REVIEW ARTICLE



Endovascular thrombectomy for ischemic stroke with large infarct, short- and long-term outcomes: a meta-analysis of 6 randomised control trials

Ali Mortezaei¹ · Mahmoud M. Morsy² · Bardia Hajikarimloo³ · Ahmed Y. Azzam² · Adam A. Dmytriw^{4,5} · Osman Elamin⁶ · Mohammed A. Azab⁷ · Zuha Hasan⁸ · Redi Rahmani⁹

Received: 2 March 2024 / Accepted: 3 June 2024 © Fondazione Società Italiana di Neurologia 2024, corrected publication 2024

Abstract

Endovascular Thrombectomy (EVT) as first-line treatment of patients with large core ischemic infarct is a subject of debate. A systematic literature search was conducted in four electronic databases for randomized control trials (RCTs) comparing EVT to best medical treatment (BMT) for large core infarcts (ASPECTS \leq 5). Relevant studies were added after screening for titles, abstracts, and complete text. Meta-analysis was performed. The continuous outcomes were analyzed using the standardized mean difference (SMD) and 95% CI, while the binary outcomes were analyzed using the risk ratio (RR) and 95% confidence interval (CI). A funnel plot was used to visually evaluate publication bias, and if feasible, Egger's test was used to validate. We included 1918 patients from six RCTs that compared EVT plus BMT and BMT alone in patients with large core infarct due to large vessel occlusion in the anterior circulation. There were 946 patients in the EVT group and 972 patients in the BMT group. The one-year outcomes are available for 314 patients in the EVT group and 292 patents in the BMT group from two RCTs. EVT group had statistically significant higher rate of 90-day mRS 0-1 (RR=3.1, P-value < 0.0001), mRS 0-2 (RR = 2.64, P-value < 0.0001), mRS 0-3 (RR = 1.80, P-value < 0.0001), lower 90-day mean mRS score (SMD = -0.29, *P*-value < 0.0001), lower 90-day mortality rate (RR = 0.85, *P*-value = 0.015), and greater early neurological improvement (RR=2.16, P-value < 0.00001) compared to the BMT group. However, the rates of symptomatic intracerebral hemorrhage (sICH) (RR = 1.76, P-value = 0.01) and any ICH (RR = 2.18, P-value < 0.00001) were higher in EVT group. Our finding showed that EVT plus BMT led to in an absolute improvement of 5%, 12%, and 16% in 90-day mRS 0-1, 0-2, and 0-3, respectively. In addition, patients in EVT plus BMT group had a 3% increased probability of experiencing sICH and were 32% more susceptible to any ICH. Moreover, the one-year mRS 0–2 (RR = 2.16, P-value < 0.00001) and mRS 0–3 (RR = 1.80, *P*-value < 0.0001) was significantly favor the EVT plus BMT over BMT alone. Although, the one-year mortality rate was not significantly differed between two groups (RR = 0.91, *P*-value = 0.31). There was no statistically significant difference observed between the EVT plus BMT group and the BMT group concerning new stroke, decompressive craniectomy, and serious adverse events. Combined data from six RCTs shows that EVT plus BMT provides significantly better short- and longterm functional outcomes with minimal increase in symptomatic hemorrhage over BMT in patient with large core infarcts.

Keywords Endovascular thrombectomy · Large core stroke · Low ASPECTS

Introduction

Endovascular thrombectomy (EVT) plus best medical treatment (BMT) has been considered as a therapeutic option in individuals with acute ischemic stroke (AIS) with large vessel occlusion and is associated with more favorable outcomes compared to BMT alone [1, 2]. EVT is indicated in patient presentation within six hours of stroke onset and a National Institutes of Health Stroke Scale score (NIHSS) and an Alberta Stroke Program Early CT Score (ASPECTS) of ≥ 6 [2–4]. Therefore, the mentioned criteria indicate that EVT should only performed in small to medium-sized infarcts [4].

Nevertheless, previous exclusion criteria for EVT are actively being challenged with the expansion of

Ali Mortezaei and Mahmoud M. Morsy contributed equally to this work.

Extended author information available on the last page of the article

indications. First, the time window was expanded from 6 to 24 h for patients fulfilling advanced imaging criteria [3]. Several ongoing RCTs are evaluating the potential of EVT for patients with distal occlusions (DISTALS: NCT06034847) and low NIHSS (MOSTE: NCT03796468 and ENDO-LOW: NCT04167525). The next boundary is the interventional treatment of patients with large infarcts (ASPECTS of < 6). Application of EVT is generally avoided in the setting of large-core infarcts due to concern of symptomatic intracranial hemorrhage (sICH) will minimally benefit. According to the presence of limited data in the literature, the feasibility and efficacy of EVT in these patients remains unclear [1, 4]. Several recent randomized control trials (RCTs) have investigated the feasibility and safety of EVT plus BMT in large-core ischemic infarcts [4–8]. These studies demonstrated that EVT plus BMT was associated with favorable outcomes and was superior to BMT alone in the management of patients presenting with large-core ischemic infarcts [4–8].

Due to this underrepresented application of EVT in the management of large-core ischemic infarcts and questions of generalizability, we performed a systematic review and meta-analysis of high-quality RCTs to assess the effectiveness and practicability of EVT plus BMT versus BMT alone in patients with large-core ischemic infarcts.

Methods

Methodology and inclusion criteria

We performed a PRISMA guided literature search up to February 2024. A comprehensive search of all peerreviewed articles and abstracts was conducted using PubMed/Medline, Google Scholar, Web of Science, and Scopus for RCTs comparing EVT and BMT in patients with large core ischemic infarct (low ASPECTS). The MeSH phrases "Large core", "Acute Ischemic Stroke", "Cerebrovascular Accident", "Endovascular Thrombectomy", and "Randomized Controlled Trial" were used in conjunction.

Two investigators (AM and BHK) separately evaluated the title and abstracts of articles and one investigator (AA) assessed the full-text of articles that were considered to be eligible. One investigator (BHK) performed manual collection of the required data. The extraction of variables was focused on presenting symptoms and patient characteristics (age, gender proportion, and past medical history), and outcomes (90-day Mortality, Functional Outcome, sICH, Any ICH, Decompressive Craniectomy, Serious Adverse Event, and New Stroke).

Statistical analysis

We performed a meta-analysis of EVT compared to BMT. Binary outcomes were analyzed and reported through the risk ratio (RR) and 95% confidence interval (CI). The heterogeneity of results among the included studies was examined using Cochrane's Q-test and the I2 statistic. The common-effects (fixed-effect) model was used for outcomes without significant heterogeneity, while the random-effects model was used for outcomes with significant heterogeneity. Heterogeneity was assessed through visual inspection of the forest plots and measured using the I2 and chi-square (χ^2) tests. The χ^2 test was employed to determine the presence of significant heterogeneity, while the I2 test was utilized to quantify the magnitude of heterogeneity, if present. The interpretation of the I2 test followed the recommendations provided by the Cochrane Handbook (Part 2, Chapter 9). For testing statistical heterogeneity, a significance level (α) below 0.1 was considered indicative of significant heterogeneity, as recommended by the Cochrane Handbook. Publication bias was visually assessed with a funnel plot and confirmed by Egger's test if possible. All p-values were two-sided, and a p-value < 0.05 was considered statistically significant. Also, statistical significance was assessed in alliance with confidence interval range. The analysis was conducted using RevMan Software.

Results

Literature review the and risk of bias assessment

182 studies were found in our systematic search; duplicates were eliminated, leaving 98 studies. Six studies qualified for full-text screening after passing the title and abstract screening. Six papers were included in final examination and qualified for quantitative synthesis following a thorough evaluation. Additionally, no additional publications were included after a manual check of the listed studies' referenced sources. The research selection process flowchart is displayed in PRISMA flow diagram in Fig. 1 (Table 1).

Study characteristics

We included 1918 patients from 6 RCTs that compared EVT plus BMT and BMT alone among patients with large core ischemic infarct. There were 946 patients in EVT group and 972 patients in BMT group. The summary of demographic and clinical characteristics of included

Table 1 Included random	vized con	trolled trials chai	racteristi	ics										
Study	Year	Country	Period	l of recruitment	1	ntervention	No. of patie	ints Age		No of Fen	iale No of Pre ischemic	vious O stroke lc	cclusio	u
								Mean	SD		(TOTAL)	N	11 N	12
ANGEL-ASPECT	2023	China	Octob	er 2020-May 2022	E	TV	231	67.3	8.95	95	37(230)	1,	45 2	Ι.
					B	IMT	255	66.3	10.44	81	36(225)	1,	42 2	
SELECT2	2023	International	Septer	nber 2019-Septmber	r 2022 E	JVT	178	66.3	12.7	71	18(174)	8	8 7	
					B	IMT	174	66.6	12.7	74	13(162)	6	1 8	
RESCUE-Japan LIMIT	2022	Japan	Noven	aber 2018-Septembe	зт 2021 Е	TV.	101	76.6	10	46	25(94)	<i>'</i> L	4 0	_
					B	IMT	102	75.7	10.2	4	23(94)	7) 3	
LASTE	2024	International	Januar	y 2019 - February 20.	124 E	JVT	159	ı	ı	LL	ı		ľ	
					B	MT	165	ı	ı	LL	ı		ı	
TESLA	2023	United States	July 2(019-October 2022	Е	'VT	152	ı	ı	76	ı		'	
					В	IMT	148	·	ı	64	ı		1	
TENSION	2023	International	July 2(018-Feburary 2023	Е	'VT	125	73	12	56	11 (115)	8	3 0	_
					В	MT	128	72.6	11.9	67	18 (118)	×	8	
Study	Occ	lusion location			No of Intra thrombolys	wenous sis (IV tPA)	NIHSS sc hospital ar	ore at rrival	ASPECT: baseline	S value on	Infarction volun	ne (mL)		
	MC	A+ACA I	CA	Tandem lesion			Mean	SD	Mean	SD	Mean		SD	I
ANGEL-ASPECT	NA	∞	33	NA	66		16.3	5.22	3.33	0.74	140 < 70 ml and	lm 07 < 09 l	NA	
	NA	8	31	NA	63		15.3	5.22	3.33	0.74	129 < 70 ml and	l 96 > 70 ml	NA	
SELECT2	NA	7	19	55	37		19	5.9	4	1.4	86.6		43.3	3
	NA	9	53	41	30		18.6	5.2	4.3	0.7	85.1		35.]	-
RESCUE-Japan LIMIT	NA	4	17	20	27		22	9	3.3	0.7	104		64.(9
	NA	4	61	20	29		21.6	6.7	3.6	0.7	108		49.6	9
LASTE	ı	I					ı	ı	ı				ı	
	ı	I					I		1				·	
TESLA	ı	I		I	31		ı	ı	ı	ı	I		ī	
	ı	I		I	30		ı	ı	ı	ı	I		ī	
TENSION	1	4	11	8	49		19	4.5			205.8		139	.1
	-	3	37	7	44		18.3	5.2			227.7		107	2

Table 2Demographic andclinical summary of includedstudies

Variable	EVT plus BMT group $(n=946)$	BMT group $(n=972)$
Patient age, mean (SD), y	69.6 (22.0)	69.1 (22.7)
Females, % (n/All)	268/635 (44.1%)	266/659 (40.3%)
Previous ischemic stroke, % (n/All)	91/613 (14.7%)	90/599 (15%)
IV tPA usage, % (n/All)	265/946 (28%)	254/972 (26.1%)
ASPECTS score at admission, mean (SD)	3.6 (1.7)	3.7 (1.2)
NIHSS at admission, mean (SD)	18.5 (10.9)	17.7 (11.2)
Anesthesia, % (n/All)		
General	242/530 (45.7%)	NA
Conscious Sedation	180/530 (34%)	NA
Local	107/230 (46.5%)	NA
Vessel occlusion location		
M1	390/630 (61.9%)	391/617 (63.3%)
M2	9/630 (1.4%)	14/617 (22.7%)
MCA + ACA	1/125 (0.8%)	1/128 (0.8%)
ICA	250/630 (39.7%)	230/617 (37.3%)
Tandem lesion	83/400 (20.8%)	63/392 (16%)
mRS score at 90 days, % (n/All)		
0	13/669 (2%)	1/696 (0.1%)
1	36/669 (5.4%)	16/696 (2.3%)
2	88/669 (13.2%)	36/696 (8.8%)
3	128/669 (19.1%)	87/696 (12.5%)
4	135/669 (20.2%)	151/696 (21.7%)
5	77/669 (11.5%)	135/696 (19.4%)
Vascular injury, % (n/All)		
Arterial dissection	15/509 (2.9%)	NA
Arterial perforation	15/509 (2.9%)	NA
Vasospasm requiring treatment	13/408 (3.1%)	NA
Pseudoaneurysm	1/101(1%)	NA
Embolization in new territory	11/331 (3.3%)	NA
Other	2/178 (1.1%)	NA
Type of thrombectomy technique		
ADAPT	71/634 (11.1%)	NA
Stent retriever	251/634 (39.6%)	NA
Both	206/634 (32.4%)	NA

ASPECTS Alberta stroke program early CT score; *NIHSS* National Institutes of Health Stroke Scale; *mRS* modified Rankin Score; *IV-tPA* Intravenous tissue-type plasminogen activator; *ADAPT* A direct aspiration first pass technique; *MCA* Middle cerebral artery; *ICA* Internal carotid artery; *ACA* Anterior cerebral artery

patients are shown in (Table 2). The middle cerebral artery was the most prevalent artery in both groups. A majority of patients in EVT group underwent local anesthesia. Successful revascularization was achieved in 82% (519/633) of patients and stent retriever was the most common technique employed in the EVT group. The rate of procedure-related vascular injury was 11.2% (57/509). Distal embolization occurred in 7.6% (27/355) and 15.6% (20/128) of patients in the EVT group and BMT group, respectively. The incidence of arterial access-site complications was 2.8% (5/178). Some data on demographic for

LASTE and TESLA were missed as these were abstract presentations only.

Short-term functional outcomes

90-day mRS 0-1

The proportion of patients with mRS 0–1 at three months was statistically significant higher in the EVT group versus the BMT group [7.6% (59/776) vs 2.4% (19/771),



Fig. 1 PRISMA study selection flow chart

(RR = 3.1, 95% CI (1.86—5.13), *P*-value < 0.0001)], Fig. 2A. No statistically significant heterogeneity was found so the Fixed effect model was implicated ($I^2 = 0\%$, *P*-value = 0.87). The funnel plot of the outcome is attached on Supplementary Fig. 2A.

90-day mRS 0-2

The incidence of patients with mRS 0–2 at three months was statistically significant greater in the EVT group versus the BMT group [19.3% (180/931) vs 7.3% (68/922), (RR = 2.64, 95% CI (2.03–3.43), *P*-value < 0.0001)], Fig. 2B. No statistically significant heterogeneity was found so the Fixed effect model was implicated (I^2 =0.1%, *P*-value=0.41). The funnel plot of the outcome is attached on Supplementary Fig. 2B.

90-day mRS 0-3

The proportion of patients with 90-day mRS 0–3 was significantly higher in the EVT group versus the BMT group [36.4% (343/942) vs 20% (188/935), (RR = 1.80, 95% CI (1.55-2.1), *P*-value < 0.0001)], Fig. 2C. No statistically significant heterogeneity was found so the Fixed effect

model was implicated ($I^2 = 35\%$, *P*-value = 0.19). The funnel plot of the outcome is attached on Supplementary Fig. 2C.

Mean mRS score at three months

The mean mRS score at three months was significantly higher in the EVT group compared to the BMT group [4.3 (2.2) vs 5.3 (1.4), (SMD = -0.29, 95% CI (-0.4—-0.17), *P*-value < 0.0001)], Fig. 2D. No statistically significant heterogeneity was found so the Fixed effect model was implicated (I²=33%, *P*-value = 0.22).

Early neurological improvement

Early neurological improvement was defined as a reduction of ≥ 4 points in the NIHSS score from baseline to 24 h after presentation. The incidence was significantly higher in EVT group compared to the BMT group [21.4% (90/420) vs 10% (41/414), (RR = 2.16, 95% CI (1.54–3.04), *P*-value < 0.00001)], Fig. 2E. No statistically significant heterogeneity was found so the Fixed effect model was implicated (I² = 32%, *P*-value = 0.23). The funnel plot of the outcome is attached on Supplementary Fig. 2D.

90-day mortality

Long-term functional outcomes

The 90-day mortality was statistically significantly lower in EVT group versus BMT group [31% (295/938) vs 37% (343/933), (RR = 0.85, 95% CI (0.81–1.07), *P*-value = 0.015)], Fig. 2F. No statistically significant heterogeneity was found so the Fixed effect model was implicated ($I^2 = 44.6\%$, *P*-value = 0.1). The funnel plot of the outcome is attached on Supplementary Fig. 2E.

One-year mRS 0-2

The proportion of patients with mRS 0–2 was significantly higher in the EVT group versus the BMT group [22.9% (72/314) vs 5.8% (17/292), (RR=3.94, 95% CI (1.55—2.8), *P*-value < 0.0001)]. No statistically significant heterogeneity was found so the Fixed effect model was implicated (I^2 =0%, *P*-value=0.85).

A	Forest	Plot fo	or 90	-day	mRS	0-1.	
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Study	Events	Total	Events	Total	Weight	MH, Fixed, 95%	CI	М	H, Fixed	l, 95%	CI
ANGEL-ASPECT	26	219	8	222	41.8%	3.29 [1.53; 7.1	2]				
SELECT2	11	177	3	171	16.1%	3.54 [1.01; 12.4	18]				
RESCUE-Japan LIMIT	5	94	3	94	15.8%	1.67 [0.41; 6.7	'8 <u>]</u>			-	
LASTE	7	159	3	165	15.5%	2.42 [0.64; 9.2	20]		_		
TENSION	10	127	2	119	10.9%	4.69 [1.05; 20.9	94]				-
Total (95% CI) Heterogeneity: $Tau^2 = 0$:	Chi ² = 1 3	776	4 (P = 0	771 87): 1 ²	100.0%	3.09 [1.86; 5.1	4]	Г 			
neterogeneity. rau = 0,	0111 - 1.2	_ _ , ui =	4 (i = 0.	07), 1	- 070			0.1	0.5 1	2	10
							Favr	ous [E	BMT]	Fa	rous [EVT]

B Forest Plot for 90 day mRS 0-2.

Study	Events	EVT Total	Events	BMT Total	Weight	Risk Rat MH, Fixed, 9	io 5% Cl	М	Risk R H, Fixed,	atio 95% C	:1
ANGEL-ASPECT	66	219	25	222	36.5%	2.68 [1.76;	4.08]			- i	
SELECT2	36	177	12	171	17.9%	2.90 [1.56;	5.38]			-	
RESCUE-Japan LIMIT	14	94	7	94	10.3%	2.00 0.85;	4.73]		-	-	
LASTE	21	159	8	165	11.5%	2.72 [1.24;	5.97]		-	-	-
TESLA	22	152	13	148	19.3%	1.65 [0.86;	3.15]		+	•	
TENSION	21	124	3	122	4.4%	6.89 [2.11; 2	2.49]			-	•
Total (95% CI)	001· Chi	925) df - 5 (l	922	100.0%	2.64 [2.03;	3.43]	[<u> </u>	
Heterogeneity. Tau < 0.0		= 5.00	, ai = 5 (i	0.4	2), 1 = 0	70		0 1	051	2	10
							Fa	avrous [E	BMT]	∠ Favro	ous [EVT]

C Forest Plot for Independent Ambulation at 90 days.

Study	Events	EVT Total	Events	BMT Total	Weight	Risk Ratio MH, Fixed, 95%	Risl CI MH, Fix	k Ratio ed, 95% Cl
ANGEL-ASPECT	108	230	75	225	40.1%	1.41 [1.12; 1.77]	
SELECT2	67	177	32	171	17.2%	2.02 [1.40; 2.91]	
RESCUE-Japan LIMIT	31	100	15	104	7.8%	2.15 [1.24; 3.73	5]	
LASTE	53	159	21	165	10.9%	2.62 [1.66; 4.13]	
TESLA	45	152	29	148	15.5%	1.51 [1.00; 2.27]	
TENSION	39	124	16	122	8.5%	2.40 [1.42; 4.06]	
Total (95% CI) Heterogeneity: Tau ² = 0.0)259: Chi ²	942 = 9.43	df = 5 (935 P = 0.0	100.0% 9): ² = 4	1.80 [1.55; 2.1 0	ı	↓ ↓
······			,		-,, -		0.5 Favrous [BMT]	1 2 Favrous [EVT]

Fig. 2 Forest plot for short-term functional outcomes. A Forest plot for 90-day mRS 0–1. B Forest plot for one-year mRS 0–2. C Forest plot for independent ambulation at 90 days. D Forest Plot for Mean

mRS score at three months ${\bf E}$ Forest plot for early neurological improvement. ${\bf F}$ Forest plot for 90-day mortality

D Forest Plot for Mean mRS score at three months



E Forest Plot for Early Neurological Improvement.



F Forest Plot for 90-day Mortality.

Study	Events	EVT Total	Events	BMT Total	Weight	Risk Ratio MH, Fixed, 95%	R CI MH, F	isk Ra ixed, 9	tio 5% Cl
ANGEL-ASPECT	50	230	45	225	13.3%	1.09 [0.76; 1.56	51 –		
SELECT2	68	177	71	171	21.1%	0.93 [0.72; 1.20	- DI		-
RESCUE-Japan LIMIT	18	100	24	102	6.9%	0.76 [0.44; 1.32	2] —	+	
LASTE	57	159	91	165	26.0%	0.65 [0.51; 0.83	3] —	-	
TESLA	53	150	49	147	14.4%	1.06 [0.77; 1.45	5] –	- D	
TENSION	49	122	63	123	18.3%	0.78 [0.59; 1.03	3] —		
Total (95% Cl)		938		933	100.0%	0.86 [0.76; 0.97	n –	-	
Heterogeneity: Tau ² = 0.0	0170; Chiʻ	= 9.02	2, df = 5 (l	P = 0.1	1); l ² = 4	5%			
							0.5	1	2
							Favrous [EVT	1	Favrous [BMT]

Fig. 2 (continued)

One-year mRS 0-3

The rate of patients with mRS 0–3 was significantly higher in the EVT group versus the BMT group [35.7% (112/314) vs 17.1% (50/292), (RR = 2.1, 95% CI (1.55—2.8), *P*-value < 0.0001)]. No statistically significant heterogeneity was found so the Fixed effect model was implicated ($I^2 = 0\%$, *P*-value = 0.85).

One-year mortality rate

The mortality rate was non-significantly lower in the EVT group versus the BMT group [44.9% (141/314) vs 49% (143/292), (RR = 0.91, 95% CI (0.77 – 21.08), *P*-value = 0.31)]. No statistically significant heterogeneity was found so the Fixed effect model was implicated ($I^2 = 0\%$, *P*-value = 0.47).

Complications and safety outcomes

Symptomatic intracerebral hemorrhage

The prevalence of sICH was statistically significantly higher in the EVT group versus the BMT group [5.6% (52/932) vs 3.2% (30/940), (RR = 1.76, 95% CI (1.14—2.7), *P*-value = 0.01)], Supplementary Fig. 1A. No statistically significant heterogeneity was found so the Fixed effect model was utilized ($I^2 = 0\%$, *P*-value = 0.8). The funnel plot of the outcome is attached on Supplementary Fig. 2F.

Any intracerebral hemorrhage

The proportion of patients had any ICH within 48 h was statistically significantly in the EVT group compared with the BMT group [53.6% (171/319) vs 21.9% (71/324), (RR=2.18, 95% CI (1.85–2.57), *P*-value < 0.00001)], Supplementary Fig. 1B. No statistically significant heterogeneity was found so the Fixed effect model was implicated (I^2 =38%, *P*-value=0.19). The funnel plot of the outcome is attached on Supplementary Fig. 2G.

New stroke

Recurrence of (New) cerebral infarction was non-significantly lower in EVT group versus BMT group [6.2% (25/403) and 7.4% (30/404), (RR=0.85, 95% CI (0.51–1.40), *P*-value=0.52)], Supplementary Fig. 1C. No statistically significant heterogeneity was found so the Fixed effect model was implicated ($I^2=0\%$, *P*-value=0.95). The funnel plot of the outcome is attached on Supplementary Fig. 2H.

Serious adverse event

The rate of at least one serious adverse event non-significantly higher in EVT group and BMT group, [45.4% (207/456) and 43.5% (198/455), (RR = 1.06, 95% CI (0.83–1.35), *P*-value = 0.63), Supplementary Fig. 1D. Statistically significant heterogeneity was found so the Random effect model was implicated ($I^2 = 80\%$, *P*-value = 0.002). Sensitivity analysis was conducted to resolve the significant heterogeneity; however, it was not successful, so the random-effect model was implemented. The funnel plot of the outcome is attached on Supplementary Fig. 2I.

Decompressive craniectomy

The number of patients underwent the decompressive craniectomy did not significantly differ between the EVT group and the BMT group [8.1% (36/444) vs 6.9% (31/452), (RR = 1.18, 95% CI (0.75–1.88), *P*-value = 0.47)], Supplementary Fig. 1E. No statistically significant heterogeneity was found so the Fixed effect model was implicated ($I^2 = 29\%$, *P*-value = 0.25). The funnel plot of the outcome is attached on Supplementary Fig. 2J.

Quality assessment

The quality of included studies was assessed using the Cochrane a revised tool for assessing the risk of bias in randomized trials (RoB2). The risk of bias was low among all RCTs included in the study. However, because of the TESLA and LASTE is not officially published we cannot evaluate the risk of bias of this trial. A detailed summary of risk of bias assessment is available in Supplementary Appendix 2.

Discussion

The current systematic review and meta-analysis included 6 RCTs encompassing approximately 1594 patients investigating the impact of EVT with BMT versus BMT alone in patients who presented with large core infarct due to large vessel occlusion (LVO). The findings demonstrated that the EVT group had statistically significant higher rate of better functional outcome (mRS 0-1, mRS 0-2, and mRS 0-3) at three months, lower 90-day mean mRS score, lower 90-day mortality rate, and greater early neurological improvement. Though the rate of sICH and any ICH were significantly higher in EVT group, there was only an increase of approximately 2% in symptomatic hemorrhage. The one-year functional outcome (mRS 0-2 and mRS 0-3) at one year were significantly higher in EVT group compared with BMT group. There were no statistically significant differences observed between the EVT group and the BMT group concerning one-year mortality rate, new stroke, decompressive craniectomy, and serious adverse events. Trends favored the EVT across several of these endpoints.

Our findings support the results of previous metaanalyses demonstrating that EVT is safe and superior for improving functional outcomes in patients with large infarcts [9-11]. The majority of these meta-analyses included observational studies with high data heterogeneity (especially in imaging modality), due predominance of single-arm and single-center studies and thus considerable risk of bias. Furthermore, some of the studies included patients with an ASPECT score of 5 or a low ASPECT score (0–4), which potentially weakens reported results. Moreover, our study included the TENSION [8] and LASTE [12] trials and long-terms outcomes, which initially demonstrated a significant benefit in survival with EVT. The current study provides the largest sample size (six RCTs) and importantly more detailed functional and safety outcomes than two recent meta-analyses [1, 2].

Quantification of infarct core volume for patient selection in the majority of RCTs is based either on MRI (diffusionweighted sequence) [4] or CT perfusion imaging and a specialized post-processing software [4–7]. The TENSION [8] and TESLA [5] trials employed visual assessment of infarct size on unenhanced CT augmented with CTA to demonstrate the location of vascular occlusion, which is the most commonly used imaging technique globally for stroke management [13, 14].

Our finding indicated that EVT plus BMT led to in an absolute improvement of 5%, 12%, and 16% in excellent functional outcome, independent functional outcomes, and ability to walk independently at 90 days, respectively. Moreover, one-year functional outcomes was significantly higher in the EVT group compared with the BMT group [5, 15]. Although the 90-day mortality rate was lower in the EVT group in all except two RCTs (21.7 and 35.3% in EVT versus 20% and 33.3% in BMT) [7, 8], EVT showed an absolute pooled decrease of 6% in mortality at 90 days. Furthermore, one-year mortality rate showed pooled decreased of 5%. In the LASTE trial [12], incidence of patients with critically large core infarct (56%, ASPECTS 0-2) was about 4 to 13 times more than other RCTs, nevertheless, they showed significant benefit of EVT over BMT in mortality rate (36% vs. 55%) and independent functional outcome at three months (13% vs. 5%).

The current study shows that EVT was associated with a substantial revascularization rate of 82% (mTICI 2b/3), which fits within the typical range of revascularization rates reported in neuroendovascular literature [4–8]. Nevertheless, there are still lingering concerns over EVT potentially exacerbating the risk of ICH. Our findings revealed that patients who received EVT had a 3% increased probability of experiencing sICH and were 32% more susceptible to any ICH. It is unclear if this increase is clinically meaningful. Concerning recurrence or new cerebral infarction within 90 days, there is no statistically significant difference between two group (6% vs. 7%). We observed no significant difference in rate of 90-day decompressive craniotomy between EVT and BMT. Contrary to TENSION (9% vs. 7%) and ANGEL-ASPECT (7% vs. 34%), RESCUE-Japan LIMIT (10% vs. 14%) showed a lower rate of 90-day decompressive craniotomy in the EVT group than the BMT group.

Although ANGEL-ASPECT revealed a similar occurrence of serious adverse events between the two groups, TENSION reported that 7% of patients in the EVT group experienced at least one procedure-related adverse event without any procedure-related mortality. They also showed a statistically significantly lower rate of at least one serious adverse event in the EVT group (56% vs. 70%). On the other hand, RESCUE-Japan LIMIT showed significantly higher rate of serious events in the EVT group compared to the BMT group (44% vs. 24%). We showed a comparable non-significant rate of at least one serious adverse event between the two groups.

SELECT2 and TENSION demonstrated that patients in the EVT group had statistically significantly better threemonth quality of life scores than the BMT group [6, 8]. In a trial, one out of ten patients in the EVT group were discharged to a home, which was approximately twice the number of patients in the BMT group. Additionally, the EVT group exhibited a smaller proportion of patients discharged into hospice (6% vs. 11%) and a lower in-hospital death rate (24% vs. 25%) compared to the BMT group [6].

To the best of our knowledge, the current study is the largest systematic review and meta-analysis that exclusively assessed all available RCTs. The present study had few study-specific limitations that need to be acknowledged. First, trials enrolled a limited number of participants and were stopped prematurely. Additionally, our findings indicated that patients in the BMT group received approximately a similar quantity of IV tPA compared to the EVT group, which can affect the overall outcomes of the BMT group. Second, international enrollment of patients was performed only in two trials, and three other trials were conducted in Japan, China, and the United States. Although this difference can lead to some concerns about the applicability of reported results, our research revealed neglectable rate of heterogeneity in the analysis. Third, there is some heterogeneity in the criteria for selecting or excluding patients in the trials. The homogenous criteria definition is crucial for upcoming trials to enhance the generalizability of findings. Last but not least, short-term and one-year results of TESLA, and LASTE has not yet been formally published, and data collection of this study is based on reported results in the abstract presented at the European Stroke Organization Conference 2023 and International Stroke Conference 2024.

Conclusion

EVT could be beneficial in patients presenting with large infarct core. However, there are some safety concerns which can be resolve with progressive development of thrombectomy devices and techniques.

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s10072-024-07662-x.

Author contributions AM contributed to the study conception and design, performed search. AM and MMM edited the manuscript. AM, ZH, OE, BHK, and AYA analyzed the data and wrote the first draft of the manuscript. AM, MAA, and BHK collected data and evaluated the quality assessment. RR, AM and AAD contributed to the study design, revised the manuscript, analyzed data, and drew figures. All authors commented on previous versions of the manuscript and revised it. All authors read and approved the final manuscript."

Funding There is no funding source with authors to declare.

Data availability N/A.

Declarations

Ethical approval NA.

Consent to participate N/A.

Consent to publish N/A.

Conflict of interest The authors received no financial or material support for the research, authorship, and/or publication of this article.

Informed consent None.

References

- Kobeissi H, Adusumilli G, Ghozy S, Kadirvel R, Brinjikji W, Albers GW et al (2023) Endovascular thrombectomy for ischemic stroke with large core volume: an updated, post-TESLA systematic review and meta-analysis of the randomized trials. Interv Neuroradiol 28:15910199231185738
- Palaiodimou L, Sarraj A, Safouris A, Magoufis G, Lemmens R, Sandset EC et al (2023) Endovascular treatment for large-core ischaemic stroke: a meta-analysis of randomised controlled clinical trials. J Neurol Neurosurg Psychiatry 94(10):781–785
- Turc G, Bhogal P, Fischer U, Khatri P, Lobotesis K, Mazighi M et al (2019) European Stroke Organisation (ESO) – European Society for Minimally Invasive Neurological Therapy (ESMINT) guidelines on mechanical thrombectomy in acute ischaemic

StrokeEndorsed by Stroke Alliance for Europe (SAFE). Eur Stroke J 4(1):6–12

- Yoshimura S, Sakai N, Yamagami H, Uchida K, Beppu M, Toyoda K et al (2022) Endovascular therapy for acute stroke with a large ischemic region. N Engl J Med 386(14):1303–1313
- Zaidat OO, Kasab SA, Sheth S, Ortega-Gutierrez S, Rai AT, Given CA et al (2023) TESLA trial: rationale, protocol, and design. SVIN 3(4):e000787
- Sarraj A, Hassan AE, Abraham MG, Ortega-Gutierrez S, Kasner SE, Hussain MS et al (2023) Trial of endovascular thrombectomy for large ischemic strokes. N Engl J Med 388(14):1259–1271
- Huo X, Ma G, Tong X, Zhang X, Pan Y, Nguyen TN et al (2023) Trial of endovascular therapy for acute ischemic stroke with large infarct. N Engl J Med 388(14):1272–1283
- Bendszus M, Fiehler J, Subtil F, Bonekamp S, Aamodt AH, Fuentes B et al (2023) Endovascular thrombectomy for acute ischaemic stroke with established large infarct: multicentre, open-label, randomised trial. Lancet 402(10414):1753–1763
- Cagnazzo F, Derraz I, Dargazanli C, Lefevre PH, Gascou G, Riquelme C et al (2020) Mechanical thrombectomy in patients with acute ischemic stroke and ASPECTS ≤6: a meta-analysis. J Neurointerv Surg 2(4):350–5
- Li Q, Abdalkader M, Siegler JE, Yaghi S, Sarraj A, Campbell BCV et al (2023) Mechanical thrombectomy for large ischemic stroke: a systematic review and meta-analysis. Neurology 101(9):e922–32
- Sarraj A, Grotta JC, Pujara DK, Shaker F, Tsivgoulis G (2020) Triage imaging and outcome measures for large core stroke thrombectomy - a systematic review and meta-analysis. J Neurointerv Surg 12(12):1172–9
- 12. Costalat V, Lapergue B, Albucher J, Labreuche J, Henon H, Gory B et al (2024) Evaluation of acute mechanical revascularization in large stroke (ASPECTS ≤5) and large vessel occlusion within 7 h of last-seen-well: the LASTE multicenter, randomized, clinical trial protocol. Int J Stroke 19(1):114–119
- Kim Y, Lee S, Abdelkhaleq R, Lopez-Rivera V, Navi B, Kamel H et al (2021) Utilization and availability of advanced imaging in patients with acute ischemic stroke. Circ Cardiovasc Qual Outcomes 14(4):e006989
- Nogueira RG, Haussen DC, Liebeskind D, Jovin TG, Gupta R, Jadhav A et al (2021) Stroke imaging selection modality and endovascular therapy outcomes in the early and extended time windows. Stroke 52(2):491–497
- Sarraj A, Abraham MG, Hassan AE, Blackburn S, Kasner SE, Ortega-Gutierrez S et al (2024) Endovascular thrombectomy plus medical care versus medical care alone for large ischaemic stroke: 1-year outcomes of the SELECT2 trial. Lancet 403(10428):731–740

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Authors and Affiliations

Ali Mortezaei¹ · Mahmoud M. Morsy² · Bardia Hajikarimloo³ · Ahmed Y. Azzam² · Adam A. Dmytriw^{4,5} · Osman Elamin⁶ · Mohammed A. Azab⁷ · Zuha Hasan⁸ · Redi Rahmani⁹

Redi Rahmani redir90@gmail.com

> Ali Mortezaei alimortezaei97@yahoo.com

Mahmoud M. Morsy mm.darwesh20@yahoo.com

Bardia Hajikarimloo bardiakarimloo@gmail.com

Ahmed Y. Azzam ahmedyazzam@gmail.com

Adam A. Dmytriw adam.dmytriw@gmail.com

Osman Elamin drosman.elamin@gmail.com

Mohammed A. Azab AZABM2@ccf.org

Zuha Hasan hasan.zuha@gmail.com

¹ Gonabad University of Medical Sciences, Gonabad, Iran

- ² Faculty of Medicine, October 6 University, Giza, Egypt
- ³ Department of Neurosurgery, Shohada Tajrish Hospital, Tehran, Iran
- ⁴ Neuroendovascular Program, Massachusetts General Hospital & Brigham and Women's Hospital, Harvard University, Boston, MA, USA
- ⁵ Neurovascular Centre, Divisions of Therapeutic Neuroradiology & Neurosurgery, St. Michael's Hospital, University of Toronto, Toronto, ON, Canada
- ⁶ Department of Neurosurgery, Jordan Hospital, Amman, Jordan
- ⁷ Department of Neurosurgery, Cleveland Clinic Foundation, Cleveland, OH, USA
- ⁸ Neuroendovascular Program, Massachusetts General Hospital, Harvard Medical School, Boston, MA, USA
- ⁹ Department of Neurosurgery, Barrow Neurological Institute, St. Joseph's Hospital and Medical Center, 2910 North Third Avenue, Phoenix, AZ 85013, USA