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Type of anaesthesia for acute ischaemic stroke endovascular treatment (Protocol)

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[Intervention Protocol]

Type of anaesthesia for acute ischaemic stroke endovascular treatment

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A B S T R A C T

Objectives

This is a protocol for a Cochrane Review (intervention). The objectives are as follows:

To assess the effects of different types of anaesthesia for endovascular interventions in patients with acute ischaemic stroke.

BACKGROUND

See Table 1 for a glossary of terms.

Description of the condition

Stroke is an important cause of neurological disability and death worldwide, producing a negative socio-economic impact. About 30% of ischaemic strokes are related to an acute proximal large vessel occlusion (LVO) by a thrombus, and early interventions have substantial impingement over good neurological outcomes (Benjamin 2019; Flumignan 2017a; Goyal 2014; Lakomkin 2019; Meretoja 2017; Norrving 2013; Wilson 2002).

Restoration of blood flow after a major cerebral artery blockage by a thrombus can be performed in two different interventions: chemical or mechanical. Chemical thrombolysis is achieved by intravenous (IV) or the intra-arterial administration of a thrombolytic agent, or both, in order to dissolve the thrombus, while mechanical thrombectomy (MT) uses intra-arterial devices for fragmenting and/or removing the thrombus. These two techniques, that is thrombolysis or thrombectomy, can also be used together as pharmacomechanical thrombolysis (Goyal 2016; Wardlaw 2014).

MT may have some benefits over intravenous thrombolysis for the treatment of cerebral LVO. The American Heart Association (AHA) recommends IV recombinant tissue plasminogen activator (rt-TPA) within 4.5 hours and MT within six hours with an Alberta Stroke Program Early Computed Tomography score (ASPECTS) > 6, or 6 to 24 hours with a good clinical-radiological mismatch, after the onset stroke (Albers 2018; Goyal 2016; Lindekleiv 2018; Nogueira 2018; Powers 2018; Powers 2019).

Among ischaemic strokes, there are some special causes of cervicocerebral artery injury, such as dissection, atherosclerosis, fibromuscular dysplasia, web vessels, and dolichoectasia, that might produce pseudo-occlusions and embolic events. Such lesions may have stenting or balloon angioplasty as an alternative intervention (Bang 2018; Flumignan 2017b; Kim 2016; Luo 2018; Naylor 2018; Pereira 2018).

In order to diagnose and classify LVO following a stroke, there are some complementary imaging tests: duplex ultrasound (DUS), magnetic resonance image (MRI), computed tomography (CT), or digital subtraction angiography (DSA). The AHA recommends CT and MRI and their multimodal protocols (non-contrast, angiography and perfusion) for acute ischaemic stroke to predict risk-benefit, plan any therapeutic intervention, and also exclude stroke mimics. In the stroke setting, CT is the main imaging method used due its speed, cost-effectiveness, and availability in most stroke centres (Cassola 2018; Powers 2019).

Description of the intervention

In addition to different endovascular approaches for acute ischaemic stroke, the type of anaesthesia technique has been debated as having relevant impact on neurological outcomes. Anaesthetic interventions, which can be performed by administering inhaled, intravenous (IV) or percutaneous agents to reduce pain, anxiety, and patient mobility, thereby reducing the procedural time and complications, might make it safer and achieve better clinical results. General anaesthesia (GA) is normally used in those patients with worse neurological symptoms in the

endovascular treatment of acute LVO stroke. Local anaesthesia, conscious sedation anaesthesia and monitored anaesthesia care have potential for faster recovery, use smaller amounts of medication and enable the conscious monitoring of neurological intervention effects (ASA 2019).

Local anaesthesia

Local anaesthesia is a percutaneous approach drug that numbs a small specific area, disrupting the sensations of pain in the body. The patient will remain conscious during the procedure and may feel some pressure without pain in this specific anaesthetised area (ASA 2019).

Conscious sedation anaesthesia (CSA)

Conscious sedation anaesthesia is considered as a moderate sedation/analgesia, defined as a drug-induced slightly deeper depression of consciousness after intravenous administration of sedative and analgesic agents. The patient responds purposefully to verbal commands, either alone or accompanied by light tactile stimulation. The physician provider must be prepared to recognize 'deep' sedation, manage its consequences, and adjust the level of sedation to a 'moderate' or lesser level. Usually, spontaneous ventilation and cardiovascular function are maintained and no intervention is required to keep a patent airway (ASA 2019).

Monitored anaesthesia care (MAC)

Monitored anaesthesia care is defined as a specific type of anaesthesia service requested of the anaesthesiologist for the care of a patient undergoing a procedure which may fluctuate between the different levels of sedation anaesthesia as minimal (anxiolysis), moderate (CSA), and deep (MAC). The anaesthesia care includes pre-procedure evaluation, intra-procedure care, and post-procedure management, as well the flexibility to match sedation levels to patient needs and procedural requirements. MAC is considered as a deep sedation/analgesia, defined as a drug-induced depression of consciousness after intravenous administration of sedative, analgesic, amnesic, and anxiolytic agents or other medications as necessary for patient safety. Normally it is associated with local anaesthesia. The patients cannot be easily aroused but respond purposefully after repeated or painful stimulation. The ability to independently maintain ventilatory function may be impaired. Patients may require assistance in maintaining a patent airway, and spontaneous ventilation may be inadequate. Cardiovascular function is usually maintained. The presence of a qualified anaesthesiologist is essential and patient oxygenation, ventilation, circulation, and temperature must be monitored continuously. MAC may lead to conversion to general anaesthesia at any time and must assure return to full consciousness, pain relief, and management of adverse effects from medications administered during the procedure. In some cases the anaesthesiologist may provide only monitored care without any anaesthetic administration (ASA 2019).

General anaesthesia (GA)

General anaesthesia is a complete drug-induced loss of consciousness after administration of inhalation or intravenous agents, or both. The patient cannot be aroused, even after pain stimulation. A significant respiratory and cardiovascular depression occurs and the airway patently is lost, which normally requires insertion of a laryngeal mask airway or endotracheal

tube. Positive pressure ventilation is often necessary due to hypoventilation and drug-induced depression of neuromuscular function. Cardiovascular function may be affected (ASA 2019).

How the intervention might work

The anaesthetic team is increasingly involved in patient care during the endovascular treatment of acute ischaemic stroke. They have to monitor the heart rhythm, haemodynamic changes, temperature, blood glucose, oxygen saturation, and level of consciousness, as well as neuromuscular blockade, during anaesthesia management, which has been correlated with a better neurological outcome (Talke 2014).

Most professionals prefer performing mechanical thrombectomy (MT) under non-GA (local anaesthesia, conscious sedation anaesthesia or monitored anaesthesia care) than GA (Peng 2018; Rasmussen 2017; Steinberg 2019).

GA keeps the patient immobile, lowering the risk of vascular injury, such as perforation or dissection, protecting the airways against broncho-aspiration, and promoting pain and anxiety control. Although MT can be more effective and safer, it may also be faster than non-GA with regard to revascularisation time. The major disadvantages of GA are the delay to the start of the procedure and blood pressure hypotension, which can increase the ischaemic area of the brain, leading to a poor functional outcome. Usually, GA is performed in those patients with worse neurological symptoms of acute ischaemic stroke (McDonald 2015; Molina 2010; Takahashi 2014).

Non-GA enables the patient to remain awake, permitting the monitoring of neurological status and haemodynamic stability, and decreasing procedural time, but does not protect the airways. Nevertheless, not controlling patient movement during the procedure might prolong the revascularisation time and increase the incidence of intra-procedural complications. During MT, the patient sometimes shows a decrease in their level of consciousness and develops agitation, vomiting or swallowing difficulties, making it necessary to convert the non-GA to GA, further delaying the procedure time. Any delay to the procedure might result in impaired neurological outcome. Indeed, anaesthetic intervention can be faster and more feasible in non-GA than GA, with fewer haemodynamic changes, and may result in better neurological outcomes. The effects of the type of anaesthesia for endovascular interventions in acute ischaemic stroke remains unclear (McDonald 2015; Molina 2010; Takahashi 2014; Talke 2014).

Why it is important to do this review

Currently, the number of endovascular interventions for acute ischaemic stroke is increasing and, regardless of the device or technique used, the type of anaesthesia has been proven to be one of the main factors for the best neurological outcomes. Among the anaesthesia types, there are GA and non-GA (local anaesthesia, CSA or MAC), both of which have several advantages and disadvantages. There is no consensus in the decision of the best anaesthesia type for acute ischaemic stroke endovascular treatment (Rusy 2019).

A direct comparison is required at this time and may help the neurointerventionalist to make the procedure safer and promote the best neurological outcomes for the patient.

There are some randomised controlled trials (RCTs) attempting to establish which anaesthesia type promotes better patient-centred outcomes with fewer complications. To date, none have shown a robust difference in clinical outcomes between the GA and non-GA groups. A systematic review reported significantly less disability for GA at three months (Schonenberger 2019); however, the effect of types of anaesthesia for the treatment of acute ischaemic stroke is still under debate (Lowhagen 2017; Schonenberger 2016; Simonsen 2018).

OBJECTIVES

To assess the effects of different types of anaesthesia for endovascular interventions in patients with acute ischaemic stroke.

METHODS

Criteria for considering studies for this review

Types of studies

We will include all randomised controlled trials (RCTs) with a parallel (e.g. cluster or individual) design. We will include studies reported as full-text, those published as abstract only, and unpublished data. We will not include quasi-randomised trials, i.e. studies in which participants are allocated to intervention groups based on methods that are not truly random, such as hospital number or date of birth.

Types of participants

We will consider the inclusion of participants of any gender and any age with acute ischaemic stroke defined by any related extracranial or intracranial artery occlusion, irrespective of the time at which the patient underwent any type of endovascular intervention. All patients who experienced the onset of stroke symptoms will be included, and grouped into those with an unknown length of symptom onset and those with symptoms for less or more than six hours. We will only consider participants with large vessel occlusion (LVO) undergoing endovascular treatment under anaesthesia for inclusion, i.e. the anaesthesia type will be the unique difference between the control and experimental groups. Acute ischaemic stroke will be defined as an occlusion of the internal and/or common carotid artery (extracranial) or any intracranial artery occlusion diagnosed by at least one valid objective test (e.g. DUS or angiography by tomography, magnetic resonance or digital subtraction). All trials involving patients with LVO who underwent an endovascular procedure will be considered, irrespective of the degree or the method used to determine the degree of the brain ischaemic injury. If we find studies with mixed populations (e.g. haemorrhagic and ischaemic stroke), and only a subset of the participants meet our inclusion criteria, i.e. ischaemic stroke with LVO, we will attempt to obtain data for the subgroup of interest from the triallists for inclusion in our review. For studies with mixed populations, such as haemorrhagic and ischaemic stroke, which we cannot get data from the subgroup of interest, but for which at least 50% of the study population are of interest, we will include all participants in our analysis. Moreover, we will explore the effect of this decision in a sensitivity analysis. We will exclude studies where less than 50% of the population are of interest and the subgroup of interest data are not available.

Types of interventions

We will include trials comparing one type of anaesthesia versus another with any combination of interventions, providing that the co-treatments are balanced between the experimental and control arms. We will also include studies that compare different types and doses of drugs. We do not foresee identifying any study comparing placebo anaesthesia, but we will consider them if we do.

We will consider the following interventions.

- Local anaesthesia.
- Conscious sedation anaesthesia (CSA).
- Monitored anaesthesia care (MAC).
- General anaesthesia (GA).

Possible comparisons include:

- general anaesthesia versus conscious sedation anaesthesia;
- general anaesthesia versus local anaesthesia;
- general anaesthesia versus monitored anaesthesia care;
- general anaesthesia versus conscious sedation anaesthesia plus local anaesthesia;
- any combination of the above interventions versus any combination.

Types of outcome measures

Primary outcomes

- Functional outcome at the end of the scheduled follow-up period, categorised by the modified Rankin Scale (mRS): good outcome: scores 0 to 2 (i.e. functional independence); poor outcome: scores 3 to 6 (i.e. functional dependency or death). If the mRS score was not reported, we will use the trial's own definition of functional outcome. If more than one of functional outcome score is reported, we will use the mRS as our main score of interest. If we identify both dichotomous and continuous variables related to independence, we will report them separately as independent outcomes (Wilson 2002).
- Neurological impairment assessed using clinical outcome measures or any validated international scales (e.g. the National Institutes of Health Stroke Scale (NIHSS). If we identify both dichotomous and continuous variables related to neurological impairment, we will report them separately as independent outcomes (Brott 1989).

Secondary outcomes

- Stroke-related mortality.
- All intracranial haemorrhage: asymptomatic and symptomatic, as classified in the third European Cooperative Acute Stroke Study (Hacke 2008), reported as the proportion of participants with intracranial haemorrhage.
- Target artery revascularisation status: revascularised or not-revascularised or assessed by any validated scale (e.g. the modified thrombolysis in cerebral infarction (mTICI) scale (Fugate 2013), cerebral infarction perfusion categories (Higashida 2003)). If we identify both dichotomous and continuous variables related to neurological impairment, we will report them separately as independent outcomes.

- Time to revascularisation: we will consider time (in minutes) from the groin puncture or start of the endovascular treatment until the arterial reperfusion.
- Adverse events: any reported adverse events (excluding death). We will report them separately as independent outcomes.
- Quality of life (QoL): participant's subjective perception of improvement (yes or no) as reported by the study authors or using any validated scoring system such as the Short Form-36 Health Survey (SF-36) (Ware 1992).

We will present all the secondary outcomes at the following two time points after the start of the intervention, if data are available.

- Early outcomes (up to one month after the start of the intervention).
- Long-term outcomes (more than one month after the start of the intervention).

We will present the primary outcomes at the early time-point established.

Search methods for identification of studies

See the 'Specialised register' information available at the Cochrane Stroke Group's web site. We will search for trials in all languages and arrange for the translation of relevant articles where necessary.

Electronic searches

- Cochrane Central Register of Controlled Trials (CENTRAL) (Cochrane Library; latest issue);
- MEDLINE Ovid (from 1946) (Appendix 1);
- Embase Ovid (from 1974);
- Literatura Latino-Americana e do Caribe em Ciências da Saúde (LILACS) (from 1982), via Virtual Health Library;
- Indice Bibliográfico Español de Ciencias de la Salud (IBECS), via Virtual Health Library.

We will model the subject strategies for databases on the search strategy designed for MEDLINE by the Cochrane Stroke Group's Information Specialist (Appendix 1). We will combine all search strategies deployed with subject strategy adaptations of the highly sensitive search strategy designed by Cochrane for identifying RCT and controlled clinical trials, as described in the Chapter 4 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Lefebvre 2019).

We will search the following ongoing trial registers:

- US National Institutes of Health Ongoing Trials Register ClinicalTrials.gov (www.clinicaltrials.gov/);
- World Health Organization (WHO) International Clinical Trials Registry Platform (who.int/ictrp/en/);
- Stroke Trials Registry (www.strokecenter.org/trials/).

Searching other resources

In an effort to identify further published, unpublished and ongoing trials, we will:

- check the bibliographies of included studies and any relevant systematic reviews identified for further references to relevant

trials and search Google Scholar to forward track relevant references (scholar.google.co.uk/);

- contact original trial authors for clarification and further data if trial reports are unclear;
- where necessary, contact experts/triallists/organisations in the field to obtain additional information on relevant trials using a standard letter template (Appendix 2); and
- conduct a search of various grey literature sources, dissertation and theses databases, and databases of conference abstracts, including:
  * British Library EThOS (UK E-Theses Online Service);
  * ProQuest Dissertation and Theses Global.

Data collection and analysis

Selection of studies

Two review authors (RT, CNBC) will independently screen titles and abstracts of the references obtained as a result of our searching activities and will exclude obviously irrelevant reports using the Covidence tool (Covidence). We will retrieve the full text articles for the remaining references and two review authors (RT, CNBC) will independently screen the full text articles and identify studies to determine and record reasons for exclusion of the ineligible studies. We will resolve any disagreements through discussion or, if required, we will consult a third review author (RLGF). We will collate multiple reports of the same study so that each study, rather than each reference, is the unit of interest in the review. We will record the selection process and complete a PRISMA flow diagram (Moher 2010).

Data extraction and management

We will use a data collection form for study characteristics and outcome data, which we will pilot on at least one study in the review. Two review authors (RT, CNBC) will independently extract data from the included studies. We will extract the following study characteristics.

- Methods: study design, total duration of study, details of any 'run in' period, number of study centres, and the location, study setting and date of study.
- Participants: number randomised, number lost to follow-up/ withdrawn, number analysed, mean age, age range, gender, severity of condition, diagnostic criteria, inclusion criteria and exclusion criteria.
- Interventions: intervention, comparison, concomitant medications and excluded medications.
- Outcomes: primary and secondary outcomes specified and collected, and time points reported.
- Notes: funding for trial, and notable conflicts of interest of trial authors.

We will resolve disagreements by consensus or by involving a third review author (RLGF). One review author (RT) will transfer data into Review Manager (RevMan 2014). We will double-check that the data are entered correctly by comparing the data presented in the systematic review with the data extraction form. A second review author (CNBC) will spot-check study characteristics for accuracy against the trial report.

Assessment of risk of bias in included studies

Two review authors (RT, CNBC) will independently assess the risk of bias for each study using the criteria outlined in Chapter 8 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2017). We will resolve any disagreements by discussion or by involving another review author (RLGF). We will assess the risk of bias according to the following domains.

- Random sequence generation.
- Allocation concealment.
- Blinding of participants and personnel.
- Blinding of outcome assessment.
- Incomplete outcome data.
- Selective outcome reporting.
- Other bias.

In cluster-randomised trials, we will consider particular biases, as recommended in Chapter 8 of the *Cochrane Handbook for Systematic Reviews of Interventions*: 1) recruitment bias; 2) baseline imbalance; 3) loss of clusters; 4) incorrect analysis; and 5) comparability with individually-randomised trials (Higgins 2017). We will grade each potential source of bias as high, low, or unclear and provide a quote from the study report, together with a justification for our judgment in the 'Risk of bias' table. We will summarise the 'Risk of bias' judgements across different studies for each of the domains listed. Where information on the risk of bias relates to unpublished data or correspondence with a trialist, we will note this in the 'Risk of bias' table. When considering treatment effects, we will take into account the risk of bias for the studies that contribute to that outcome.

Assessment of bias in conducting the systematic review

We will conduct the review according to this published protocol and report any deviations from it in the 'Differences between protocol and review' section of the systematic review.

Measures of treatment effect

We will analyse dichotomous data as risk ratios (RRs) with 95% confidence intervals (CIs). We will analyse continuous data using the mean difference (MD) when the same scale/score is used, or the standardised mean difference (SMD) when different scales/scores are used, with 95% CIs. We will enter data presented as a scale with a consistent direction of effect. We will narratively describe skewed data reported as medians and interquartile ranges.

Unit of analysis issues

Individuals will be the unit of analysis. If trials include multiple intervention arms, we will consider only the arms relevant to the scope of our review. Where a study includes multiple intervention groups, we will combine groups to create a single pair-wise comparison.

Cluster-randomised trials

We do not anticipate identifying any cluster-RCTs. However, if we identify any such studies, we will include cluster-randomised trials in the analyses along with individually-randomised trials. We will adjust their sample sizes using the methods described in Chapter 23 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2019a), using an estimate of the intra-cluster

correlation coefficient (ICC) derived from the trial (if possible), from a similar trial, or from a study of a similar population. If we use ICCs from other sources, we will report this and conduct sensitivity analyses to investigate the effect of variation in the ICC. If we identify both cluster-randomised trials and individually-randomised trials, we will synthesise the relevant information. We will consider it reasonable to combine the results from both types of trials if there is little heterogeneity between the study designs, and the interaction between the effect of intervention and the choice of randomisation unit is considered to be unlikely. We will also acknowledge heterogeneity in the randomisation unit and perform a sensitivity analysis to investigate the effects of the randomisation unit.

Dealing with missing data

We will contact investigators or study sponsors in order to verify key study characteristics and obtain missing numerical outcome data where possible (e.g. when a study is identified as an abstract only). Where possible, we will use the RevMan calculator to calculate missing standard deviations using other data from the trial, such as confidence intervals. Where this is not possible, and the missing data are thought to introduce serious bias, we will explore the impact of including such studies in the overall assessment of results by a sensitivity analysis. For all outcomes, we will follow intention-to-treat (ITT) principles to the greatest degree possible, where we will analyse participants in their randomised group regardless of the intervention received. We will use available-case data for the denominator if ITT data are not available.

We will present study-level data so that missing and unclear data are clearly indicated and to make any unpublished data acquired from investigators available.

Assessment of heterogeneity

We will inspect forest plots visually to consider the direction and magnitude of effects and the degree of overlap between confidence intervals. We will use the I^2 statistic to measure heterogeneity among the trials in each analysis; we acknowledge that there is substantial uncertainty in the value of I^2 when there is only a small number of studies. If we identify substantial heterogeneity, we will report it and explore possible causes by pre-specified subgroup analysis. We will consider an $I^2 > 50\%$ as substantial heterogeneity. If an $I^2 > 50\%$, we will explore the individual trial characteristics to identify potential sources of heterogeneity (Deeks 2019).

Assessment of reporting biases

We will use funnel plots to investigate reporting biases if we identify 10 or more studies, as recommended in Chapter 13 by the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2019b).

Data synthesis

We will synthesise the data using Review Manager 5 (RevMan 2014). We will undertake meta-analyses only where this is meaningful, i.e. if the treatments, participants, and the underlying clinical question are similar enough for pooling to be appropriate.

If we are confident that trials are estimating the same underlying treatment effect, i.e. the included studies are homogenous (considering population, interventions, comparators and outcome characteristics), we will use a fixed-effect meta-analysis. If clinical heterogeneity is sufficient to expect that underlying treatment effects differ between trials, or if at least substantial heterogeneity is identified, we will use a random-effects meta-analysis. If there is substantial clinical, methodological, or statistical heterogeneity across trials that prevents the pooling of data, we will use a narrative approach to data synthesis (Deeks 2019).

We will address all outcomes listed in the Types of outcome measures section in the 'Results' section of the review under the heading 'Effects of interventions', with outcomes addressed in the order in which they are shown in Types of outcome measures.

We will include the results of individual studies and any statistical summary of these in 'Data and analyses' tables in the review.

GRADE and 'Summary of findings' table

We will create a 'Summary of findings' table for the early time point using the following outcomes: 1) functional outcome at the end of the scheduled follow-up; 2) neurological impairment; 3) stroke-related mortality; 4) all intracranial haemorrhage; 5) target artery revascularisation status; 6) time to revascularisation; 7) adverse events.

We will use the five GRADE considerations (study limitations, consistency of effect, imprecision, indirectness and publication bias) to assess the certainty of a body of evidence as it relates to the studies that contribute data to the meta-analyses for the pre-specified outcomes (Atkins 2004). We will use methods and recommendations described in Chapter 14 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Schunemann 2019) using the GRADEproGDT software (GradePro 2015). We will create a separate 'Summary of findings' table for each comparison, for example: 1) general anaesthesia versus conscious sedation anaesthesia; 2) general anaesthesia versus local anaesthesia; 3) general anaesthesia versus monitored anaesthesia care; and 4) general anaesthesia versus conscious sedation anaesthesia plus local anaesthesia. We will justify all decisions to downgrade the quality of studies using footnotes, and we will make comments to aid the reader's understanding of the review where necessary.

Two review authors (RT, CNBC), working independently, will make judgements about evidence quality, with disagreements resolved by discussion or involving a third review author (RLGF). We will justify, document, and incorporate judgements into the reporting of results for each outcome.

We plan to extract study data, format our comparisons in data tables and prepare a 'Summary of findings' table before writing the results and conclusions of our review. A template 'Summary of findings' table is included as Table 2.

Subgroup analysis and investigation of heterogeneity

We plan to carry out these subgroup analyses when there are six or more studies included in a single analysis, all with sufficient information to determine the subgroups.

- Participant characteristics:

- age: e.g. adults (18 years to 74 years) and elderly (75 years and over);
- co-morbidities: e.g. diabetes, tobacco addiction;
- artery occlusion site: e.g. common or internal carotid artery; anterior, medial or posterior cerebral artery; vertebrobasilar system and hemisphere side;
- ASPECTS score (until 6 versus more than 6) (Barber 2000).

- Intervention characteristics:

  - types of drugs: e.g. analgesic, anti-muscarinic, anxiolytic, barbiturates, benzodiazepines, dissociative, hypnotic, inhaled anaesthetics, opioids, muscle relaxants, vasoactive;
  - doses of drugs;
  - time from stroke onset until the start of the revascularisation (in minutes);
  - anaesthesia duration (in minutes);
  - blood pressure during intervention.

We will use the following outcomes, i.e. primary outcomes, in subgroup analyses.

- Functional outcome at the end of the scheduled follow-up.
- Neurologic impairment.

We will use the formal test for subgroup differences in Review Manager 5 (RevMan 2014), and base our interpretation on this.

Sensitivity analysis

We plan to carry out the following sensitivity analyses, to test whether key methodological factors or decisions have affected the main result. These analyses will be grouped according to study design (individual, or cluster).

- Only studies with a low risk of bias will be included. We will consider a study to have a low risk of bias overall if there is no high-risk judgement in any of the four main domains, i.e. random sequence generation, allocation concealment, incomplete outcome data, and selective reporting.
- We will examine both the fixed-effect model and the random-effects model meta-analyses, and will explore the differences between the two estimates.
- If we identify studies with missing data that are unobtainable, we will repeat analyses excluding these studies to determine their impact on the primary analyses.

We will use the following outcomes (i.e. the primary outcomes) in the sensitivity analyses.

- Functional outcome at the end of the scheduled follow-up.
- Neurological impairment.

Reaching conclusions

We will base our conclusions only on findings from the quantitative or narrative synthesis of included studies for this review. We will avoid making recommendations for practice and our implications for research will suggest priorities for future research and outline the remaining uncertainties in the area.

A C K N O W L E D G E M E N T S

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ADDITIONAL TABLES

Table 1.   Glossary of terms

Term	Definition

Table 1.   Glossary of terms *(Continued)*

Acute ischaemic stroke (AIS)	A sudden loss of blood circulation to an area of the brain, caused by the thrombotic or embolic occlusion of a cerebral artery, resulting in a corresponding loss of neurological function from the onset of symptoms to a week.
Alberta stroke programme early CT score (ASPECTS)	A 10-point quantitative score used to assess early ischaemic changes on non-contrast CT head.
American Heart Association (AHA)	A non-profit organisation in the USA that funds cardiovascular medical research, educates consumers on healthy living and fosters appropriate cardiac care in an effort to reduce disability and deaths caused by cardiovascular disease and stroke.
Angioplasty	A minimally invasive, endovascular procedure to widen narrowed or obstructed arteries or veins.
Atherosclerosis	A disease characterised by a build-up of abnormal fat, cholesterol and platelet deposits on the inner wall of the arteries.
Computed tomography (CT)	A computerised X-ray imaging procedure in which a narrow beam of X-rays is aimed at a patient and quickly rotated around the body, producing signals that are processed by the machine's computer to generate cross-sectional images—or "slices"—of the body.
Computed tomography angiography (CTA)	Computed tomography scanning that uses an injection of contrast material into the blood vessels to help diagnose and evaluate blood vessel disease or related conditions.
Computed tomography perfusion (CTP)	Uses special X-ray equipment to show which areas of the brain are adequately supplied with blood (perfused) and provides detailed information about blood flow to the brain.
Digital subtraction angiography (DSA)	Fluoroscopy technique used in interventional radiology to clearly visualise blood vessels in a bony or dense soft tissue environment.
Diffusion-weighted imaging (DWI)	MR imaging based upon measuring the random Brownian motion of water molecules within a voxel of tissue, particularly useful in tumour characterisation and acute cerebral ischaemia.
Direct thrombin inhibitors	A drug that acts as anticoagulant by directly inhibiting the enzyme thrombin (factor IIa).
Arterial dissection	A blister-like de-lamination between the outer and inner walls of a blood vessel, generally originating with a partial leak in the inner lining.
Dolichoectasia	Arteries throughout the human body which have shown significant deterioration of their tunica intima (and occasionally the tunica media), weakening the vessel walls and causing the artery to elongate and distend.
Duplex ultrasound	Non-invasive evaluation of blood flow through the arteries and veins by ultrasound devices.
Embolism	Obstruction of an artery or vein, typically by a clot of blood or an air bubble.
Fibromuscular dysplasia	A non-atherosclerotic, non-inflammatory disease of the blood vessels that causes abnormal growth within the wall of an artery.
Magnetic resonance imaging (MRI)	A test that uses powerful magnets, radio waves, and a computer to make detailed pictures inside your body.
Magnetic resonance angiography (MRA)	A group of techniques based on magnetic resonance imaging (MRI) to image blood vessels.
Placebo	Substance or treatment with no active effect, like a sugar pill.

Table 1. Glossary of terms *(Continued)*

Randomised controlled trial (RCT)	A study in which the participants are divided randomly into separate groups to compare different treatments.
Tissue recombinant plasminogen activator (rt-TPA)	A protein involved in the breakdown of blood clots.
Stent	A metal or plastic tube inserted into the lumen of an anatomic vessel or duct to keep the passageway open.
Stent retriever	A self-expanding stent used to retrieve the thromboembolus and restore blood flow.
Stroke	Neurological deficit attributed to an acute focal injury of the central nervous system by a vascular cause, persisting ≥24 hours or until death.
Thrombectomy	Interventional procedure of removing a blood clot (thrombus) from a blood vessel.
Thromboaspiration	Aspiration of occlusive thrombi with suction devices to restore blood flow.
Thrombolysis	Breakdown (lysis) of blood clots formed in blood vessels.
Thrombosis	Local coagulation of blood (clot) in a part of the circulatory system.
Transient ischaemic attack (TIA)	A transient episode (less than 24 hours) of neurological dysfunction caused by focal brain, spinal cord, or retinal ischaemia without acute infarction.
Vascular	Relating to blood vessels (arteries and veins).

Table 2. Template for 'Summary of findings' table

General anaesthesia compared with local anaesthesia for acute ischaemic stroke endovascular treatment

Patient or population: adults with acute ischaemic stroke endovascular treatment

Settings: community

Intervention: general anaesthesia

Comparison: local anaesthesia

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with local anaesthesia	**Risk with general anaesthesia**				
	[control]	**[experimental]**				
Functional outcome at the end of the scheduled follow-up	**[value] per 1000**	**[value] per 1000** ([value] to [value])	**RR [value]** ([value] to [value])	[value] ([value])	⊕⊝⊝⊝ **very low** ⊕⊕⊝⊝ **low** ⊕⊕⊕⊝ **moderate**	

Table 2. Template for 'Summary of findings' table *(Continued)*

					⊕⊕⊕⊕ **high**
Neurological impairment	[mean difference](CI)	[mean difference](CI)	-	[value] ([value])	⊕⊝⊝⊝ **very low** ⊕⊕⊝⊝ **low** ⊕⊕⊕⊝ **moderate** ⊕⊕⊕⊕ **high**
Stroke-related mortality	**[value] per 1000**	**[value] per 1000** ([value] to [value])	**RR [value]**([value] to [value])	[value] ([value])	⊕⊝⊝⊝ **very low** ⊕⊕⊝⊝ **low** ⊕⊕⊕⊝ **moderate** ⊕⊕⊕⊕ **high**
All intracranial haemorrhage	**[value] per 1000**	**[value] per 1000** ([value] to [value])	**RR [value]**([value] to [value])	[value] ([value])	⊕⊝⊝⊝ **very low** ⊕⊕⊝⊝ **low** ⊕⊕⊕⊝ **moderate** ⊕⊕⊕⊕ **high**
Target artery revascularisation status	**[value] per 1000**	**[value] per 1000** ([value] to [value])	**RR [value]**([value] to [value])	[value] ([value])	⊕⊝⊝⊝ **very low** ⊕⊕⊝⊝ **low** ⊕⊕⊕⊝ **moderate** ⊕⊕⊕⊕ **high**
Time to revascularisation	**[value] per 1000**	**[value] per 1000** ([value] to [value])	**RR [value]**([value] to [value])	[value] ([value])	⊕⊝⊝⊝ **very low** ⊕⊕⊝⊝ **low** ⊕⊕⊕⊝ **moderate** ⊕⊕⊕⊕ **high**

Table 2.   Template for 'Summary of findings' table *(Continued)*

Adverse events	[value] per 1000	[value] per 1000 ([value] to [value])	RR [value]([value] to [value])	[value] ([value])	⊕⊖⊖⊖ **very low**
					⊕⊕⊖⊖ **low**
					⊕⊕⊕⊖ **moderate**
					⊕⊕⊕⊕ **high**

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: confidence interval; **RR:** risk ratio

GRADE Working Group grades of evidence

High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.

Moderate certainty: we are moderately confident in the effect estimate; the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.

Low certainty: our confidence in the effect estimate is limited; the true effect may be substantially different from the estimate of the effect.

Very low certainty: we have very little confidence in the effect estimate; the true effect is likely to be substantially different from the estimate of effect.

A P P E N D I C E S

Appendix 1. MEDLINE search strategy

1. cerebrovascular disease/ or cerebral artery disease/ or cerebrovascular accident/ or stroke/ or vertebrobasilar insufficiency/ or carotid artery disease/ or exp carotid artery obstruction/ or exp brain infarction/ or exp brain ischemia/ or exp occlusive cerebrovascular disease/
2. (isch?emi$ adj6 (stroke$ or apoplex$ or cerebral vasc$ or cerebrovasc$ or cva or attack$)).tw.
3. ((brain or cerebr$ or cerebell$ or vertebrobasil$ or hemispher$ or intracran$ or intracerebral or infratentorial or supratentorial or middle cerebr$ or mca$ or anterior circulation) adj5 (isch?emi$ or infarct$ or thrombo$ or emboli$ or occlus$ or hypoxi$)).tw.
4. or/1-3
5. anesthesia/ or anesthesia, conduction/ or exp anesthesia, epidural/ or anesthesia, local/ or anesthesia, spinal/ or anesthesia, general/ or exp anesthesia, inhalation/ or balanced anesthesia/ or anesthesia, intravenous/ or conscious sedation/ or deep sedation/
6. an?esthe$.tw.
7. anesthetics/ or exp anesthetics, combined/ or anesthetics, general/ or exp anesthetics, inhalation/ or exp anesthetics, local/
8. (amydricaine or amylocaine or articaine or articainic acid or aslavital or benzocaine or benzofurocaine or benzyl alcohol or bucricaine or bumecaine or bupivacaine or butacaine or butanilicaine or butethamine or butoxycaine or butylcaine or carbisocaine or carcainium chloride or centbucridine or cetacaine or chloroprocaine or cinchocaine or cocaine or cyclomethycaine or dimethocaine or diperodon or dyclonine or etidocaine or eugenol or euprocin or fluress or fomocaine or guafecainol or heptacaine or hexathricin or hexylcaine or instillagel or ipravacaine or isobutamben or ketocaine or levobupivacaine or lidamidine or lidocaine or mepivacaine or meprylcaine or metabutethamine or myrtecaine or oxetacaine or oxybuprocaine or pentacaine or phenacaine or phenol or piperocaine or polidocanol or pramocaine or prilocaine or procaine or propanocaine or propipocaine or propoxycaine or propylcaine or proxymetacaine or pyrrocaine or quinisocaine or ropivacaine or tanax or tetracaine or tolycaine or tricaine or trimecaine or xyloproct or zolamine).tw.
9. (alcohol or alfadolone or alfadolone acetate or alfaxalone or althesin or azd 3043 or betaxalone or chloralose or eltanolone or equithesin or esketamine or etomidate or flunitrazepam or flutomidate or fospropofol or hydroxydione or ketamine or methohexital or metomidate or midazolam or midazolam maleate or minaxolone or oxybate or phencyclidine or propanidid or propofol or remimazolam or renanolone or sameridine or thiamylal or thiobutabarbital or thiopental or tiletamine or trichloroethanol or xenon or xylazine).tw.
10. (aliflurane or bromethol or chloroethane or chloroform or cyclopropane or desflurane or dichloromethane or enflurane or ether or fluroxene or halothane or isoflurane or methoxyflurane or nitrous oxide or sevoflurane or trichloroethylene).tw.

11. analgesia/ or analgesia, epidural/ or analgesia, patient-controlled/ or conscious sedation/ or deep sedation/
12. exp analgesics/
13. (sedat$ or (pain adj3 (manag$ or relief))).tw.
14. analges$.tw.
15. or/5-14
16. endarterectomy/ or endovascular procedures/ or exp angioplasty/
17. vascular surgical procedures/
18. cerebral revascularization/ or Blood Vessel Prosthesis/ or Blood Vessel Prosthesis Implantation/
19. balloon dilatation/ or stents/ or dilatation/ or catheterization/
20. (endarterect$ or endovasc$ or angioplasty or stent$ or pta or revasculari?ation or catheter$ or dilatation).tw.
21. or/16-20
22. randomized controlled trial.pt.
23. controlled clinical trial.pt.
24. randomized.ab.
25. placebo.ab.
26. randomly.ab.
27. trial.ab.
28. groups.ab.
29. or/22-28
30. 4 and 15 and 21 and 29

Appendix 2. Enquiry Letter

Dear Doctor

I am currently conducting a systematic review entitled 'Type of anaesthesia for acute ischaemic stroke endovascular treatment' with Cochrane Stroke Group based in the University of Edinburgh. To ensure that the results are valid, it is essential that all relevant trials are included.

Cochrane was established to ensure all forms of health care will be subject to critical evaluation using standard criteria and specialised software.

As a [expert/triallist] of [intervention name], it is possible that a trial of this has been conducted in patients with acute ischaemic stroke endovascular treatment. If so, we would be grateful if you could supply us with copies of any relevant protocols, reports or publications in the first instance; later it may become necessary to obtain the raw data. If the trial is eligible for inclusion in the review, [specialist name] will be cited in the final report which will be published electronically within the Cochrane Database of Systematic Reviews, and in standard medical journals.

I would be grateful if you could fill in the accompanying form, and forward any information which you feel may be appropriate.

Thank you for your help.
Yours faithfully

Form for reply from Pharmaceutical Company/Triallist/Expert
Trials that fulfil the following criteria will be eligible for inclusion in the review:
- Types of participants:
- Treatment regimen:
- A valid randomisation method:

for example: a centralised scheme, e.g. by telephone or scheme controlled by pharmacy, e.g. pre-coded or numbered containers or on-site computer system where allocations are in a locked unreadable file or assignment envelopes - sequentially numbered, sealed and opaque or other combinations which provide assurance of adequate concealment.

Name of Pharmaceutical Company/Triallist/Expert
Name (person to whom any future correspondence should be addressed):
Trials fulfilling the above criteria:
Have not been conducted ( )
Are currently underway * ( )
Have been conducted in the past * ( )
* Please enclose relevant protocols, citations, reports or other publications
Thank you for your valuable help.
Please complete and return to:

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H I S T O R Y

Protocol first published: Issue 7, 2020

C O N T R I B U T I O N S   O F   A U T H O R S

RT: drafted the protocol and is the guarantor of the review.
RR: drafted the protocol.
GT: drafted the protocol.
CNBC: drafted the protocol.
JEA: drafted the protocol.
VV: drafted the protocol.
BBJ: drafted the protocol.
RLGF: drafted the protocol.

All authors reviewed and approved the protocol content prior to submission.

D E C L A R A T I O N S   O F   I N T E R E S T

RT: none known.
RR: none known.
GT: none known.
CNBC: none known.
JEA: none known.
VV: none known.
BBJ: none known.
RLGF: none known.

N O T E S

Parts of this protocol are based on a standard template established by Cochrane.