considered as an mRS ≤ 2 . The mRS will be assessed by trained research nurse blinded to the randomisation group.

An additional exploratory analysis of the primary endpoint will be performed to assess treatment effects according to baseline NIHSS (≤ 14 or >14) and the administration or not of intravenous thrombolysis.

Secondary outcomes measures

- ▶ Time between the beginning of the clinical symptoms and the last angiography.
- ▶ Time between the arrival of the patient at the stroke centre and the beginning of the endovascular therapy (time of puncture).
- ▶ Quality of the recanalisation after the endovascular treatment evaluated by the neuroradiologist (not blinded). A good quality recanalisation corresponds to a 2b or 3 mTICI (modified treatment in cerebral ischaemia scale).¹⁸
- ▶ NIHSS score at day 1 (day after the endovascular treatment) and day 7 (or the day the patient leaves the hospital if scheduled before D7).¹⁹
- ▶ Complications during the procedure (dissection, rupture of the artery and thrombus in another territory).
- ▶ Mortality rate 3 months after the endovascular treatment.
- ▶ Number of hypotension or hypertension events during the procedure and the first 24 hours after the procedure (hypotension defined as SBP <140 mm Hg or a drop of the MBP of 40% or more, hypertension defined as SBP >185 mm Hg or DBP >110 mm Hg).
- ▶ Number of patients who received norepinephrine.
- ▶ Number of conversion of CS to GA.

Statistical analysis

Statistical analysis will be performed on all randomised and evaluated patients (intention-to-treat analysis). It will be performed with SAS software, version 9, in the Methodology/Biometrics department of the Inserm 1414 Clinical Investigation Centre of Rennes. A first overall descriptive analysis and analysis by group will be performed. This consists of separate estimates, numbers and percentages for qualitative variables, means, SE, medians and interquartile intervals for quantitative variables. The normal feature of the distribution of quantitative variables will be checked. Student's t-test or a Mann-Whitney U test, if necessary, will be used to compare quantitative variables, and a χ^2 or Fisher's exact test, if necessary, will be used to compare qualitative variables between two groups at inclusion. The primary endpoint will be compared between

the two groups with the χ^2 test. Two interim analyses after inclusion of 1/3 and 2/3 of the patients and one final analysis are planned. Stopping rules will use the alpha spending function with the O'Brien-Fleming boundary. The cumulative values of alpha for each analysis are: 0.00021 at the first analysis, 0.01202 at the second analysis and 0.04626 at the final analysis (nTerim, V.1.1, Statistical solutions Ltd, Cork, Ireland). The trial will be stopped early if the significance of the χ^2 test is below these alpha values. For the analysis of the other endpoints, the same strategy as for baseline comparisons will be used. Continuous endpoints repeatedly measured during the study will be compared using a repeated measure two-way (time and group) analysis of variance. For all these analyses, adjustments can be made in case of heterogeneity at inclusion. Except for the interim analyses, a p value <0.05 will be considered as significant for all analyses.

Missing values

Missing data will not be replaced. Mixed models can be used in analysis of repeated data to avoid deleting subjects with any missing values.

Sample size estimation

A previous study reported 30% of the patients with an mRS score of ≤ 2 after endovascular therapy under GA.²⁰ We aim to show an increase of patients with a good prognostic (defined as mRS ≤ 2) up to 45% after endovascular treatment under CS. Therefore, 166 patients per group will be needed to have 80% power at a two-sided alpha level of 0.05. A total of 350 patients will be included to take into account non-evaluable patients and drop outs.

Data registration

Data will be entered into the web-based eCRF by trial or clinical personnel under the supervision of the trial site investigators at each participating centre. From the eCRF, the trial database will be established. Data collection will be monitored by trained research coordinators.

The following data will be registered:

Baseline characteristics at randomisation

Demographic data (age, height, weight, gender and body mass index); American Society of Anesthesiologists physical status; significant comorbidities (cardiovascular, respiratory, neurological, psychiatric and/or abdominal disease, cancer, preoperative chemotherapy or radiotherapy), NIHSS score, time of arrival at the hospital, time of the beginning of the symptoms, time of the cerebral angiography or MRI (meaning time of first image for diagnosis), time between the first contact of the patient with the anaesthesiologist and the induction of anaesthesia (GA or CS), localisation of the stroke, intravenous fibrinolysis if applicable, creatinine clearance and haemostasis (PT and ACT if available).

Intraoperative data

Time of arterial puncture, time of recanalisation, mTICI score,¹⁶ doses of norepinephrine, intraoperative

complications (hypotension defined as SBP <140 mm Hg or a drop of the MBP of 40% or more, hypertension defined as SBP >185 mm Hg or DBP >110 mm Hg) necessity to convert the CS onto a GA, duration of anaesthesia and procedure, procedure-related complications (distal embolisation in a different territory, intramural arterial dissection, arterial perforation and access site complications leading to surgery).

Postoperative data

The following data will be collected:

- ▶ Duration of invasive ventilation.
- ▶ NIHSS day 1 and day 7 or the day the patient leaves the hospital if before day 7.
- ▶ Necessity of norepinephrine during the first 2 hours after the endovascular treatment.
- ▶ Hypotension or hypertension events as defined above during first 24 hours.
- ▶ Bradycardia with atropine treatment during first 24 hours.
- ▶ Hospitalisation in intensive care unit.
- ▶ Number of hours of invasive ventilation.
- ▶ Pneumonia.
- ▶ Death until the final call for mRS (3 months after the procedure).
- ▶ mRS 3 months after the procedure during a telephone interview.²¹

Patient withdrawal

A participant who no longer agrees to participate in the clinical trial can withdraw the informed consent at any time without need of further explanation. Participants who will withdraw from the study will be followed up, according to routine clinical practice in each participating centre. In order to conduct intention-to-treat analyses with as little missing data as possible, the investigator may ask the participant which aspects of the trial he or she wishes to withdraw from (participation in the remaining follow-up assessments and use of already collected data). Whenever possible, the participant will be asked for permission to obtain data for the primary outcome measure. All randomised patients will be reported, and all data available with consent will be used in the analyses. If appropriate, missing data will be handled in accordance with multiple imputation procedures if missing data are greater than 5%.

Safety

Every serious adverse event related to the studied treatment or not, expected or unexpected, will be reported within 24 hours by the investigator to the sponsor on a 'Serious adverse event' form on which will be indicated the date of occurrence, criterion of severity, intensity, relationship with the treatment (or the study) evaluated and the outcome. The period in which serious adverse events should be reported begins from the day of the written informed consent to the end of the follow-up (day of the evaluation of mRS 3–4 months after the procedure). Whenever a serious adverse event persists at the end of the study, the

investigator will follow the patient until the event is considered resolved. The following events: hypotension or hypertension will be recorded as study endpoints criterion in the case report form. In order to avoid collection duplication, they will not be reported on the 'adverse event' page of the case report form. As planned in the study, they will be analysed at the time of interim analyses (two interim analyses after inclusion of 1/3 and 2/3 of the patients), which will permit to show potential difference between the two groups during the study.

In addition, serious adverse events will be submitted to the data monitoring and safety committee (DMSC). The DMSC is independent of the trial investigators and will perform an ongoing review of safety parameters and overall study conduct. The DMSC is composed of a neurologist, an anaesthesiologist, a neuroradiologist, a pharmacologist and a methodologist. The DMSC will be responsible for safeguarding the interests of trial participants, assessing the safety and efficacy of the interventions during the trial and for monitoring the overall conduct of the clinical trial. To contribute to enhancing the integrity of the trial, the DMSC may also formulate recommendations relating to the recruitment/retention of participants, their management, improving adherence to protocol-specified regimens and retention of participants and the procedures for data management and quality control. Recommendations for pausing or stopping the study will be made by the DMSC in case of serious adverse reactions and suspected unexpected serious adverse reaction.

All adverse events for which the investigator or the sponsor considers that a causal relationship with the investigational medicinal products can be reasonably considered will be considered as suspected adverse reactions. If they are unexpected, they are qualified as being suspected unexpected serious adverse events (SAR) and will be notified in a report by the sponsor to Eudravigilance (European pharmacovigilance database) and to local regulatory agency within the regulatory time periods for reporting: immediate declaration if seriousness criteria is death or life-threatening condition, declaration within 15 days for other seriousness criteria.

Data handling and retention

Data will be handled according to French law. All original records (including consent forms, reports of suspected unexpected serious adverse reactions and relevant correspondences) will be archived at trial sites for 15 years. The clean trial database file will be anonymised and maintained for 15 years.

Patient and public involvement

Patient and public were not involved in any of the phases of this study

ETHICS AND DISSEMINATION

Ethical and legislative approvals

GASS Trial was approved by the French National Safety and Drug Agency (Agence Nationale de Sécurité du

Médicament (8 September 2016). By 13 June 2016, the study has been approved for all centres by a central ethics committee (Comité de Protection des Personnes de Poitiers). The GASS Trial is registered in the European Clinical Trials Database (EudraCT 2016-000795-25) and at ClinicalTrials.gov with the trial identification number NCT02822144. Trial methods and results will be reported according to the Consolidated Standards of Reporting Trials 2010 guidelines.²²

Publication plan

Scientific presentations and reports corresponding to the study will be written under the responsibility of the coordinating investigator of the study with the agreement of the principal investigators and the methodologist. The coauthors of the report and of publications will be the investigators and clinicians involved, on a pro rata basis of their contribution in the study, as well as the biostatistician and associated researchers. All trial sites will be acknowledged, and all investigators at these sites will appear with their names under 'the GASS investigators' in the final manuscript. Rules on publication will follow international recommendations.²³

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Contributors AM as anaesthetist contributed to the conception and design of the research protocol and wrote the research protocol. AM wrote the first draft of the protocol. AM critically revised and modified the protocol and the article. AM is including patients in the ongoing study in the Rennes teaching hospital. AM approved the final version to be published. J-CF as neuroradiologist contributed to the conception and design of the research protocol. J-CF critically revised and modified the protocol and the article. J-CF approved the final version to be published. TR as neurologist contributed to the conception and design of the research protocol. TR critically revised and modified the protocol and the article. TR approved the final version to be published. J-MD as anaesthetist critically revised and modified the protocol and the article. J-MD is including patients in the ongoing study in the Fondation Rothschild hospital in Paris. J-MD approved the final version to be published. AS as anaesthetist critically revised and modified the protocol and the article. AS is including patients in the ongoing study in the Brest teaching hospital. AS approved the final version to be published. ML as anaesthetist critically revised and modified the protocol and the article. ML is including patients in the ongoing study in the Tours teaching hospital. ML approved the final version to be published. BL designed the study and its statistical analysis plan. HB provided critical input pertaining to the design of the trial interventions and procedures. HB wrote this manuscript. HB is including patients in the ongoing study in the Rennes teaching hospital.

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