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# Efficacy and safety of emergent microsurgical embolectomy in patients with acute ischemic stroke after the failure of intravenous thrombolysis and mechanical thrombectomy – a systematic review protocol

# Účinnost a bezpečnost urgentní mikrochirurgické embolektomie při selhání intravenózní trombolýzy a mechanické trombektomie u pacientů s akutním ischemickým iktem – protokol systematického review


## Abstract

*Introduction:* Intravenous thrombolysis (IVT) with recombinant tissue plasminogen activator within 4.5 h since onset of symptoms is the first line treatment in acute ischaemic stroke (AIS). In case of emergent large vessel occlusion (ELVO), IVT is insufficient with 13–33% of early recanalization of middle cerebral artery (MCA) only. Endovascular mechanical thrombectomy (MT) within 6 h since the onset of symptoms has increased the rate of recanalization and improved clinical outcomes significantly. If appropriate and if there are no contraindications, IVT is followed by MT. This combination therapy is the second line therapy and the best currently available treatment for patients with AIS and MCA occlusion. Successful recanalization is one of the predictors of favourable outcomes as well as negative predictive marker of mortality. The third line option, microsurgical embolectomy, has been discussed for the treatment of patients with AIS and MCA occlusion after failed MT. The objective of this review will be to evaluate the efficacy and safety of ME in patients with AIS and MCA occlusion, after the failure of IVT and MT on revascularization within 8, 16 and 24 h. *Methods:* The initial search will be conducted using the MEDLINE and EMBASE databases. The extensive search will involve the listed databases for published literature (MEDLINE, EMBASE, BMC, Cinahl, Scopus, and WoS) and unpublished literature (Open Grey, MedNar, Cos Conference Papers Index, and ProQuest). Following the Joanna Briggs Institute methodology, two independent reviewers will analyse the titles, abstracts and full texts, and then perform critical appraisal of methodological quality and data extraction from selected studies using the standardized tools. Narrative synthesis of the findings from the included studies, structured around the type of intervention, target population characteristics, and type of outcome will be performed. Funnel plots will be used to detect and/or correct publication bias.



## Key words

brain ischemia – embolectomy – thrombectomy – microsurgery – middle cerebral artery – tissue plasminogen activator

## Klíčová slova

ischemie mozku – embolektomie – trombektomie – mikrochrurgie – střední mozková tepna – tkáňový aktivátor plazminogenu


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M. Klugar[1], J. Fiedler[2,3], R. Líčeník[1], S. Ostrý[4,5]

[1] The Czech National Centre for Evidence-Based Healthcare and Knowledge Translation (Cochrane Czech Republic, Czech Republic CEBHC; JBI Centre of Excellence, Masaryk University GRADE Centre), Institute of Biostatistics and Analyses, Faculty of Medicine, Masaryk University, Brno, Czech Republic
[2] Department of Neurosurgery, České Budějovice Hospital, Czech Republic
[3] Department of Neurosurgery, Faculty of Medicine in Plzeň, Charles University in Prague, Czech Republic
[4] Department of Neurology, České Budějovice Hospital, Czech Republic
[5] Department of Neurosurgery and Neurooncology, First Faculty of Medicine, Charles University in Prague and Military University Hospital Prague, Czech Republic

✉ Jiří Fiedler, MD, PhD
Department of Neurosurgery
České Budějovice Hospital
L. B. Schneidera 381/30
370 01 České Budějovice
Czech Republic
e-mail: fiedler@nemcb.cz

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## Souhrn

*Úvod:* Intravenózní trombolýza (IVT) podaná v okně 4,5 h od počátku příznaků je léčbou první volby akutní ischemické CMP (iCMP). V případě akutního uzávěru velké mozkové cévy vede IVT k časné kanalizaci střední mozkové tepny (a. cerebri media; ACM) pouze ve 13–33 % případů. Endovaskulární mechanická trombektomie (MT) během 6 h od počátku symptomů signifikantně zvyšuje úspěšnost rekanalizace a zlepšuje výsledný klinický stav pacientů. V indikovaných případech a pokud nejsou kontraindikace, MT následuje IVT. Tato kombinovaná terapie jako léčba druhé volby je nejlepší dostupná léčba akutní iCMP s uzávěrem ACM. Mikrochirurgická embolektomie (ME) je diskutovanou léčbou třetí volby u pacientů s akutní iCMP a okluzí ACM po selhání MT. Cílem tohoto review je zhodnocení účinnosti a bezpečnosti ME u pacientů s akutní iCMP při okluzi ACM a selhání IVT a MT v časovém okně 8, 16 a 24 h od začátku symptomů. *Metodika:* Iniciální vyhledávání bude provedeno v databázích MEDLINE a EMBASE. Komprehenzivní systematické vyhledávání bude zahrnovat relevantní databáze jak pro publikované zdroje (MEDLINE, EMBASE, BMC, Cinahl, Scopus, a WoS), tak nepublikované zdroje literatury (Open Grey, MedNar, Cos Conference Papers Index a ProQuest). Na základě metodologie Joanna Briggs Institute, dva autoři systematického review nezávisle na sobě nejprve zanalyzují názvy, souhrny a texty identifikovaných literárních zdrojů a posléze kriticky zhodnotí metodologickou kvalitu relevantních studií a provedou extrakci dat pomocí standardizovaných nástrojů. Extrahovaná data budou syntetizována narativně, vč. specifikace typu intervence, charakteristiky cílové skupiny a typu výstupů. K detekci publikačního zkreslení bude použito funnel plot (trychtýřového grafu).


## Introduction

Based on current guidelines, intravenous thrombolysis (IVT) with recombinant tissue plasminogen activator (rt-PA) in a dose of 0.9 mg/kg within 4.5 h since the onset of symptoms is the first line treatment for patients with acute ischaemic stroke (AIS) [1,2].

In case of emergent large vessel occlusion (ELVO), IVT brings 13–33% of early recanalization of middle cerebral artery (MCA) only [3,4]. Successful recanalization is influenced by the length of thrombus as well as by the level of occlusion. Recanalization of proximal occlusions is less successful; probably because of the occlusions caused by larger thrombi [4].

Endovascular mechanical thrombectomy (MT) within 6 h since the onset of symptoms has increased the rate of recanalization and improved clinical outcomes significantly [5]. However, recent studies showed that the time window for MT increased to 16, resp. 24 h [6,7].

If appropriate and if there are no contraindications, IVT is followed by MT. Patients with ELVO and a contraindication for IVT do also well on MT. MT alone is not superior to IVT [5]. Combination therapy of IVT and MT is the best currently available treatment of ELVO with recanalization rate up to 71% [8–13]. There are still 3–29% of patients in whom the current recanalization therapy fails [8,9,11,12]. The reasons for MT failure are an inability to access the thrombus in 42% and failure of thrombus removal in 58% [14].

Successful recanalization is one of the predictors of favourable outcomes as well as negative predictive marker of mortality [15]. Remaining ELVO is a predictor of poor outcome despite initially mild or rapidly improving symptoms [16]. Failed MT cohort of patients has been treated with IVT only; however, the patients are still within the therapeutic window. The rescue intracranial stenting results in improved outcome in a failure of MT and can be considered with the aim to improve functional outcomes [17].

In the setting of ELVO and MT failure, microsurgery has two options to offer [18–21]: the first one being a direct vessel recanalization with microsurgical embolectomy (ME). The advantage of ME lies in the potentiality of recanalizing the perforators in the case of their branching from the occluded segment, for example sfenoidal (M1) segment of MCA. ME was published by Jacobson and Donaghy in 1962 [22]. In recently published studies with small samples of patients treated with ME only, the recanalization rate was 91–100% [23–25]. The second revascularization option is extra-intracranial (EC-IC) bypass [21]. Superficial temporal artery as a donor brings blood flow to MCA trunks or segments distal to the occlusion site with the cause of blockage left in situ. Bypass is suitable in the case of pronounced intracranial atherosclerosis where ME failure is expected [21]. The surgeon is thus often prepared for the eventuality of EC-IC bypass as well as ME during the surgery.

Microsurgical embolectomy or EC-IC bypass is not a part of current evidence-based guidelines and protocols for AIS with ELVO management. One of the main reasons is the delay of surgical procedures [1]. Minimally invasive rapid surgical embolectomy was described in cases of non-atherosclerotic artery occlusions [19,26]. ME could be an option in particular patient with ELVO following failed MT within 8 h since the onset of symptoms [11,19,27,28].

Emergent ME or EC-IC bypass immediately following IVT has been rarely documented and published [19,21,26,28–30]. Cases of successful surgical recanalization of chronic and acute traumatic MCA occlusion have been published [31,32]. Data published are not consistent.

We hypothesize that emergent ME (with or without EC-IC bypass) could be the third line option for recanalization of symptomatic MCA occlusion following failed MT in eligible patients suffering from AIS caused by MCA occlusion treated with 0.9 mg/kg of rt-PA.

The systematic review protocol described here has an extensive search strategy. It seeks to clarify efficacy and safety of emergent ME in patients with AIS after the use of IVT and failed MT on revascularization and influence on clinical practice. Preliminary searches as of March 2020 were conducted using the MEDLINE, Prospero, Epistemonikos, JBIES and Cochrane databases to establish whether previous systematic reviews on this topic were publically available. No systematic reviews or guidelines related to this issue were discovered.

### Objective

The objective of this review will be to evaluate efficacy and safety of microsurgical embolectomy (with or without EC-IC bypass) in AIS patients with ELVO and failure of combined therapy on revascularization within 8, 16 and 24 h.

## Methods and analysis

### Methods

This systematic review protocol was developed according to: 1) the Preferred Reporting Items for Systematic Reviews and Meta-Analysis Protocols (PRISMA-P) [33]; and 2) the Joanna Briggs Institute Reviewer's

Manual [34]. This protocol has been enrolled with the PROSPERO prospective register of systematic reviews: CRD42017078511.

## Study eligibility

### Types of participants

This review will consider studies that include the adult AIS patients with ELVO after the use of standard intravenous rt-PA treatment (a dose of 0.9 mg/kg or 0.6 mg/kg of rt-PA in a 4.5-h treatment window) followed by failure of MT.

### Types of interventions

This review will consider studies that include ME started within 8, 16 and 24 h after the AIS onset.

### Types of outcomes

This review will consider studies that include the following outcome measures: clinical outcome measured by standardised scales, e. g., by modified Rankin scale (mRS) at 90 days and 1 year; stroke severity measured by standardised scales, e. g., by National Institutes of Health Stroke Scale (NIHSS) at 24 h and 5–7 days or on discharge, if earlier; recanalization assessed by standardised scales, e. g., by modified treatment in cerebral ischemia (mTICI) scale, according to CTA performed immediately after surgery.

The secondary outcomes will follow: symptomatic intracranial haemorrhage including subarachnoid bleeding associated with clinical symptoms, defined as parenchymal hematoma type 2 and clinical worsening by NIHSS 4 or more [35]; mortality rate at 90 days and 1 year; surgical procedure related complications.

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### Types of studies

This review will consider all existing experimental and observational study designs. However, based on the initial search, only case reports will be most likely identified.

## Search strategy

A search strategy will be developed using medical subject headings (e. g., MeSH for MedLine) and adopted for each database included in the review. The text words related to the issue will also be identified. The search strategy aims to find both published and unpublished studies. A three-step search strategy will be utilised in this review. An initial limited search of MEDLINE and EMBASE will be undertaken followed by analysis of the text words contained in the title and abstract, and also of the index terms used to describe an article. A second search using all identified keywords and index terms will then be undertaken across all included databases. Thirdly, the reference list of all identified reports and articles will be searched for additional studies. Studies published in all possible languages, if they have a title and abstract in English, will be considered for inclusion in this review. Studies published with no time restriction will also be considered for inclusion in this review.

The databases to be searched include:

- MedLine@Ovid MEDRLINE®;
- Biomedica Czechoslovaca;
- EMBASE;
- Cinahl;
- Scopus;
- Web of Science.

The search for unpublished studies will include:

- Open Grey;
- MedNar;
- Hospital Premium Collection (ProQuest).

Examples of unpublished relevant results retrieved by initial search [36,37].

Example search strategy (MedLine – Ovid interface):

1. adult* OR adult patient* OR adult population;
2. acute ischemic stroke OR middle cerebral artery OR occlusion M1 OR occlusion M2 OR carotid terminus occlusion OR stroke;
3. surgical embolectomy OR emergency embolectomy OR MIRSE OR microsurgical embolectomy;
4. recanalization OR neurological deficit OR TIMI OR NIH stroke scale OR mRS OR modified ranking score OR modified ranking scale;
5. 1 AND 2 AND 3 AND 4.

## Study Records

The literature search results will be uploaded to EndNote X7, which will be shared by all authors of the review. This will enable a collaboration among reviewers during the process of study selection. Two reviewers (J. F. and R. L.) will independently screen and select studies for possible inclusion in the study in two phases. In the first phase, the titles and abstracts will be analysed. In the second phase, all possible relevant full texts will be analysed. Any disagreements will be resolved by discussion and a third reviewer (M. K.).

## Risk of bias in individual studies

Papers selected for the retrieval will be assessed by two independent reviewers (J. F. and S. O.) for methodological quality prior to inclusion in the review using standardised critical appraisal instruments from the JBI for example Checklist for Case Reports [38]. Any disagreements that arise between the reviewers will be resolved by discussion and a third reviewer (M. K.).

## Data collection process

The data will be extracted independently by the reviewers (J. F. and S. O.) from the papers included in the review using the data extraction tool based on the standardized Case Report Guidelines (CARE) Checklist [39]. The data extracted will include specific details about the interventions, populations, and outcomes of significance of the review objectives. Any disagreement will be resolved by discussion.

## Data items/dealing with missing data

Both generic and trade names of the intervention will be extracted. The efficacy and safety of ME after IVT will be studied, as well as patient characteristics (e. g., age, gender, given disease). The authors of the included studies will be contacted when necessary to gather relevant information.

## Outcomes and prioritisation

The primary outcome will be the evaluation of clinical efficacy:

1. stroke severity measured by standardised scales, e. g., by mRS at 90 days and 1 year;
2. stroke severity measured by standardised scales, e. g., by NIHSS at 24 h and 5 to 7 days or on discharge, if earlier;
3. recanalization assessed by standardised scales, e. g., by mTICI scale according to CTA.

The secondary outcomes will be the evaluation of safety:

1. symptomatic intracranial haemorrhage including subarachnoid bleeding associated with clinical symptoms, defined as parenchymal hematoma type 2 and clinical worsening by NIHSS 4 or more;
2. mortality at 90 days and 1 year;
3. surgical procedure related complications.

### Data synthesis

Based on the preliminary and initial searches, we anticipate that only case reports will be retrieved. We will perform a narrative synthesis of the findings from the included studies accompanied by descriptive statistics, which will be applied for the efficacy and safety for each included study, structured around the type of intervention, target population characteristics, type of outcomes and intervention content.

### Assessment of heterogeneity

If only case reports will be retrieved, clinical heterogeneity will be assessed by determining whether the studies are sufficiently similar to be narratively synthetized, based on the inclusion criteria.

### Subgroup analysis

Based on the preliminary and initial searches, we anticipate that only case reports will be retrieved; then the subgroup analysis will not be applicable.

### Meta-bias assessment

For reporting the potential reporting bias, we will use funnel plots if ≥ 10 studies are available.

### Confidence in cumulative evidence

Based on the results and quality of evidence, the tool known as 'Grading of Recommendation Assessment, Development and Evaluation' (GRADE) [40] will be used. The quality of evidence will be assessed across the domains of the risk of bias, consistency, directness, precision, and publication bias. The quality will be assessed as high (further research is very unlikely to change our confidence in the estimate of effect) or moderate (further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate) or low (further research is very likely to have an impact on our confidence in the estimate of effect and is likely to change the estimate) or very low (very uncertain about the estimate of effect).

### Ethical principles

The results will be disseminated by publishing in a peer-reviewed journal. Ethical assessment will not be needed; only existing sources of literature will be searched.

### Conflict of interest

The authors declare they have no potential conflicts of interest concerning drugs, products, or services used in the study.

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