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Surgical Decompression for Space-Occupying Hemispheric Infarction
A Systematic Review and Individual Patient Meta-analysis of Randomized Clinical Trials

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IMPORTANCE In patients with space-occupying hemispheric infarction, surgical decompression reduces the risk of death and increases the chance of a favorable outcome. Uncertainties, however, still remain about the benefit of this treatment for specific patient groups.

OBJECTIVE To assess whether surgical decompression for space-occupying hemispheric infarction is associated with a reduced risk of death and an increased chance of favorable outcomes, as well as whether this association is modified by patient characteristics.

DATA SOURCES MEDLINE, Embase, the Cochrane Central Register of Controlled Trials, and the Stroke Trials Registry were searched from database inception to October 9, 2019, for English-language articles that reported on the results of randomized clinical trials of surgical decompression vs conservative treatment in patients with space-occupying hemispheric infarction.

STUDY SELECTION Published and unpublished randomized clinical trials comparing surgical decompression with medical treatment alone were selected.

DATA EXTRACTION AND SYNTHESIS Patient-level data were extracted from the trial databases according to a predefined protocol and statistical analysis plan. The Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) reporting guideline and the Cochrane Collaboration's tool for assessing risk of bias were used. One-stage, mixed-effect logistic regression modeling was used for all analyses.

MAIN OUTCOMES AND MEASURES The primary outcome was a favorable outcome (modified Rankin Scale [mRS] score ≤3) at 1 year after stroke. Secondary outcomes included death, reasonable (mRS score ≤4) and excellent (mRS score ≤2) outcomes at 6 months and 1 year, and an ordinal shift analysis across all levels of the mRS. Variables for subgroup analyses were age, sex, presence of aphasia, stroke severity, time to randomization, and involved vascular territories.

RESULTS Data from 488 patients from 7 trials from 6 countries were available for analysis. The risk of bias was considered low to moderate for 6 studies. Surgical decompression was associated with a decreased chance of death (adjusted odds ratio, 0.16; 95% CI, 0.10-0.24) and increased chance of a favorable outcome (adjusted odds ratio, 2.95; 95% CI, 1.55-5.60), without evidence of heterogeneity of treatment effect across any of the prespecified subgroups. Too few patients were treated later than 48 hours after stroke onset to allow reliable conclusions in this subgroup, and the reported proportions of elderly patients reaching a favorable outcome differed considerably among studies.

CONCLUSIONS AND RELEVANCE The results suggest that the benefit of surgical decompression for space-occupying hemispheric infarction is consistent across a wide range of patients. The benefit of surgery after day 2 and in elderly patients remains uncertain.

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Supplemental content

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Space-occupying brain edema is a potentially life-threatening complication of ischemic stroke that has been reported to occur in 2% to 8% of patients with supratentorial infarction[1-4] and that most often manifests in the first 4 days after stroke onset.[5] Randomized clinical trials and intensive care–based series have reported death rates of up to 80% with conservative treatment alone.[5,6] Surgical decompression, consisting of a large hemicraniectomy and duraplasty, consistently reduced the risk of death in randomized clinical trials and increased the chance of a favorable outcome in some meta-analyses of these trials.[7-14] However, because of the small size of the individual trials and of pooled analyses of these trials, uncertainties still remain about the benefit of surgical decompression for specific patient groups,[15,16] including those with aphasia or involvement of an additional vascular territory next to that of the middle cerebral artery (MCA) and those presenting later than 48 hours after stroke onset. Data pooling may provide more precise estimates of treatment effects.[17,18] We therefore aimed to address these uncertainties by analyzing pooled individual patient data from randomized clinical trials that compared functional outcomes in patients with space-occupying supratentorial hemispheric infarction treated with surgical decompression with outcomes in patients who received medical treatment alone. We also sought to assess whether patient characteristics modify surgical decompression outcomes for space-occupying hemispheric infarction.

Key Points

Question How does surgical decompression compare with medical care for space-occupying hemispheric infarction, and do patient characteristics modify treatment outcomes?

Findings In this systematic review and meta-analysis of individual patient data from 488 individuals from 7 randomized clinical trials, surgical decompression was associated with an increase in the chance of a favorable outcome at 1 year, without statistically significant heterogeneity between subgroups based on age, sex, aphasia, stroke severity, time to randomization, and involvement of additional vascular territories.

Meaning Surgical decompression is associated with positive outcomes across a wide range of patients with space-occupying hemispheric infarction.

Methods

Literature Search and Selection Criteria

In this meta-analysis, 2 investigators (H.R. and H.N.) performed a systematic literature search of MEDLINE, Embase, the Cochrane Central Register of Controlled Trials (CENTRAL), and the Stroke Trials Registry from database inception to October 9, 2019, to identify randomized clinical trials reported in English of surgical decompression vs conservative treatment in patients with space-occupying hemispheric infarction. The full search strategy is described in eAppendix 1 in the Supplement. Individual articles were checked for potentially relevant citations. We contacted the investigators of the identified studies and requested coded, individual patient data. Studies were included if (1) patients were randomized to receive surgical decompression or medical treatment alone because of space-occupying hemispheric infarction; (2) functional outcome was assessed at 6 to 12 months after stroke onset using the modified Rankin Scale (mRS), a 7-point functional outcome scale ranging from 0 (no symptoms) to 5 (severe disability) and 6 (death); and (3) the authors provided individual patient data. A predefined protocol and statistical analysis plan were created and agreed on by all collaborating investigators (eAppendix 2 in the Supplement). The risk of bias in each trial was independently assessed by 2 investigators (H.R. and H.N.) with the Cochrane Collaboration's tool for assessing risk of bias.[19] In case of disagreement, a consensus meeting was convened. This study followed the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) reporting guideline.[20]

Data Collection and Management

After individual patient data were collected, variables were transformed when possible to create a uniform database. The following baseline patient-level data were extracted from the trial databases: age; sex; presence of aphasia (if unknown, aphasia was considered present if the left hemisphere was affected); score on the National Institutes of Health Stroke Scale (NIHSS) at baseline (if not available because of sedation at randomization, the patient was regarded comatose and given an NIHSS score of 35)[21]; score on the Glasgow Coma Scale at baseline; time to randomization; and vascular territory involved (MCA alone vs MCA plus anterior cerebral artery [ACA] or posterior cerebral artery [PCA] territory). If information on the vascular territory was not available, information about the site of occlusion on computed tomographic angiography or magnetic resonance angiography was used, with carotid occlusion being regarded as MCA plus ACA or PCA territory. We also collected the scores on the mRS at 6 months and 1 year after stroke onset. If the outcome at 1 year for an individual patient was missing, the latest recorded mRS score was used for estimating the 1-year outcome provided that the score was not obtained earlier than 6 months (±30 days) after stroke.

Outcomes

The primary outcome was a favorable outcome, defined as a score of 0 to 3 on the mRS at 1 year (±30 days) after stroke. Secondary outcomes were functional independence (mRS score ≤2), reasonable outcome (mRS score ≤4), and death at 6 months and 1 year after stroke. The analysis was supplemented by a shift analysis to investigate improvement across all levels of the mRS at 1 year after stroke. In addition, we aimed to analyze location of residence (home, rehabilitation service, long-term nursing facility, or hospital) and serious adverse events (limited to surgical complications) in the first year.

Statistical Analysis

All analyses were performed according to the intention-to-treat principle. No additional per-protocol analyses were performed because crossovers and major protocol violations were reported in only 16 patients (3.3%).

A 1-stage model was used for the primary and secondary analyses, which pools all data in a single regression model. We used mixed-effect logistic regression modeling, taking treatment and trial as random effects in all mixed models. This approach ensured that between-trial variance is incorporated in the estimation of all effect sizes and their CIs. Binary logistic regression was used to calculate the odds ratios (ORs) and 95% CIs for dichotomous outcomes (such as the primary outcome), and additional adjusted analyses were performed to account for potential baseline incomparability. Adjustments were planned for the following prespecified covariates: age, sex, baseline stroke severity (NIHSS), presence of aphasia, and time from stroke onset to randomization. These covariates were incorporated into the mixed models as common effects. Ordinal logistic regression was used for secondary ordinal outcomes, such as improvement on the mRS (shift analysis) at 1 year. Results are reported as absolute risk difference (RD) and crude and adjusted (common) ORs (aORs) with accompanying 95% CIs, with a 2-sided $P < .05$ considered statistically significant.

Prespecified subgroup analyses were performed to assess the potential effect modification of the association between surgical decompression and the primary outcome for age (18-50, 51-60, 61-70, and >70 years), sex (male vs female), presence of aphasia, vascular territory (MCA alone vs MCA and ACA or PCA), time from stroke onset to randomization (by day), and NIHSS score at baseline (≤20, 21-25, and >25). Because of low numbers of primary outcomes in subgroups with multiple categories, we not only combined age subgroups (≤60 vs >60 years) for visualization in a forest plot but also included the prespecified analysis with 4 age subgroups.

The consistency of the treatment effect between subgroups was assessed by interaction terms, with significant interaction defined a priori as 2-sided $P < .10$, reflecting heterogeneity. Subgroup analyses included the random-effects variables trial and treatment in addition to the multiplicative interaction term treatment × prespecified subgroup variable. To separate within-study and across-study interaction, we centered the covariate of interest (by subtracting the mean in each trial) and used the interaction term of the centered variable and treatment allocation in the model. The regression coefficient and significance level for this interaction term were used as an estimation of the within-trial covariate interaction. Age, time to randomization, and baseline NIHSS score were used as continuous variables in these analyses. Subgroup analyses were again adjusted, assuming common effects for the prespecified covariates.

In addition, we performed several post hoc analyses, including sensitivity analyses for published trials with low to moderate risk of bias, for trials that reported all 5 prespecified adjustment variables, for patients older than 60 years, and for patients randomized after 48 hours of symptom onset.

All statistical analyses were performed with R, version 3.5.1 (R Foundation for Statistical Computing).

Results

Study and Patient Characteristics

In this meta-analysis, 8 published randomized clinical trials[7,8,10-12,22-24] and 1 unpublished trial (eAppendix 3 in the Supplement) that had assessed the effectiveness of surgical decompression for space-occupying hemispheric infarction were identified (eFigure 1 in the Supplement). These trials include 7 completed published trials from 6 countries,[7,8,10-12,23,24] and 1 completed but unpublished trial. One trial[22] had only published preliminary results for the first 28 of a total of 44 included patients. Research groups of 7 trials (including the unpublished trial in eAppendix 3 in the Supplement)[7,8,10-12,22] provided full data, 1 research group provided incomplete data (10 of 29 patients) that were excluded from the analysis,[23] and data of 1 other trial[24] that randomized 26 patients were not available. The authors of the unpublished trial provided patient data and a completed manuscript, which can be found in eAppendix 3 in the Supplement. In total, the analysis comprised 488 of all 543 patients (90%) randomized.

The score on the mRS at 1 year was assessed in all studies. In all except 1 study,[8] the mRS was also assessed at 6 months. The location of residence at 1 year was recorded in only 1 study,[8] and systematically collected information about serious adverse events was available in only 1 study,[11] hindering the use of these outcomes in the current meta-analysis. Information on time to randomization was not available for individual patients in the unpublished trial (eAppendix 3 in the Supplement), and NIHSS score at baseline was not available in another trial[10] (eTable 1 in the Supplement). Therefore, the variables NIHSS score at baseline and time to randomization could not be used as adjustment covariates because doing so would lead to exclusion of these trials in the main analyses. Instead, additional sensitivity analyses with exclusion of these 2 trials were performed (eTables 2-4 in the Supplement).

Six studies[7,8,10-12] (including the unpublished study in eAppendix 3 in the Supplement), including 86% of the patients, were judged to have a low to moderate risk of bias (eAppendix 4 in the Supplement). Given the nature of treatment, blinding of participants and personnel involved in the trial was not possible. For blinding of the outcome assessment, 2 studies[7](including the unpublished study in eAppendix 3 in the Supplement) used surgical head caps for all patients, 1 study[8] blinded narratives of mRS interviews, and 1 used questionnaires[10] that were completed by patients or family at home.

Of the 488 patients included in the trial, 234 (48%) were randomized to receive surgical decompression and 254 (52%) to receive medical treatment. Baseline characteristics were

largely balanced between the populations (**Table 1**). Baseline characteristics stratified by trial are given in eTable 1 in the Supplement. Large differences were found among trials in age at randomization and time to randomization caused by differences in the relevant inclusion criteria, but differences in other clinical and radiologic eligibility criteria were small (**Table 2** and eAppendix 5 in the Supplement).

Primary and Secondary Outcomes

Figure 1 shows the distribution of mRS scores at 1 year by treatment population. Pooled analysis found an increased chance of a favorable outcome (mRS score ≤3) at 1 year in patients randomized to surgery vs those randomized to medical treatment (RD, 21%; 95% CI, 9-33; aOR, 2.95; 95% CI, 1.55-5.60) (**Table 3**). Surgical decompression was also associated with reduced risk of death and increased chance of a reasonable outcome at 1 year and was associated with a shift toward functional improvement. Similar treatment outcomes were observed after 6 months, with improvements after surgical decompression in favorable and reasonable outcomes and a reduced death rate (Table 3). Crude and adjusted ORs were essentially the same for all outcomes. Additional sensitivity analyses that excluded unpublished trials, trials with a high risk of bias, and trials that did not report all prespecified adjustment variables found a comparable reduction in mortality and improvement of acceptable outcome but lower rates of favorable outcome after decompressive surgery than the main analyses (eTables 2-4 in the Supplement).

Table 1. Baseline Characteristics in the Pooled Data[a]

Characteristic	Medical treatment (n = 254)	Surgical decompression (n = 234)	Total (N = 488)
Time to randomization, mean (SD), h	29.7 (18.2)	28.1 (14.5)	28.9 (16.5)
NIHSS score at baseline, median (IQR)	24 (21-30)	24 (20-28)	24 (21-29)
Age at randomization, mean (SD), y	60.3 (12.8)	59.1 (12.9)	59.7 (12.9)
Age per decade, y			
18-50	68 (26.8)	63 (26.9)	131 (26.8)
51-60	49 (19.3)	55 (23.5)	104 (21.3)
61-70	72 (28.3)	72 (30.8)	144 (29.5)
>70	65 (25.6)	44 (18.8)	109 (22.3)
Male sex	141 (55.5)	138 (59.0)	279 (57.2)
Aphasia present	116 (45.7)	106 (45.3)	222 (45.5)
Vascular territory			
MCA alone	103 (40.6)	97 (41.5)	200 (41.0)
MCA and ACA and/or PCA	89 (35.0)	69 (29.5)	158 (32.4)
Missing	62 (24.4)	68 (29.1)	130 (26.6)
GCS summary score, median (IQR)	10 (8-11)	9 (8-12)	10 (8-12)

Abbreviations: ACA, anterior cerebral artery; GCS, Glasgow Coma Scale; IQR, interquartile range; MCA, middle cerebral artery; NIHSS, National Institutes of Health Stroke Scale; PCA, posterior cerebral artery.

[a] Data are presented as number (percentage) of patients unless otherwise indicated.

Subgroup Analysis

In the subgroup analysis for the primary outcome (mRS score ≤3 at 1 year), no evidence of heterogeneity of treatment effect was found across the prespecified variables: age, sex, aphasia, NIHSS score at baseline, time to randomization, and vascular territories involved (**Figure 2** and eFigure 2 in the Supplement). Similar results were found in the subgroup analysis for the secondary outcomes (mRS score ≤4, death, and shift analysis) (**Figure 3** and eFigures 3 and 4 in the Supplement). Only 32 patients (6.6%) were randomized after the first 48 hours of stroke onset (eTable 5 in the Supplement). In post hoc analysis of patients older than 60 years, the proportion of patients who reached a favorable (mRS score ≤3) outcome after surgical decompression differed considerably among studies. In 4 trials,[8,10,11,22] 0% to 12.5% of patients older than 60 years reached a favorable outcome, as opposed to 66% in DEMITUR (Decompressive Surgery for the Treatment of Malignant Infarction of the Middle Cerebral Artery: A Randomized Controlled Trial in a Turkish Population) (eTable 6 in the Supplement). Treatment effects in these patients were fairly consistent, but absolute numbers of patients who reached a favorable outcome were small, especially when DEMITUR was excluded (eFigure 5 in the Supplement).

Discussion

The results of this meta-analysis of pooled, individual patient-level data suggest that surgical decompression in patients with space-occupying hemispheric infarction strongly reduces the risk of death and increases the chances of a favorable functional outcome (mRS score ≤3) compared with conservative treatment. We found no evidence of heterogeneity of treatment outcome based on the presence of aphasia, stroke severity, age, and involvement of other vascular territories in addition to that of the MCA.

These findings are consistent with the results of the first 2 pooled individual patient-level data analyses of 93 and 109 patients up to 60 years of age treated within 48 hours of stroke onset[8,9] and those of the latest published, aggregated data meta-analyses, including adult patients of all ages from the same previously published randomized clinical trials.[13,14] However, the sizes of the earlier pooled analyses were too small for reliable subgroup analyses, and meta-analyses of aggregated data cannot properly account for patient-level characteristics that may influence benefit of surgery.[17,18] In the present meta-analysis, individual data of 488 patients from a total of 7 studies[7,8,10-12,22] (including the unpublished study in eAppendix 3 in the Supplement) across different continents and health care systems were used, including data from 2 trials[22] (including the unpublished study in eAppendix 3 in the Supplement) that had not been reported in full before.[22] As a result of the large sample size of the present study and the use of individual patient data, assessment of the association of surgery with outcomes in the subgroups mentioned was possible.

Table 2. Trial Eligibility Criteria

Criterion	DECIMAL[12]	DEMITUR[a]	DESTINY[7]	DESTINY II[11]	HAMLET[8]	Slezins et al[22]	Zhao et al[10]
Inclusion criteria							
Age range, y	18-55	40-80	18-60	>60	18-60	>18	18-80
Time of stroke onset to randomization, h	≤24	NA	NA	NA	NA	NA	NA
Time of stroke onset to treatment, h	≤30	12-38	12-36	<48	≤96	≤48	≤48
Time of randomization to surgery, h	≤6	<6	≤6	≤6	≤3	NA	NA
NIHSS score (dominant hemisphere)	>15	>18	>20	>19	>20	>15	NA
NIHSS score (nondominant hemisphere)	>15	>16	>18	>14	>15	>15	NA
NIHSS item 1a score	≥1	≥1	≥1	≥1	NA	NA	NA
GCS (eyes and motor score)	NA	NA	NA	NA	≤9	NA	≤9
MCA territory involved on brain CT	>50%	≥2/3	≥2/3	≥2/3	≥2/3	≥50%	≥2/3
Infarct volume on MRI-DWI, cm^3	>145	>150	NA	NA	NA	>145	NA
Involvement of basal ganglia required	NA	Yes	Yes	Yes	NA	NA	NA
Edema formation required	NA	NA	NA	NA	Yes	Yes	Yes
Exclusion criteria							
Prestroke mRS score	≥2	≥2	≥2	≥2	≥2	≥2	≥2
Contralateral infarction	Yes	Yes	Yes	Yes	NA	NA	Yes
Severe hemorrhagic transformation of infarct	Yes	Yes	Yes	Yes	NA	NA	Yes
Life expectancy, y	<3	<3	<3	<3	<3	NA	<3
Known coagulopathy	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Pregnancy	Yes	Yes	Yes	NA	NA	NA	Yes
MRI contraindication	Yes	NA	NA	NA	NA	NA	NA
Anesthesia contraindication	NA	Yes	Yes	Yes	NA	Yes	Yes
GCS score	NA	<6	<6	<6	NA	<6	<6
Prestroke Barthel Index	NA	<95	<95	<95	<95	NA	NA
Fixed and dilated pupils	NA	Both	Both	Both	Both	Both	1
Other serious illness that could affect outcome	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Involvement of entire cerebral hemisphere	NA	NA	NA	NA	Yes	NA	NA

Abbreviations: CT, computed tomography; DECIMAL, Decompressive Craniectomy In Malignant Middle Cerebral Artery Infarction; DEMITUR, Decompressive Surgery for the Treatment of Malignant Infarction of the Middle Cerebral Artery: A Randomized Controlled Trial in a Turkish Population; DESTINY, Decompressive Surgery for the Treatment of Malignant Infarction of the Middle Cerebral Artery; DWI, diffusion-weighted imaging; GCS, Glasgow Coma Scale; HAMLET, Hemicraniectomy After Middle Cerebral Artery infarction with Life-threatening Edema Trial; MCA, middle cerebral artery; MRI, magnetic resonance imaging; mRS, modified Rankin Scale; NA, not applicable; NIHSS, National Institutes of Health Stroke Scale.

[a] See eAppendix 3 in the Supplement for the full manuscript.

In clinical practice, aphasia or involvement of an additional vascular territory may be considered a reason to withhold surgical treatment.[25-27] In the current study, however, there was no statistically significant difference in the

benefit of treatment across these subgroups. In addition, no evidence of heterogeneity was found in treatment outcomes with increasing time to randomization when used as a continuous variable. However, only 32 patients were randomized later than 48 hours from symptom onset (eTable 5 in the Supplement), and the protocol of only 1 of the included trials[8] allowed treatment of patients beyond this time window. Therefore, treatment outcomes in the first 48 hours should not be extrapolated to patients who present later.

The finding of an apparently consistent benefit of surgical decompression across age groups should be interpreted with caution. These results suggest that treatment is effective in patients up to 60 years, in line with previous meta-analyses.[8,9] In older patients, outcomes were also consistently better in surgically treated patients, and there was no evidence of heterogeneity of treatment outcome with increasing age when used as a continuous variable. However, estimates of treatment outcome in higher age decades were imprecise because of the low numbers of favorable outcomes in the medically treated group (eFigure 2 in the Supplement). In absolute terms, only 8% of patients 61 years or older achieved a favorable outcome after surgery in DESTINY II (Decompressive Surgery for the Treatment of Malignant Infarction of the Middle Cerebral Artery II)[11] compared with 66% in DEMITUR (eTable 6 and eAppendix 3 in the Supplement). This observation cannot be explained on the basis of the available data of this pooled analysis, but it may be a consequence of unreported differences in patient characteristics or differences in adjudication of outcomes on the mRS. For implementation in clinical practice, we suggest consideration of the absolute numbers of patients who reached a favorable outcome in these 2 studies (including the unpublished study in eAppendix 3 in the Supplement).[11]

Limitations

This study has limitations. Most individual studies were small in terms of number of included patients, and individual patient-level data were not available for 2 previously published small trials,[23,24] which could have added a total of 55 patients and increased the sample size by 11%. In addition, data from some studies could not be used for all subgroup analyses because the relevant variables were missing. It was also not possible to adjust for baseline stroke severity and time to randomization in the main analyses because each was missing in a single study. Although the sample is large for this specific patient

Figure 1. Scores on the Modified Rankin Scale (mRS) at 1 Year

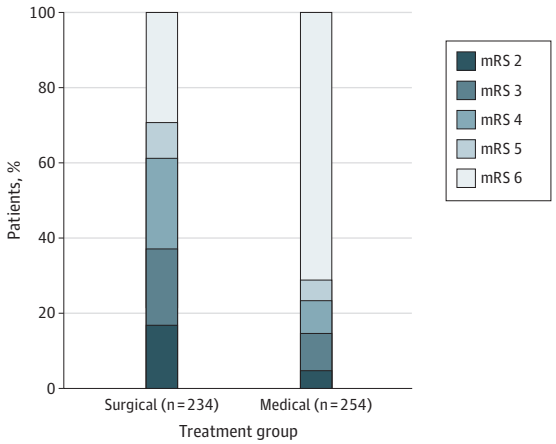


Table 3. Outcomes From the Pooled Data at 1 Year and 6 Months[a]

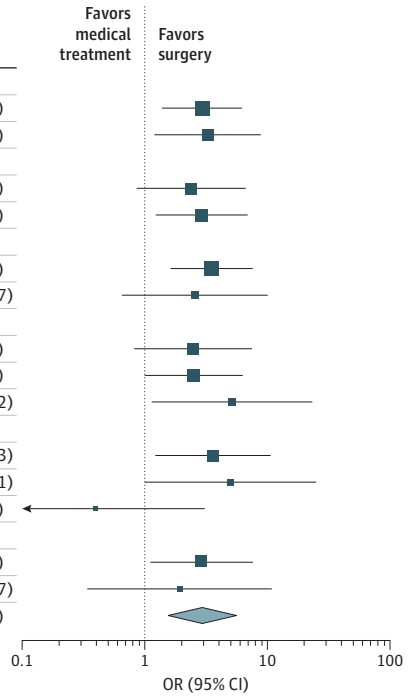
Outcome	No./total No. (%) of patients			Crude OR (95% CI)	*P* value	Adjusted OR (95% CI)	*P* value
	Surgery population	Medical population	RD				
Primary outcome							
mRS score ≤3 at 1 y	87/234 (37)	37/254 (15)	(21)	3.23 (1.75-5.94)	<.001	2.95 (1.55-5.60)	.001
Secondary outcomes							
mRS score ≤2 at 1 y	39/234 (17)	12/254 (5)	(10)	2.91 (1.06-7.99)	.04	2.77 (0.97-7.88)	.06
mRS score ≤4 at 1 y	143/234 (61)	59/254 (23)	(38)	5.55 (3.42-9.00)	<.001	5.34 (3.26-8.74)	<.001
Death at 1 y	68/234 (29)	180/254 (71)	(-41)	0.16 (0.10-0.24)	<.001	0.16 (0.10-0.24)	<.001
mRS score ≤3 at 6 mo	60/202 (30)	19/222 (9)	(20)	4.85 (2.43-9.67)	<.001	4.67 (2.20-9.87)	<.001
mRS score ≤4 at 6 mo	118/202 (58)	43/222 (19)	(39)	6.07 (3.79-9.74)	<.001	5.67 (3.18-10.09)	<.001
Death at 6 mo	55/202 (27)	158/222 (71)	(44)	0.14 (0.09-0.22)	<.001	0.13 (0.08-0.22)	<.001
Shift analysis							
mRS score at 1 y	NA	NA	NA	5.29 (3.27-8.56)	<.001	4.95 (2.99-8.20)	<.001
mRS score at 6 mo	NA	NA	NA	6.38 (4.15-9.79)	<.001	6.62 (4.01-10.92)	<.001

Abbreviations: mRS, modified Rankin Scale; NA, not applicable; RD, risk difference; OR, odds ratio.

[a] The RDs are pooled absolute RDs. The RDs and ORs are adjusted for age, sex, and presence of aphasia at randomization. All analyses are performed with a 1-stage model with random effects for trial baseline risk and treatment allocation.

Figure 2. Forest Plot of Subgroups With Modified Rankin Scale Scores of 3 or Less at 1 Year

Characteristic	No. (%) of patients: Surgery (n = 234)	Medical (n = 254)	OR (95% CI)
Aphasia (*P* = .43)			
Absent	44/128 (34)	21/138 (15)	2.93 (1.38-6.21)
Present	43/106 (41)	16/116 (14)	3.26 (1.20-8.85)
Sex (*P* = .34)			
Female	32/96 (33)	16/113 (14)	2.40 (0.86-6.66)
Male	55/138 (40)	21/141 (15)	2.91 (1.23-6.91)
Age, y (*P* = .48)			
≤ 60	54/118 (46)	23/117 (20)	3.52 (1.63-7.58)
>60	33/116 (28)	14/137 (10)	2.56 (0.65-10.07)
NIHSS score at baseline (*P* = .49)[a]			
≤ 20	23/55 (42)	11/42 (26)	2.48 (0.82-7.49)
21-25	29/72 (40)	16/83 (19)	2.51 (1.00-6.30)
>25	29/83 (35)	8/105 (8)	5.11 (1.14-22.82)
Time to randomization, h (*P* = .70)[b]			
< 24	19/68 (28)	8/71 (11)	3.60 (0.46-10.63)
24-48	19/78 (24)	8/87 (9)	5.00 (1.00-25.01)
>48	3/17 (18)	5/15 (33)	0.40 (0.05-3.09)
Vascular territory (*P* > .99)[c]			
MCA only	27/97 (28)	15/103 (15)	2.89 (1.11-7.56)
MCA and ACA and/or PCA	30/69 (44)	14/89 (16)	1.92 (0.34-10.87)
Summary			2.95 (1.55-5.60)



P values for heterogeneity across subgroups are shown (interaction term treatment × subgroup variable). Odds ratios (ORs) are adjusted for age, sex, and presence of aphasia (not National Institutes of Health Stroke Scale [NIHSS] score at baseline and time to randomization). All analyses were performed with a 1-stage model with random effects for the variables trial and treatment. ACA indicates anterior cerebral artery; MCA, middle cerebral artery; and PCA, posterior cerebral artery. Squares represent mean values, with the size of the squares indicating weight and horizontal lines representing 95% CIs. The diamond represents the summary mean with the points of the diamond representing the 95% CI.

[a] Not recorded in the study by Zhao et al[10] (n = 47) and missing (n = 1) in HAMLET (Hemicraniectomy After Middle Cerebral Artery infarction with Life-threatening Edema Trial).[8]

[b] Not recorded in DEMITUR (Decompressive Surgery for the Treatment of Malignant Infarction of the Middle Cerebral Artery: A Randomized Controlled Trial in a Turkish Population) (eAppendix 3 in the Supplement) (n = 151) and missing (n = 1) in the DESTINY II (Decompressive Surgery for the Treatment of Malignant Infarction of the Middle Cerebral Artery II) study.[11]

[c] Not recorded in the study by Slezins et al[22] (n = 44), Decompressive Craniectomy in Malignant MCA Infarction (DECIMAL) (n = 38), and DESTINY[7] (n = 32) and missing (n = 16) in DEMITUR.

population, the interaction analyses may still have too limited power to detect heterogeneity in treatment outcomes. Finally, the largest study, the unpublished study in eAppendix 3 in the Supplement, included in the meta-analysis was not registered in a database approved by the International Committee of Medical Journal Editors and was never published. However, a sensitivity analysis in which this trial was excluded did not substantially change the results of the primary and main secondary analyses (eTable 2 in the Supplement).

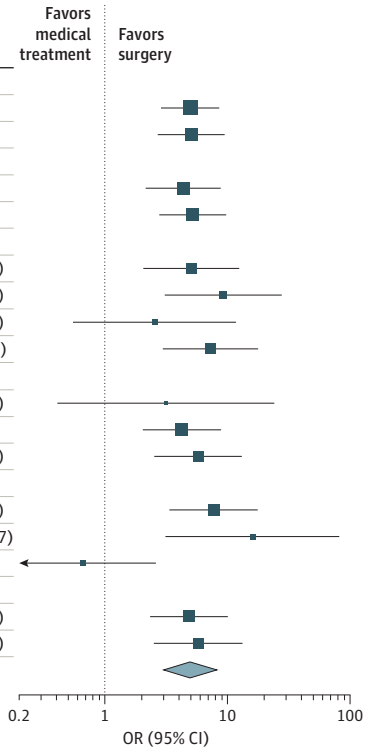
What constitutes a favorable outcome after surgical decompression remains a matter of debate, with some trials[8,12] of surgical decompression for ischemic stroke defining favorable outcome as an mRS score of 3 or less and other trials[9,10,22] defining it as an mRS score of 4 or less. What is considered acceptable may differ between patients and cultural settings, and the score on the mRS does not fully grasp all dimensions of outcome.[28] Quality-of-life outcomes were not included in this meta-analysis because the use of these instruments was limited in the included trials and the choice of instrument differed. Most importantly, however, such analyses will be strongly affected by survivor bias. Previous systematic reviews[29-31] of randomized clinical trials and nonrandomized studies concluded that most patients surviving surgical decompression experience a reasonable quality of life at long-term follow-up and are satisfied with the treatment received. The choice to perform surgical decompression remains a matter of shared decision-making between the practitioner and the patient and relatives, incorporating information about the treatment and the patient's preferences in each individual case.[28,32]

Conclusions

In this meta-analysis of patients with space-occupying hemispheric infarction, surgical decompression was associated with a substantial increase in the chance of a favorable outcome. This benefit appeared to be independent of the presence of aphasia, stroke severity, age, and the involvement of other vascular territories in addition to that of the MCA. Data on surgical decompression performed later than 48 hours after stroke onset were too limited for reliable conclusions, and the reported proportions of elderly patients who reached a favorable outcome varied widely between studies.

Figure 3. Forest Plot of Subgroups With Shift Analysis of the Modified Rankin Scale (mRS) Score

Characteristic	Surgery (n = 234)	Medical (n = 254)	OR (95% CI)
Aphasia (*P* = .45)			
Absent	128	138	4.96 (2.87-8.58)
Present	106	116	5.06 (2.70-9.49)
Sex (*P* = .44)			
Female	96	113	4.35 (2.15-8.81)
Male	138	141	5.21 (2.78-9.77)
Age, y (*P* = .45)			
≤ 50	63	68	5.07 (2.06-12.48)
51-60	55	4	9.24 (3.08-27.72)
61-70	72	8	2.55 (0.55-11.75)
>70	43	65	7.27 (2.97–17.80)
NIHSS score at baseline (*P* = .65)[a]			
≤ 20	55	42	3.16 (0.41-24.10)
21-25	72	83	4.25 (2.04-8.87)
>25	83	105	5.75 (2.53-13.10)
Time to randomization, h (*P* = .53)[b]			
<24	68	71	7.70 (3.36-17.65)
24-48	78	87	16.01 (3.12-82.07)
>48	17	15	0.66 (0.17-2.61)
Vascular territory (*P* = .52)[c]			
MCA only	97	103	4.85 (2.34-10.07)
MCA and ACA and/or PCA	69	89	5.77 (2.51-13.27)
Summary			4.95 (2.99-8.20)



P values for heterogeneity across subgroups are shown (interaction term treatment × subgroup variable). Common odds ratios (ORs) are adjusted for age, sex, and presence of aphasia (not National Institutes of Health Stroke Scale [NIHSS] score at baseline and time to randomization). All analyses were performed with a 1-stage model with random effects for the variables' trial and treatment. ACA indicates anterior cerebral artery; MCA, middle cerebral artery; and PCA, posterior cerebral artery. Squares represent mean values, with the size of the squares indicating weight and horizontal lines representing 95% CIs. The diamond represents the summary mean with the points of the diamond representing the 95% CI.

[a] Not recorded in the study by Zhao et al[10] (n = 47) and missing (n = 1) in HAMLET (Hemicraniectomy After Middle Cerebral Artery infarction with Life-threatening Edema Trial).[8]

[b] Not recorded in DEMITUR (Decompressive Surgery for the Treatment of Malignant Infarction of the Middle Cerebral Artery: A Randomized Controlled Trial in a Turkish Population) (eAppendix 3 in the Supplement) (n = 151) and missing (n = 1) in the DESTINY II (Decompressive Surgery for the Treatment of Malignant Infarction of the Middle Cerebral Artery II) study.[11]

[c] Not recorded in the study by Slezins et al[22] (n = 44), DECIMAL (Decompressive Craniectomy in Malignant MCA Infarction) (n = 38), and DESTINY[7] (n = 32) and missing (n = 16) in DEMITUR.

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