Separating surgery from stroke: the effects of surgical severity on photothrombotic animal models of cerebral ischaemia

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Review question

What is the effect of skull surgery on infarct volume and behaviour in the Rose-Bengal animal model of ischaemic stroke?

Context and rationale

All existing animal models of stroke involve some degree of surgical intervention, which could have major effects on stroke outcome and thus confound the translation of animal studies into effective human treatments (Howells et al., 2010). It is already known that soft-tissue surgery can cause a cascade of inflammatory changes which may affect lesion formation in the brain (Murray et al, 2014). Furthermore, breaching the skull to access the brain (a common requirement of many stroke models) reduces cranial pressure, which is often used in humans as a therapeutic intervention to improve outcomes after stroke (Goyal et al., 2016, Hofmeijer et al., 2009). These factors mean that surgery may modulate both the stroke outcome as well as the course of disease, creating challenges with the way the resulting data can be interpreted.

The Rose Bengal model of stroke uses a photo-sensitive dye combined with a laser shone on the vessels of the brain to induce a photochemical reaction causing the formation of thrombi and subsequent stroke (Watson et al., 1985). This model can be generated either by shining the laser directly onto the skull, onto skull that has been thinned, or directly onto the brain's surface following a craniotomy. These variations in the Rose Bengal method provide a unique opportunity to explore the effect of different surgical severities on outcome in the same model of stroke. Understanding the interaction between surgery and stroke is crucial so that the effects of surgery can be predicted and accounted for in future studies.

Searches

MEDLINE via PubMed will be the primary search with no language or publication date restrictions. A secondary search will be completed using relevant reviews picked up in the primary PubMed search. The reference lists of these reviews will be manually checked to identify any relevant studies that were missed in the primary search.

Search strategy

https://www.crd.york.ac.uk/PROSPEROFILES/115429_STRATEGY_20190124.pdf

Types of study to be included

Inclusion criteria:

Preclinical in vivo studies of focal ischaemic stroke which include at least one separate control group.

Exclusion criteria:

Case studies, studies without a separate control group.

Human disease modelled

The disease being modelled is cerebral ischaemic stroke. An ischaemic stroke occurs when a blood vessel carrying blood to the brain is blocked, causing a lack of oxygen and subsequent cell death.

Animals/population

Inclusion criteria:

All animals of any species, age, gender, strain, any comorbidities, any treatment, undergoing the Rose-Bengal photothrombotic induction of focal ischaemic stroke.

Exclusion criteria:

Human study populations, all other ischaemic stroke models and models such as haemorrhagic stroke and global ischaemia, ex vivo, in vitro, and in silico studies.

Intervention(s), exposure(s)

Inclusion criteria:

All types of intervention.

Exclusion criteria:

None.

Comparator(s)/control

Inclusion criteria:

Animals who have undergone full surgery and stroke induction but have received only sham or no treatments (such as vehicle injection instead of therapeutic drug injection, normothermic conditions instead of therapeutic hypothermia).

Exclusion criteria:

Non-controlled experiments, experiments where the control group has been given a treatment but no stroke.

Other selection criteria or limitations applied

Inclusion criteria: All languages, all publication dates.
Exclusion criteria: Reviews

Outcome measure(s)

Inclusion criteria:

infarct volume based off a histological or other measurement (such as MRI). Behavioural outcome such as neurobehavioural score.

Exclusion criteria:

studies that use only other outcome measures such as cerebral blood flow measurements of ischaemic deficit.

Study selection and data extraction

Procedure for study selection

Selection phase 1: Pre-screening phase (title + abstract only).

Selection phase 2: Full-text screening.
Phases 1 and 2 will have two reviewers. Any discrepancies will be resolved through the input of a third reviewer.

Prioritise the exclusion criteria

Selection phase: 1. Pre-screening phase (title + abstract only)

1. Not a preclinical in vivo study animal study

2. Not a study using the Rose Bengal model of stroke

Selection phase: 2. Full-text screening

1. Not a study using the Rose Bengal model of stroke

2. Does not have usable outcome measures such as infarct volume and behavioural scores

3. Does not have a control group that have received a stroke but no treatment

Methods for data extraction

Steps for data extraction:

1. Extract data from text/tables.

2. Extract data from graphs using a digital screen ruler.

3. If data are missing or unable to be extracted, contact authors via email requesting data. If there is no response after two weeks a follow up email will be sent. A final reminder email will be sent at 4 weeks if there has still been no response.

One primary reviewer will extract the data and contact authors. A secondary reviewer will select 10% of papers at random and check the data has been properly extracted.

Data to be extracted: study design

Experimental groups, cohort sizes.

Data to be extracted: animal model

Species, strain, sex, age, level of skull breach, photochemical dye type/dose/administration route/administration time, light type/ intensity/duration, anaesthetic type/administration/duration, infarct location.

Data to be extracted: intervention of interest

Type of treatment (e.g. injected or oral treatment with a certain drug, hypothermia treatment, thrombolytic treatment)

Data to be extracted: primary outcome(s)

Measure of lesion volume (continuous) in mm3, mm2, % change from control. If multiple time points are presented then all will be collected, but only the earliest time point after 24 hours post-stroke will be used for the primary meta-analysis.

Behavioural outcomes as a neurobehavioural score (eg mNSS, Benderson Scale).

Data to be extracted: secondary outcome(s)

None.

Data to be extracted: other

Study ID: Authors, year, title.

Risk of bias and/or quality assessment

Strategy for data synthesis

Planned approach

A random effects meta-analysis will be performed for each outcome measure provided there are sufficient data (>10 comparisons with our specified outcome measures).

Outcome measures:

1. Effect of surgical severity on lesion size in control animal cohorts.

2. Effect of surgical severity on treatment efficacy.

Effect measure

Standardised and normalised mean difference for behaviour and infarct volume respectively.

Effect models

Random-effects meta-analysis to consider both the between-study heterogeneity and within-study sampling error.

Heterogeneity

I^2 to detect level of heterogeneity. Meta-regression to investigate the effect of variables which appear to be contributing to heterogeneity on outcome measures. Meta-regression will not be used in cases where there are less than ten studies in a group.

Other

Number of controls assigned to analyses will be calculated by dividing the reported number of control group animals by the number of treatment groups served by that control.

Analysis of subgroups or subsets

Subgroup analyses

Meta-regression will be used to define the contribution of individual study characteristics to heterogeneity.

Subgroup analysis will be performed in the larger more homogenous subsets of data (e.g. rats, mice, sex) to examine the consistency of results.

The effect of model parameters such as laser intensity and duration, photochemical dye dose and administration time, will be examined as sources of heterogeneity.

Treatments will be split into groups based on drug/treatment type and the effect of treatment on outcome measures will be examined.

If there are sufficient data on the timing of outcome measure recording, then a sub-group analysis based on time will be undertaken. (Note: this will only be undertaken if the different time points are from different animals. If there are multiple time points from the same animal such as with MRI measurements, only one measurement will be taken to avoid repeated measures.)

If there are sufficient data, subgroup analysis based on study quality will be undertaken. This will be done using the CAMARADES study quality checklist, namely randomisation, blinding, control of temperature, and anaesthetic properties, which have all been shown to have a marked effect on outcome in previous stroke reviews.

Sensitivity

To analyse sensitivity, sub-group analyses will be repeated with the removal of various groups of papers to see if this has an effect on the combined outcome estimate. For example, studies perceived to be of lower quality (such as those that did not report randomisation or blinding, sample size calculation, or temperature control) will be removed and analysis will be repeated.

Publication bias

Funnel plot, trim-and-fill, Egger regression. These tests will be used to examine whether the types of intervention (level of skull surgery) may be subject to differing levels of publication bias.

Note that if the between study heterogeneity is very large, these bias tests may not be considered reliable and this will be taken into consideration when completing them.

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Conflicts of interest
None known

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Details of any existing review of the same topic by the same authors

Stage of review at time of this submission

Stage	Started	Completed
Preliminary searches	Yes	No
Piloting of the study selection process	No	No
Formal screening of search results against eligibility criteria	No	No
Data extraction	No	No
Risk of bias (quality) assessment	No	No
Data analysis	No	No

Versions

06 February 2019