Comparison between collateral status and DEFUSE 3 or DAWN criteria in patient selection for endovascular thrombectomy within 6–24 hours after stroke: a protocol for meta-analysis

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ABSTRACT

Introduction Perfusion imaging according to the DEFUSE 3 or DAWN criteria has been applied to select patients with large vessel occlusive stroke undergo endovascular therapy (EVT) in the extended time window. Emerging studies have shown that collateral blood flow-based criteria may be as effective as DEFUSE 3 and DAWN criteria for the evaluation of EVT eligibility beyond 6 hours. We will conduct a meta-analysis to compare collateral status-based criteria with DEFUSE 3 or DAWN criteria.

Methods and analysis We will conduct a search for the studies comparing collateral blood flow-based imaging with CT perfusion using the DEFUSE 3 or DAWN criteria in selecting patients with acute ischaemic stroke undergo EVT in the Web of Science, PubMed, EMBASE and the Cochrane Library databases between November 2017 and November 2021. We will also search the sources of grey literature, the reference lists of included studies and the newly published studies during the review period. Two investigators will independently screen the eligible studies and extract data. The study quality will be assessed by using the Newcastle-Ottawa Scale or the Cochrane risk bias tool. Stata V.17 will be used to conduct data analysis.

Ethics and dissemination Patient informed consent and ethics approval are not necessary as this study uses only published studies. The finding of this meta-analysis will be propagated through committee conferences or peer-reviewed journals.

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INTRODUCTION

Endovascular therapy (EVT) has become a standard care for patients with large vessel occlusive stroke within 6 hours. Subsequently, the DEFUSE 3 and DAWN trials have revealed that patients who had an acute ischaemic stroke (AIS) beyond 6 hours due to large vessel occlusion (LVO) can benefit from EVT by using strict imaging selection criteria. American Heart and Stroke Association 2018 guidelines suggested that the two trial-defined eligibility criteria should be applied for EVT selection in the extended time window. The clinical mismatch (DAWN trial) and the core mismatch (DEFUSE 3 trial) selection criteria are both based on advanced imaging with CT perfusion (CTP). However, CTP is not available in many stroke centres, and the rigorous selection criteria are more likely to exclude patients who may benefit from EVT beyond 6 hours after stroke. Moreover, patients with LVO in the extended time window can potentially benefit from EVT selected by simpler imaging triage. Collateral vasculature status is important to compensate blood flow to the ischaemic area when the principal supplying arteries are occluded. Good collaterals are related to limited ischaemic core and favourable clinical outcomes. Besides, good collateral status on CT angiography (CTA) is comparable with CTP parameters in predicting clinical outcomes in AIS patients. Moreover, patients with LVO in the extended time window selected following collateral-based triage for EVT obtained comparable clinical outcomes with those selected by CTP using the DAWN and DEFUSE 3 criteria. Unfortunately, patient selection for EVT using collateral-based imaging in the late time window is not widely accepted. Here, we will...
compare patient selection for EVT beyond 6 hours after stroke onset using collateral imaging criteria with CTP using DEFUSE 3 or DAWN criteria using clinical outcomes to evaluate the comparative utility of each triage.

**METHODS**

This protocol will be performed in compliance with the Cochrane Handbook for Intervention Reviews. Our protocol for this meta-analysis abides the statement of Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA). 

**Inclusion criteria**

Eligibility criteria include five items: population, intervention, comparison, outcome and study design. Studies conforming to the following criteria will be included.

**Participants**

Eligible studies will involve patients meeting the following criteria: (1) patients with large vessel occlusive stroke, presenting in the late time window; (2) all patients who underwent collateral-based CTA and CTP prior to EVT; (3) patients who had clinical and prognosis data.

**Interventions**

The eligible patients for EVT are selected following the collateral-based imaging.

Although many tools can be used for collateral evaluation, CTA is considered as a reliable tool for assessing collateral status quickly, non-invasively and with highly accurate results. Collateral-based criteria and grading methods on CTA differ in several important ways, including:

1. The method of grading reconstructions of branches of occlusive middle cerebral artery (MCA) with the good collateral is defined as major MCA branches restored distal to the occlusive site.
2. The method of comparing collaterals in the leptomeningeal convexity and the Sylvian sulcus of the affected hemisphere with the normal hemisphere, with the good collateral, is designated as augmented collateral vessels versus the normal hemisphere.
3. The method of grading leptomeningeal collateral flow in the occluded MCA territory, 50%–100% collateral blood flow of occluded MCA region, is considered good collateral.
4. The method of comparing the extent of contrast opacification in MCA cortical territory, parasagittal anterior cerebral artery (ACA) region, Sylvian sulcus and basal ganglia of the symptomatic hemisphere with normal side, with the good collateral, is related to a higher score.
5. The method of comparing the scope and eminence of pial arteries in the posterior cerebral artery (PCA)-MCA and ACA-MCA regions of the symptomatic hemisphere with the normal side, with a lack of filling delay and normal or increased eminence of collaterals, illustrates good collateral status.

**Comparison**

The eligible patients for EVT are selected based on CTP using DEFUSE 3 or DAWN criteria.

**DEFUSE 3 based criteria:**

National Institutes of Health Stroke Scale (NIHSS) >6, infarct volume ≤70 mL, penumbra volume ≥15 mL and a penumbra/infarct core ratio ≥1.8.

**DAWN based criteria:** (1) age <80 years old, NIHSS >20 and infarct volume of 31 mL to less than 51 mL; (2) age <80 years old, NIHSS >10 and infarct volume <31 mL and (3) age >80 years old, NIHSS >10 and infarct volume <21 mL.

**Outcomes**

We will contrast the clinical outcome of the patients selected according to the collateral-based criteria for EVT with those selected following the DEFUSE 3 or DAWN criteria in the extended time window.

The modified Rankin Scale score of 0–2 at 90 days will be the first primary outcome. The secondary outcomes will be: (1) the infarct volume at 24 hours, (2) the successful recanalisation, (3) the symptomatic intracranial haemorrhage (sICH) at 7 days and (4) the death due to any cause at 90 days.

Successful recanalisation is designated as a grade of 2b or 3 on the modified thrombolysis scale in cerebral infarction in line with postprocedural angiography.

sICH is related to symptoms worsening or the NIHSS increase by at least four points from baseline according to criteria established in European Cooperative Acute Stroke Study II.

**Study design**

Randomized controlled trials (RCTs) and observational studies including case control and cohort studies will be included. Case reports, single-arm studies, reviews, duplicate studies and animal studies will be excluded.

**Search method and analysis**

**Search strategy**

Two independent investigators (YC and SL) will systematically search the following databases: Web of Science, PubMed, EMBASE and Cochrane Library between November 2017 and November 2021. The sources of grey literature, the reference lists of included studies and the newly published studies during the review period will also be searched. The search strategies for all databases are presented in online supplemental tables 1–4.

**Study selection and data extraction**

We will use EndNote X9, the software of reference management, to manage the records. Two independent reviewers (YC and SL) will select the studies via reading the title and abstract according to inclusion and exclusion criteria. If it is insufficient to assess the eligibility of the study, the full article will be reviewed. When necessary, a third investigator (DY) will be involved. Detailed
selection processes presented as a PRISMA flow chart are shown in Figure 1.

Two independent reviewers (ML and JL) will extract the following data from included studies: (1) literature characteristics (author, journal, publication year, design of study and sample size), (2) participant information (age, sex, time from last known well to groin puncture, occlusion site, collateral grading method and type of EVT) and (3) outcomes. If the necessary data are missing from the included studies, we will contact the author(s) for information. We will analyse the available data only when there is no response.

Assessment for risk of bias in included studies

Two independent investigators (YC and ML) will assess the quality of RCTs using the Cochrane risk bias tool, which includes the categories as below: random sequence generation, allocation concealment, blind participants and researchers, blind evaluation of results, integrity of result data, selective result reporting and other bias. Each dataset will be designated at a high, low or unclear risk of bias.

The quality of retrospective comparative studies will be assessed by two investigators (YC and ML) independently using the Newcastle-Ottawa Scale, which includes the following items: comparability (two stars), exposure (three stars) and selection (four stars) for an aggregate quality score.

Data synthesis

Stata V.17 will be used for statistical analysis. To deal with the confounding factors among groups, the included studies used regression model. For one thing, logistic regression model is employed to evaluate the effect sizes of categorical endpoints; for another, linear regression model is employed to evaluate the effect sizes of continuous endpoints. Continuous outcomes are expressed as the $\beta$ coefficients with 95% CI, while binary outcomes are presented as ORs with their 95% CI. We will extract the OR and the $\beta$ coefficient from each study. The logarithm of OR (log OR) will be calculated. Since there may exist interaction effects among variables in the multivariate regression model, we pool the adjusted and unadjusted $\beta$ coefficient and adjusted and unadjusted log OR separately using random effect method proposed by DerSimonian and Laird, which takes the variability within and between the studies into consideration. $I^2$ statistics will be used for evaluating the statistical heterogeneity. If there is significant heterogeneity ($I^2 \geq 50\%$), we will conduct subgroup analysis.

Meta-regression

To explore whether the demographic and clinical variables affect the pooled results, we perform random effect meta-regression to analyse the following variables: age, percentage of male patients, baseline NIHSS scores and stroke onset to groin puncture.

Subgroup analysis

If significant clinical and statistical heterogeneity among studies is found, we will conduct subgroup analysis regarding the following aspects: study design, collateral grading method, time from last known well to groin puncture and mode of EVT.

Sensitivity analysis

In a bid to ensure the credibility as well as stability of our findings, Leave-one-out approach will be executed in this section. And in line with evidence-based critical appraisal, ‘high-risk’ studies will be excluded in turn preferentially, which provides reference for exclusion of several low-certainty studies that might impact greatly on serious explanation of this work.

Publication bias

If a minimum of 10 studies are included, we will establish a funnel plot to evaluate the publication bias.

Summary of evidence

YS and ML will independently rate the evidence quality according to GRADE guidelines (Grading of Recommendations Assessment, Development and Evaluation).

Patient and public involvement

As the data collected for our meta-analysis comes from previously published literature, patients are not involved in the conduct, outcome assessment or dissemination of this study.

Ethics and dissemination

Patient informed consent and ethics approval are not necessary as this study uses only published studies. The
funding of this meta-analysis will be propagated through committee conferences or peer-reviewed journals.

Contributors YS conceived, designed this study and drafted this manuscript. YC and SL searched and selected the eligible studies. ML and JL extracted related information. YC and ML assessed the risk of bias. SL and JL performed the statistical analysis. YS and ML independently evaluated the strength of the evidence. DY critically revised and supervised this study. All authors agreed to be responsible for this study and approved of the final version to be considered for publication.

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