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Endovascular Clot Retrieval for M2 Segment Middle Cerebral Artery Occlusion: a systematic review and meta-analysis.

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Key Words:

- Stroke, Ischaemic Stroke, Thrombectomy, Endovascular Clot Retrieval, M2 Segment, Middle Cerebral Artery, Distal Occlusions

Key Abbreviations:

- AIS: Acute Ischaemic Stroke
- ECR: Endovascular Clot Retrieval
- MCA: Middle Cerebral Artery
- ICA: Internal Carotid Artery
- LVO: Large Vessel Occlusion
- mRS: Modified Rankin Scale
- TICI: Treatment In Cerebral Ischemia
- sICH: Symptomatic Intracranial Haemorrhage
- NIHSS: National Institutes of Health Stroke Scale

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- ASPECTS: Alberta Stroke Program Early Computed Tomography Score

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Abstract

Introduction: Endovascular clot retrieval (ECR) is the standard of care for acute ischaemic stroke (AIS) due to large vessel occlusion (LVO). However, isolated occlusion of the M2 segment of the Middle Cerebral Artery (MCA) was underrepresented in the landmark trials. Given the potential treatment benefit associated with M2 MCA occlusions, we aimed to evaluate the outcome of patients undergoing ECR for M2 occlusion.

Methods: We conducted a systematic review and meta-analysis of the available literature that included patients with M2 MCA occlusions who underwent ECR. Successful reperfusion was defined as a treatment in cerebral ischemia (TICI) score of 2b-3. Good outcome was defined as a modified Rankin Scale (mRS) score $\leq$ 2. We also analysed complications such as post-procedure symptomatic intracranial haemorrhage (sICH) and mortality at 3 months.

Results: 15 studies including 1105 patients with isolated M2 occlusions were analysed. Successful reperfusion occurred in in 75.4% (95% CI 67.7-84.1%) of patients; good outcome was observed in 58.3% (95% CI 51.7-63.8% of patients. The rate of sICH was 5.1% (95% CI 4.2-8.3%), and 3-month mortality rate was 12.2% (95% CI 10.4-16.3%).

Conclusion: The outcomes of ECR treatment of M2 occlusions are favourable, with good safety profile. Comparison to medical management from large registries or randomized controlled trials is warranted.

Introduction

Stroke is a leading cause of adult morbidity and mortality in the developed world with an estimated incidence of 216 per 100,000.[15] It results in significant costs to the healthcare system, with stroke in Australia estimated to have cost $5 billion in 2012.[26]

Endovascular clot retrieval (ECR) is the standard of care for acute ischaemic stroke (AIS) due to large vessel occlusion (LVO) with recent trials demonstrating significant benefit over best medical therapy[1-8]. While data from these trials was predominantly drawn from internal carotid artery (ICA) and proximal middle cerebral artery M1 segment occlusions, the subsequent 'Highly Effective Reperfusion evaluated in Multiple Endovascular Stroke Trials' (HERMES) meta-analysis suggested benefit across multiple patient subgroups including those with an M2 segment occlusion.[18]

However, isolated occlusion of the MCA M2 segment has been underrepresented in these recent trials and therefore the treatment benefit in more distal occlusions (M2 segment and beyond) remains controversial. In the REVASCAT,[5] ESCAPE,[2] EXTEND-IA,[4] THRACE,[27] PISTE[28] and THERAPY[29] protocols, no more than 10 patients with an isolated M2 occlusion were treated with ECR. Similarly, the MR CLEAN protocol included less than 8% of patients with an isolated M2 occlusion,[1] and the SWIFT PRIME protocol excluded M2 occlusions entirely.[3] Furthermore, these trials did not specifically describe any functional outcomes for those patients with M2 occlusions. MCA M2 occlusions can be associated with significant morbidity and mortality.[15]

Current guidelines from the American Heart Association and American Stroke Association (AHA/ASA) state that endovascular therapy has class I level A (strong) evidence for LVO AIS, but only class II level C (reasonable) evidence for distal occlusions.[16]

The estimated incidence of M2 occlusions in the population is 7 per 100,000, with M2 segment strokes accounting for approximately 4.2% of all AIS.[15] Multiple studies and registries have attempted to explore outcomes in patients with M2 and M3 occlusions treated with ECR.[29-31] To date, no randomised control studies have been published for this M2/M3 subgroup, however, as described below, retrospective studies demonstrated efficacy of treatment with good recanalization rates and good patient outcomes comparable to many studies investigating ECR in more proximal occlusions.

The aim of this meta-analysis is to evaluate the outcomes of patients with an M2 occlusion treated with ECR.

Methods

Inclusion Criteria

In order to include the most relevant and comparable studies, the site of occlusion had to specify the M2 segment of the MCA, and tandem occlusions were excluded. The type of therapy used had to include ECR and functional outcomes had to be recorded. The studies had to include a minimum of 10 patients, with patients >18yo, and be written in English.

Outcomes

The outcomes included were: mRS (modified Rankin Scale) score at 3 months, TICI score (treatment in cerebral ischemia), post-procedural sICH (symptomatic intracranial haemorrhage) at 24hrs, and NIHSS (National Institutes of Health Stroke Scale) on discharge. A good outcome was classified as a mRS score of ≤ 2 at 3 months and successful reperfusion was classified as a TICI score of at least 2b-3.

Search Strategy and Study Selection

A comprehensive literature search was conducted using key terms in keeping with the PRISMA (Preferred Reporting items for Systematic Reviews and Meta- Analyses) guidelines. After duplicate studies were removed, studies that did not match our inclusion criteria were filtered out through their titles, abstracts and full texts. A literature review from the following databases was conducted on May 20th 2018 - EBM Reviews – Cochrane Register of Controlled Trials, EBM Reviews – Cochrane Database of Systematic Reviews, EBM Reviews – Cochrane Clinical Answers, EBM Reviews – Cochrane Methodology Register, Embase Classic+Embase, Ovid Medline Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid Medliner(R), Ovid Medline and Versions, EBM Reviews – ACP Journal Club, and EBM Reviews – Database of Abstracts of Reviews of Effects.

There were a total of 683 search results with a further 8 articles added from additional sources. 154 duplicate articles were removed, a further 272 articles were removed based on their title and another 201 articles were removed based on their abstracts. From the remaining 63, 23 were conference abstracts, a further 26 articles were removed based on their full texts. This left 15 articles for final analysis. (Figure 1).

Data extraction and critical appraisal

All data were extracted from article texts, tables and figures. Two investigators independently reviewed each retrieved article. Data from the selected studies that were extracted included the details and methods of the study, patient demographics (age and gender), medical comorbidities (hypertension, diabetes mellitus, hypercholesterolemia, atrial fibrillation, smoking, previous CVA/TIA, other cardiac history), side of occlusion, baseline Alberta Stroke Program Early Computed Tomography Score (ASPECTS), NIHSS on admission and discharge, initial imaging used, treatment windows, pre-procedure IV tPA use, timeline between 'last known normal' (LKN) and groin puncture, procedure time, thrombectomy device(s) used, and functional outcomes as described above. The final results were reviewed by senior investigators.

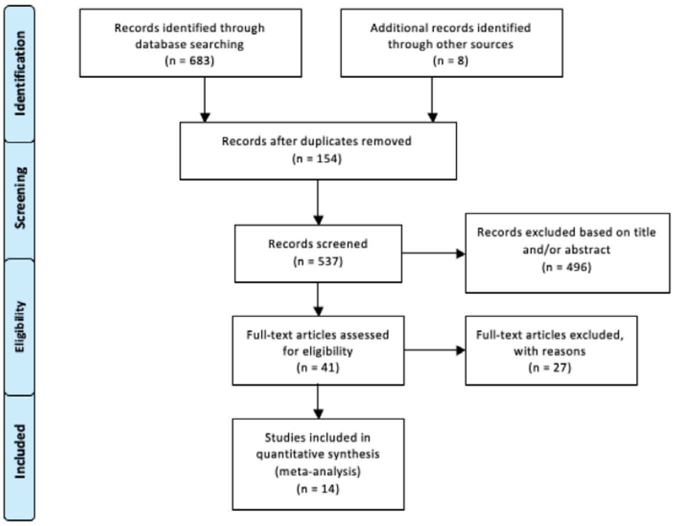

Figure 1. PRISMA Flow Diagram (Preferred Reporting items for Systematic Reviews and Meta-Analyses)

Statistical Analysis

A meta-analysis of proportions was conducted for the available main perioperative and postoperative variables. Firstly, to establish variance of raw proportions, a logit transformation was applied. To incorporate heterogeneity (anticipated among the included studies), transformed proportions were combined using DerSimonian-Laird random effects models. Finally the pooled estimates were back-transformed. Heterogeneity was evaluated using Cochran Q and I^2 test. Weighted means were calculated by determining the total number of events divided by total sample size. All analyses were performed using the metafor package for R version 3.01. P values <0.05 were considered statistically significant.

Results

Study Characteristics

A total of 15 articles were analysed, with each article's study type, location, study period, comparisons, and M2 definition recorded (table 1). There were 6 single centre studies and 9 multicentre studies, performed between 2004 and 2016. 13 of the study types were retrospective and 2 were prospective from a range of countries worldwide. Our search algorithm did not include a specific control group for this analysis. Four of the selected studies had no comparison group, six compared ECR between M2 segment occlusion to M1 and or ICA segment occlusions, two compared different methods of ECR, while three studies compared ECR to best medical management.

M2 Definition

There remains heterogeneity in the description of what constitutes the M2 segment in the available literature. Nine out of the fifteen studies selected defined the M2 segment (table 1). The most common definition of the M2 segment was the vertical portion of the MCA in the Sylvian fissure, extending from the genu to the apex of the circular sulcus. However, another common definition is to include any branches after the bifurcation at the M1 segment and define them as M2. Considering it is not uncommon for there to be an early bifurcation in some people, this may lead to a disparity during treatment decision making.

Patient Characteristics and Demographics

Baseline demographics of the 1105 patients (table 2) showed 47.4% were female, 58.9% presented with a left sided occlusion. The mean age was 67.6 years and the median age of 69.4 years, the NIHSS on admission of 14.5 and the ASPECTS score was 9.0. Pre-procedure IV-tPA was used in 52.6% of cases. The most common comorbidity was hypertension (71.5%). This was followed by atrial fibrillation (41%), hypercholesterolemia (36.7%) and diabetes mellitus (22.1%). A further 19.2% had other cardiac history and 14.9% had a history of CVA or TIA. 27% of the patients were smokers (table 3).

Treatment Characteristics

The average time from LKN to groin puncture was 4.1 hours, with an average time from groin puncture to reperfusion being 40.2 minutes and an overall average procedure time of 60.2 minutes. Pre-procedure IV tPA was used in 52.6% of cases (table 4). Seven of the studies defined a set treatment window ranging from 6 hours to 24 hours. All studies mentioned the type of clot retrieving device used.

Initial Imaging

All studies used at least non-contrast computed tomography (CT) of the brain as the initial form of imaging. This was usually followed up by either CT or magnetic resonance angiography (MRA) to assess angiographic status and further perfusion studies to investigate infarct volumes.

Clinical Outcomes

Table 5 and Figures 2 to 4 summarise the overall patient outcomes.

Good Clinical Outcomes (mRS)

The overall rate of a good clinical outcome (mRS ≤ 2 at 3 months) ranged between 40.7% and 80.5% and a mean good clinical outcome occurred in 58.3% of patients (95% CI 51.7 – 63.8%)

Successful Reperfusion (TICI)

Successful reperfusion (TICI ≥2b) was observed in 75.4% of patients (95% CI 67.7 – 84.1%) with a range of 44.3% to 93.3%.

Symptomatic ICH

Regarding adverse events, the rate of sICH was 5.1% (95% CI 4.2 – 8.3%)

Mortality

The 3-month mortality rate was 12.2% (95% CI 10.4 – 16.3%)

Discharge NIHSS

Only five studies recorded a discharge NIHSS, with a mean score of 6, significantly lower than the NIHSS of 14.5 on admission. Kim et al. recorded a NIHSS score at 7 days (2.0)[7] and Flores et al. recorded a NIHSS score at 24-36 hours (14.5).[9]

Comparing Devices

There are a number of techniques for ECR, with commonly described techniques being stent retrievers and variations of aspiration techniques. Two studies compared these techniques and the clinical outcomes from each one. Kim et al. showed no statistically significant technique-dependent differences in final TICI 2b-3 (p=0.441), 3 month mRS of 0-2 (p=0.689), sICH (p=1.00) or mortality (p=0.390).[7] There was however a statistically significant difference in median groin puncture to recanalization time, with stent retrievers shown to be quicker (38.5 mins versus 53 mins, p=0.045). Similarly, Mokin et al. showed no statistically significant difference in functional outcomes or complications between the two techniques.[11]

M1 versus M2

Of the 6 studies that directly compared M2 occlusions to M1 or ICA occlusions, none showed a statistically significant difference in patients' age, pre-procedure IV tPA rates, TICI score of 2b-3, 3 month mRS of 0-2, sICH or mortality.

Baseline comparisons of NIHSS between M1 and M2 occlusions showed mixed results. Coutinho et al. found a statistically significant lower baseline NIHSS score for M2 occlusions (13 for M2 vs. 17 for M1, P = <0.01), and higher baseline ASPECTS for M2 occlusions (9 for M2 vs. 8.2 for M1, P = 0.003), but no statistically significant differences in successful reperfusion, good functional outcomes, sICH, or mortality.[13] Salahuddin et al. also found a significantly lower admission NIHSS score in M2 occlusions (P = 0.017).[19] The other studies comparing M2 and M1 occlusions showed no significant difference in these parameters.

Protto et al. also found a significantly higher ASPECTS for M2 clots in non-contrast enhanced CT scans, mean transit time and cerebral blood volume studies (P = 0.04, <0.001, 0.005 respectively).[8] However, there were no significant differences in successful reperfusion, good functional outcomes, sICH, or mortality.

The only significant difference in comorbidities among the 6 studies comparing M1 and M2 clots was demonstrated by Sheth et al., with 25% of M1 occlusions having diabetes mellitus compared to 1% of M2 occlusions (P≤0.001).[24]

Table 1. Summary of Studies Selected for Inclusion

Study	Centres	Study Type	Location	Study Period	M2 Definition	Comparison
Park et al. 2016	Single	Retrospective	Korea	Jan 13 – Nov 14	NR	No comparison
Dorn et al. 2015	Single	Retrospective	Germany	Oct 11 – April 13	Portion starting at the Sylvian fissure after passage of the limen insulae	M2 vs. M1
Mokin et al. 2017	6	Retrospective	USA	Mar 12 – Mar 16	Vertical MCA branches in the Sylvian fissure originating at the genu and extending to the next genu at the level of the operculum	Stent retriever vs. Aspiration thrombectomy
Kim et al. 2016	Single	Retrospective	Korea	Jan 11 – Jun 15	Extending from the genu to the top of the Sylvian fissure and the circular sulcus	Stent retriever vs. FAST
Flores et al. 2014	Multiple	Retrospective	Spain	Jan 11 – Dec 12	NR	No comparison
Coutinho et al. 2016	3	Retrospective	USA, Europe	SWIFT, STAR, SWIFT PRIME 2010-2014	Vertical MCA branches in the Sylvian fissure originating at the genu and extending to the next genu at the level of the operculum	M2 vs. M1
Protto et al. 2016	Single	Retrospective	Finland	Jan 13 – Dec 14	NR	M2 vs. M1 vs. ICA
Sarraj et al. 2016	10	Retrospective	USA	Jan 12 – April 15	Vertical segment lying within the mesial margin of the Sylvian fissure	ECR vs. best medical management
Sheth et al. 2014	1	Retrospective	USA	Sep 2004 – Dec 2012	NR	M2 vs. M1 ECR
Shi et al. 2016	30	Retrospective	USA	Jan 2004 – Dec 2006	NR	M2 vs. M1 ECR
Bhogal et al. 2017	Single	Retrospective	Germany	Jan 2008 – Aug 2016	Vertical MCA branches in the Sylvian fissure originating at the genu and extending to the next genu at the level of the operculum	No comparison
Munich et al. 2015	Single	Retrospective	USA	Jan 2010 – May 2015	Beginning at the limen insulae, where the middle cerebral artery makes a superior turn, and ending at the apex of the circular sulcus	No comparison
Salahuddin et al. 2017	2	Retrospective	USA	Sep 2013 – Sep 2016	Beyond the bifurcation of the M1 artery and extending to the apex of the circular sulcus	M2 vs. M1 ECR
Tomsick et al. 2017	Multiple	Prospective	Global	Aug 2016 – April 2012	MCA segment beyond the posterior temporal or holotemporal branch	ECR vs. medical management
Goyal et al. 2016	5	Prospective	Global	2015	NR	ECR vs. medical management

NR, not reported; ECR, endovascular clot retrieval; FAST, forced arterial suction thrombectomy

Table 2. Summary of the Patient Demographics							
Study	**Patients**	**Gender (% female)**	**Mean Age**	**Median Age**	**Side of occlusion (% Left)**	**NIHSS Admission**	**ASPECTS**
Park et al. 2016	32	14 F, 18 M (43.8)	70.1	72.5	10 L, 22 R (31.3)	10.9	NR
Dorn et al. 2015	15	NR	68.1	NR	NR	13.7	NR
Mokin et al. 2017	117	50 F, 67 M (42.7)	67	NR	75 L, 42 R (64.1)	15	9
Kim et al. 2016	41	17 F, 24 M (41.5)	NR	72	26 L, 15 R (63.4)	13	NR
Flores et al. 2014	65	31 F, 34 M (47.7)	66	NR	45 L, 20 R (69.2)	16	NR
Coutinho et al. 2016	50	24 F, 26 M (48)	71	NR	27 L, 23 R (54)	13	9
Protto et al. 2016	22	7 F, 15 M (31.8)	69.8	NR	NR	14	10
Sarraj et al. 2016	288	144 F, 144 M (50)	66	68	NR	16	9
Sheth et al. 2014	52	28 F, 24 M (53.8)	NR	72	29 L, 23 R (55.8)	11	NR
Shi et al. 2016	28	19 F, 9 M (67.9)	NR	71.5	19 L, 9 R (67.9)	17	NR
Bhogal et al. 2017	106	48 F, 58 M (45.3)	68	NR	50 L, 56 R (47.2)	11.8	8.5
Munich et al. 2015	53	30 F, 23 M (56.6)	70.1	NR	37 L, 16 R (69.8)	16	NR
Salahuddin et al. 2017	59	21 F, 38 M (35.6)	69.6	NR	37 L, 22 R (62.7)	14	9
Tomsick et al. 2017	83	NR	66.7	NR	NR	NR	NR
Goyal et al. 2016	94	NR	NR	NR	NR	NR	NR
TOTAL	***1105***	***433 F, 480 M (47.4)***	***67.5***	***69.4***	***355L, 248 R (58.9)***	***Mean 14.5***	***Mean 9.0***

NR, not reported; NIHSS, National Institutes of Health Stroke Scale; ASPECTS, Alberta Stroke Program Early CT Score; L, Left, R; Right

Table 3. Summary of the Patient Comorbidities							
Study	**HTN (%)**	**DM (%)**	**Cholesterol (%)**	**AF (%)**	**Cardiac Hx (%)**	**Hx CVA/TIA (%)**	**Smoker (%)**
Park et al. 2016	16 (50)	4 (12.5)	5 (15.6)	3 (9.4)	3 (9.4)	5 (15.6)	6 (18.8)
Dorn et al. 2015	NR	NR	NR	NR	NR	NR	NR
Mokin et al. 2017	88 (75.2)	31 (26.5)	46 (39.3)	49 (41.9)	32 (27.4)	NR	45 (38.5)
Kim et al. 2016	26 (63.4)	8 (19.5)	13 (31.7)	27 (65.9)	4 (9.8)	5 (12.2)	10 (24.4)
Flores et al. 2014	43 (66.2)	NR	NR	23 (35.4)	NR	NR	NR
Coutinho et al. 2016	35 (70)	9 (18)	15 (30)	19 (38)	NR	6 (12)	7 (14)
Protto et al. 2016	9 (40.9)	4 (18.2)	NR	11 (50)	3 (13.6)	NR	NR
Sarraj et al. 2016	216 (75)	60 (20.8)	120 (41.7)	103 (35.8)	NR	NR	66 (22.9)
Sheth et al. 2014	32 (61.5)	1 (1.9)	12 (23.1)	23 (44.2)	NR	10 (19.2)	NR
Shi et al. 2016	22 (78.6)	7 (25)	10 (35.7)	16 (57.1)	6 (21.4)	NR	3 (10.7)
Bhogal et al. 2017	75 (70.7)	31 (29.2)	29 (27.3)	54 (50.9)	NR	NR	21 (19.8)
Munich et al. 2015	41 (78.8)	NR	14 (26.5)	23 (44.2)	NR	NR	36 (67.3)
Salahuddin et al. 2017	44 (74.6)	19 (32.2)	39 (66.1)	24 (40.7)	NR	NR	15 (25.4)
Tomsick et al. 2017	65 (78.3)	20 (24.1)	NR	33 (39.8)	14 (16.9)	NR	NR
Goyal et al. 2016	NR	NR	NR	NR	NR	NR	NR
TOTAL	***712/996 (71.5)***	***194/878 (22.1)***	***303/826 (36.7)***	***408/995 (41.0)***	***62/323 (19.2)***	***26/175 (14.9)***	***209/774 (27)***

NR, not reported; HTN, Hypertension; DM, Diabetes Mellitus; AF, Atrial Fibrillation; CVA, Cerebrovascular Accident; TIA, Transient Ischaemic Attack

Table 4. Summary of the Procedure Details

Study	Tx Window	Initial Imaging	IV tPA (%)	Sx to groin puncture (hrs)	Groin puncture to reperfusion (mins)	Procedure Time (mins)	Device Used
Park et al. 2016	8 hrs	CT or MRI	28 (87.5)	3.9	NR	33.2	Aspiration (MAT)
Dorn et al. 2015	NR	NR	7 (46.7)	3.3	49.3	NR	Stent Retriever
Mokin et al. 2017	24 hrs	CT or MRI	52 (44.4)	4.0	NR	43	Stent Retriever, Direct Aspiration, balloon guided catheter
Kim et al. 2016	8 hrs	CT or MRI	20 (48.8)	4.0	45	NR	Stent Retriever, forced arterial suction thrombectomy
Flores et al. 2014	NR	NR	35 (53.8)	4.8	NR	NR	Stent Retriever
Coutinho et al. 2016	Swiftprime 8 hrs Star/Swift 6 hrs	CT or MRI	36 (72)	NR	29	NR	Stent Retriever
Protto et al. 2016	NR	CT	9 (40.9)	3.0	NR	32	Stent Retriever
Sarraj et al. 2016	8 hrs	CT	172 (59.7)	4.5	41	NR	Stent Retriever, Aspiration
Sheth et al. 2014	NR	CT or MRI	31 (59.6)	2.5	NR	NR	IA tPA, MERCI, Angioplasty, Soltaire, Penumbra
Shi et al. 2016	8 hrs	CT or MRI	14 (50)	4.7	NR	90	Merci clot retriever
Bhogal et al. 2017	NR	CT or MRI	23 (21.7)	4.9	NR	103	Stent Retriever
Munich et al. 2015	NR	CT or MRI	20 (38.5)	NR	NR	NR	Angioplasty, MERCI, ADAPT, Penumbra Aspiration, Retrievable stent
Salahuddin et al. 2017	6 hrs	CT	32 (54.2)	3.9	NR	30	Trevo or Solitaire
Tomsick et al. 2017	NR	CT	83 (100)	3.5	NR	NR	Microcatheter thrombolysis, MERCI, Solitaire, Penumbra
Goyal et al. 2016	NR	NR	NR	NR	NR	NR	Stent Retriever, aspiration techniques
TOTAL			***562/1011 (52.6)***	**4.1**	**40.2**	**60.2**	

NR, not reported; MAT, Manual Aspiration Thrombectomy; MERCI, Mechanical Embolus Removal in Cerebral Ischemia; ADAPT, A Direct Aspiration First Pass Technique; tPA, tissue plasminogen activator; CT, Computed Tomography; MRI, Magnetic Resonance Imaging

Table 5. Summary of the Outcomes Following ECR

Study	Final recanalization of TICI ≥2b (%)	Final recanalization of TICI = 3 (%)	NIHSS on Discharge	sICH (%)	Vessel Perforation/ Dissection	mRS ≤ 2 at 3 months (%)	Mortality at 3 months (%)
Park et al. 2016	27 (84)	15 (47)	4.3	0	NR	25 (78)	1 (3.1)
Dorn et al. 2015	14 (93.3)	NR	7.4	1 (6.7)	NR	9 (60)	1 (6.7)
Mokin et al. 2017	99 (85)	64 (55)	NR	NR	4 (3 perforations, 1 dissection)	65 (56)	18 (15.4)
Kim et al. 2016	36 (87.8)	NR	NR (2 at 7 days)	1 (2.4)	NR	33 (80.5)	1 (2.4)
Flores et al. 2014	46 (78.5)	NR	NR (14.5 24-36h)	6 (9)	1 (dissection)	39 (60)	9 (13.8)
Coutinho et al. 2016	34 (68)	NR	NR	1 (12)	NR	30 (60)	6 (12)
Protto et al. 2016	17 (77.3)	NR	NR	4 (18.2)	NR	11 (50)	3 (13.6)
Sarraj et al. 2016	225 (78)	NR	NR	16 (5.6)	NR	181 (62.8)	NR
Sheth et al. 2014	23 (44.2)	NR	NR	NR	NR	NR	NR
Shi et al. 2016	23 (82.1)	NR	NR	1 (3.6)	NR	11 (40.7)	7 (25.9)
Bhogal et al. 2017	96 (90.5)	73 (68.9)	7.2	5 (4.7)	NR	58 (54.6)	15 (14.1)
Munich et al. 2015	40 (76.9)	18 (34.6)	5.5	0	1 (perforation)	NR	3 (5.7)
Salahuddin et al. 2017	50 (84.7)	NR	5	2 (3.7)	0	33 (59)	8 (13.6)
Tomsick et al. 2017	32 (40.5)	NR	NR	6 (7.2)	1 (perforation)	34 (41)	10 (12)
Goyal et al. 2016	NR	NR	NR	NR	NR	NR	NR
TOTAL	***762/1011 (75.4)***	***170/308 (55.2)***	***6.0***	***43/838 (5.1)***	***7***	***529/907(58.3)***	***82/673 (12.2)***

NR, not reported; TICI, Thrombolysis in Cerebral Infarction; NIHSS, National Institutes of Health Stroke Scale; sICH, symptomatic Intracranial Haemorrhage; mRS, modified Rankin Score

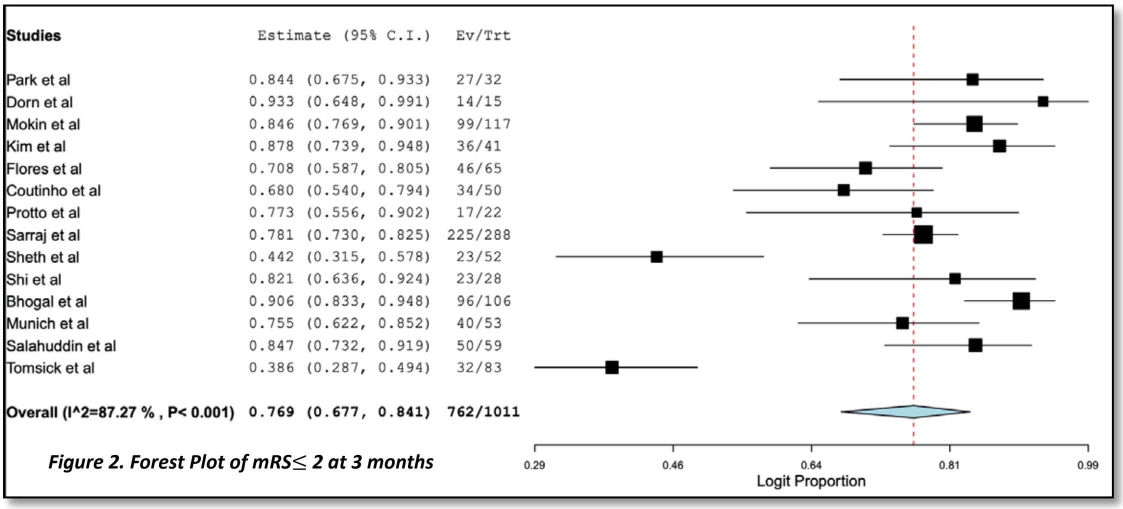

Figure 2. Forest Plot of mRS≤ 2 at 3 months

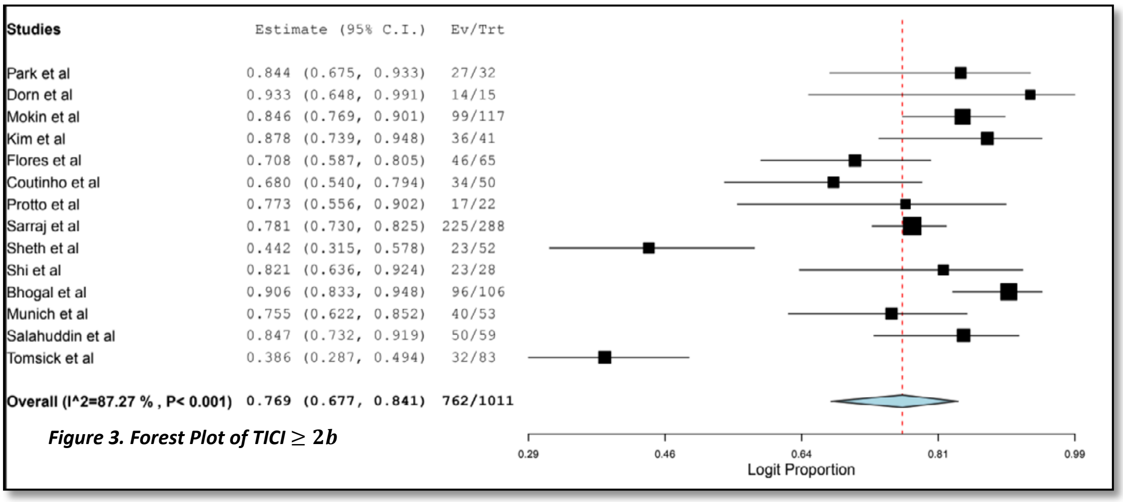

Figure 3. Forest Plot of TICI ≥ 2b

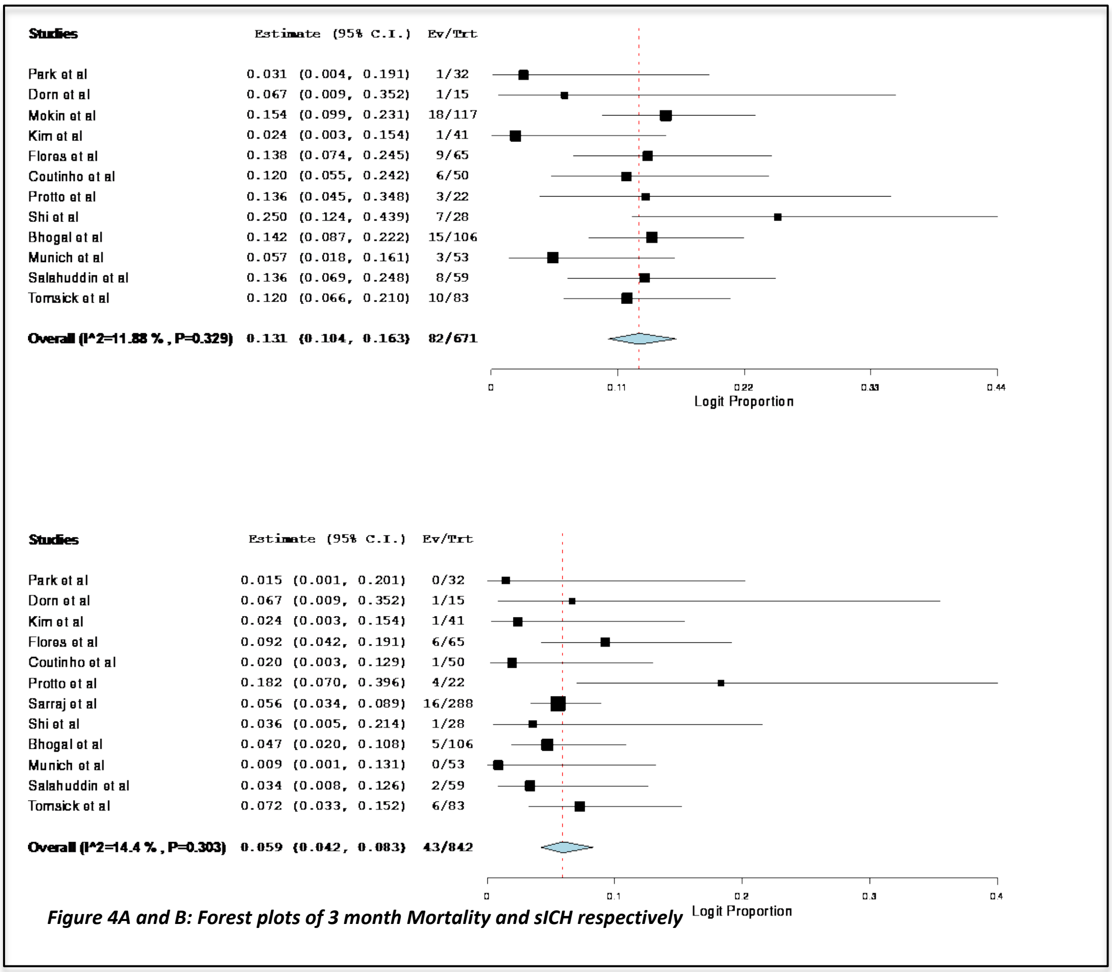

Figure 4A and B: Forest plots of 3 month Mortality and sICH respectively

Discussion

Endovascular clot retrieval of clots in the M2 segment of the middle cerebral artery has shown to have positive outcomes with limited adverse events compared to best medical management and these results are comparable to ECR for large vessel occlusions.

The current evidence for ECR of M2 occlusions is limited and the majority of evidence available is for large vessel occlusions. The release of 8 large clinical trials along with a subsequent meta-analysis has changed clinical practice for AIS therapy, with ECR now widely accepted as the standard of care for LVO demonstrating both improved clinical outcomes and reduced mortality compared to best medical therapy.[18]

There has been an increase in interest regarding occlusions of the M2 segment given the lack of strong evidence in previous trials and the potential for high morbidity and mortality. The natural history of M2 occlusions has been described in Rai et al., who found 56% of patients with M2 occlusions had poor clinical outcomes and a mortality rate of 27%.[15] Similarly, Lima et al. showed 46% of patients had poor clinical outcomes and a mortality rate of 21%, and a 6-month mortality similar to patients with M1 occlusions.[17]

Currently available ECR evidence derives from retrospective analyses predominantly, sample sizes varying from 15 to 288 patients, with limited generalizability to clinical practice. To date, there are no published randomized control studies evaluating ECR for isolated M2 occlusions in comparison to IV-tPA or best medical management.

With the M2 segment being more distal, the volume of tissue at risk is conceptually smaller than an occlusion of a more proximal branch. As a result, there may be a reduced benefit or less significant improvement in functional status of EVT for M2 occlusions compared to M1 segment occlusions. However, small distal M2 occlusions involving the eloquent cortex may cause significant neurological impairment, and these patients may benefit from reperfusion therapy.

Furthermore, M2 segment branches have been shown to have thinner vessel walls and a narrower lumen, making the procedure technically more difficult and the vessel wall more prone to damage, increasing the risk of complications and early re-occlusion.[8] Smaller and newer aspiration and stent retriever devices are making more distal retrieval procedures technically feasible and safer, necessitating re-evaluation of the latest available evidence.

Outcomes

The outcomes of our analysis compare well to a successful reperfusion rate of 71% and a good functional outcome of 46% in the thrombectomy group of the HERMES collaboration.[18] Furthermore, amongst the 6 studies comparing outcomes between M1 and M2 occlusions, there were no statistically significant differences in good functional outcomes, successful reperfusion, symptomatic ICH, discharge NIHSS or mortality, again suggesting comparable benefits of ECR for distal occlusions as well.

The haemorrhagic complications from ECR therapy were commented on in all the studies. The rates of these complications are important factors to consider when deciding a patient's suitability for ECR. Haemorrhages include subdural, subarachnoid, intracerebral, and intraventricular bleeds. Post procedural haemorrhages often occur secondary to pathophysiological bleeding from damaged reperfused vessels,[32] but also occur from vascular injury due to distal wire access. With distal M2 branches tortuosity leads to a theoretical increased risk of vessel perforation and dissection.[19] Five studies commented on findings of vessel perforation and/or dissection in their results of complications,[9,11,19,33,34] with 5 patients experiencing a vessel perforation and a further 2 experiencing a vessel dissection. The remaining studies failed to specifically comment on the aetiology of post procedural haemorrhage. Some haemorrhages do not compromise a patient's neurological function or prognosis and therefore our particular focus was on the rate of symptomatic ICH. A change in NIHSS by ≥ 4 points is largely considered an indicator of neurological deterioration.[32] The Heidelberg Bleeding Classification is a modern classification system of bleeding after reperfusion in ischaemic strokes that can assist clinicians determine the type and significance of post procedure ICH.[32] 12 of the 15 studies in our analysis defined sICH using varying well known classification systems to comment on the types of post-procedural haemorrhages that they observed.

ECR vs. medical management

Sarraj et al., who compared ECR with best medical management, found that patients managed with ECR were younger (68 vs. 73 years, P = 0.003) and received IV tPA less frequently (59.7% vs. 74.4% P = 0.001). Patients managed with ECR had significantly better 90-day clinical outcomes (62.8% vs. 35.4%, P = 0.001) and although the ECR group did show higher frequency of sICH (5.6% vs. 2.1%), this was not statistically significant (P = 0.10). Both groups had comparable baseline characteristics such as gender, comorbidities, ASPECTS and NIHSS score. Interestingly, the improved clinical and functional outcomes among the ECR group were despite the medically managed group having a statistically significant shorter LKN time to arrival in ED (158 mins vs. 86 mins P = 0.001).[10]

Time Factors

A critical factor in determining the best management for patients presenting with AIS is the time since LKN and the time from presentation to groin puncture. In a hospital setting, the ability to transfer patients to the angiography suite in a timely manner is crucial. Previous guidelines regarding timelines for ECR therapy suggest Class 1A evidence when performed within 6 hours of symptom onset.[16] However, two recent randomised trials (DAWN and DEFUSE 3) demonstrated powerful benefits for treatment beyond 6 hours,[22,23] with the updated guidelines now supporting Class 1A evidence for ECR up to 16 hours, and Class 2a evidence between 16 and 24 hours. Mokin et al., who directly compared patients presenting within 6 hours and beyond 6 hours, showed no statistically significant difference in favourable clinical outcome (55% vs. 60%, P= 0.69) between the two groups.[11]

None of the six studies comparing M2 and M1 or ICA occlusions showed a statistically significant difference in the time from LKN to groin puncture or time to recanalization, suggesting that although ECR for M2 occlusions may be technically more difficult, procedure times were comparable to M1 occlusions.[8,12,13,14,19,24]

Kim et al., who compared different thrombectomy devices, did show a statistically significant difference in time from LKN to reperfusion between stent retriever and aspiration techniques.[7] However, this did not translate to a statistically significant difference in functional outcomes or adverse events. This difference in time was not seen in another trial comparing the two techniques,[11] and therefore may reflect operator preference and familiarity with the selected device.

Radiographic Imaging

None of the selected studies directly commented on the time taken to perform appropriate imaging for patients and the delay that this caused in reaching the angiography suite. One study that looked into impact of comprehensive CT scan protocols on diagnosis and treatment of AIS demonstrated that although comprehensive CT protocols increased examination time, including CT angiography and CT perfusion, they did not impact overall treatment initiation.[21]

Limitations

There are several limitations to our analysis. This meta-analysis was primarily limited to a small number of retrospective studies, with very limited number of prospective studies available containing data on clinical outcomes. Furthermore, some of the studies did not report on all the key data that was being extracted for the purposes of this review. There was also significant heterogeneity amongst some of the clinical outcomes between the studies; this could be due to the differences in sample sizes, the differing thrombectomy techniques used, clinician experience, and the time periods of the studies with the use of more modern devices in recent studies. Furthermore the anatomical definition of the M2 segment varied between the studies, with some studies not defining the segment at all. Four of the studies had no control group to compare functional outcomes with. Finally, we could not account for any selection bias within each individual study.

Conclusion

Based on the current limited evidence and small sample sizes available, endovascular clot retrieval therapies in the treatment of M2 segment AIS can be considered in eligible patients. The outcomes of ECR treatment of M2 occlusions are favourable, with good safety profile. Comparison to medical management from large registries or randomized controlled trials is warranted to confirm evidence for improved outcomes.

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