Decompressive Hemicraniectomy in the Treatment of Malignant Middle Cerebral Artery Infarction: A Meta-Analysis

Suparna Das[1], Patrick Mitchell[1], Nicholas Ross[1], Peter C. Whitfield[2]

Key words
- Decompressive hemicraniectomy
- Infarction
- Malignant MCA stroke
- Middle cerebral artery

Abbreviations and Acronyms
CT: Computed tomography
DC: Decompressive hemicraniectomy
ICP: Intracranial pressure
MCA: Middle cerebral artery
mRS: Modified Rankin Scale
QoL: Quality of Life
RCT: Randomized controlled trial

From the [1]Royal Victoria Infirmary, Newcastle-upon-Tyne; and [2]Derriford Hospital, Plymouth, UK

To whom correspondence should be addressed: Suparna Das, M.B.B.S., M.Res., M.R.C.S. [E-mail: suparna.das1@nhs.net]

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BACKGROUND: **Malignant middle cerebral artery infarctions are large space-occupying infarctions involving massive edema, herniation, and frequently death. Survivors are disabled. Management involves medical treatment, with or without decompressive hemicraniectomy and later duraplasty. This meta-analysis aimed to determine whether surgery is worthwhile with particular regard to views on quality of life of professionals and patients.**

METHODS: **A Medline search was performed with the search terms "decompressive surgery," "craniectomy," "hemicraniectomy," "decompressive hemicraniectomy," and "middle cerebral artery," "MCA," "infarct,*" "stroke,*" "embolus," "emboli," "thrombosis," "occlusion," "infarction," and "middle cerebral artery stroke," A second search was also done for views on postoperative quality of life. Studies retrieved were randomized controlled trials, observational studies, and reviews. We compared patients who received only medical treatment with those who had decompressive surgery. Participants were adult patients presenting with malignant middle cerebral artery infarction.**

RESULTS: **270 abstracts were reviewed. 40 articles were identified: 8 randomized controlled trials and 4 observational studies. There were a total of 692 patients: 268 surgical and 424 medical. The 2 groups were comparable, with similar demographics. In most trials, mortality was lower with surgery. However, morbidity tended to be higher, particularly in the elderly population. Morbidity was lower with medical treatment. Twelve articles on postoperative quality of life were reviewed; views differed between professionals, and survivors and caregivers. A patient-level comparison could not be made between all studies.**

CONCLUSIONS: **Surgical decompression results in lowered mortality but high morbidity, especially in the elderly. There is an increase in Quality Adjusted Life Years but at high costs. Professionals think that surgery is not worth the high disability rate. However, patients and caregivers are satisfied with their postoperative quality of life. Survey data from healthy study participants who are not professionals in stroke care were not available. The decision to treat surgically needs to be decided on an individual basis.**

INTRODUCTION

Rationale

Malignant middle cerebral artery (MCA) infarctions are large space-occupying lesions associated with extensive edema, herniation, and high mortality. They usually involve infarction of at least two thirds of the MCA territory.[1] They make up 10% of all strokes and are the most devastating ischemic strokes.[2,3]

Patients present with symptoms and signs of severe hemispheric stroke syndrome, including hemiplegia and deteriorating consciousness in the first 48 hours resulting from raised intracranial pressure (ICP).[1,4] Impaired consciousness can develop as early as 3 hours after stroke onset because of mass effect from brain edema,[5] which can progress rapidly over minutes to hours, causing subfalcine, uncal, transtentorial, and/or tonsillar herniation, often terminating in brain death.[5] Despite full medical therapy, mortality rates are high (about 80%), with death occurring as a complication of raised ICP.[6,7] Survivors of malignant MCA infarction are usually significantly disabled.

The prognosis of MCA infarction is associated with clinical and radiologic factors. Clinically, risk factors for death include a high initial National Institutes of Health Stroke Scale score and early signs of transtentorial herniation.[2] Young patients are more at risk because of lack of atrophy and less ability to accommodate increases in brain volume. Radiological factors associated with poor outcome include on computed tomography (CT), greater than 50% of MCA territory low-density infarction.[3,5] Diffusion-weighted imaging provides early diagnostic information showing ischemic changes before the appearance of CT hypodensity.[3] On CT and magnetic resonance angiography, internal carotid artery occlusion as opposed to purely

MCA, an absence of collateral supply and an absence of recanalization are predictors of death.[5]

Medical treatment for raised intracranial pressure includes ventilation, blood pressure control, osmotherapy, hyperventilation, and barbiturate sedation. Ipsilateral decompressive hemicraniectomy (DC) after MCA stroke was first reported in 1956.[8] Dural opening decompresses ischemic cerebral tissue[7,8] and may improve global cerebral and penumbral blood flow, improving brain tissue oxygenation.[7,8] Surgery has been reported to reduce mortality to 20%, especially if the procedure is done within 24 hours of symptom onset.[9] Historically, DC was not performed frequently because of fears over survivor disability.[2] However, with improvements in intensive care, there is some evidence that postoperative outcomes have improved.[2] DC saves lives, but disability is a problem.

Until recently, there was no level 1 evidence on the outcomes of malignant MCA infarction patients undergoing DC. Most evidence came from case series, case reports, prospective observational studies, or retrospective studies, which stated that this operation was life saving. Also, no review has been performed summarizing the opinions of professionals, patients, and family members on postoperative quality of life (QoL).

In this article we consider the published evidence evaluating outcomes in patients with malignant MCA infarction undergoing DC versus best medical management. The outcomes recorded from randomized controlled trials (RCTs) and observational studies were mortality and morbidity at 3 to 12 months. Descriptive results were also collated from studies on the views of professionals, patients, and caregivers on QoL after DC.

Objectives

In patients with malignant MCA stroke, is DC more effective than medical treatment alone in improving mortality and morbidity? A meta-analysis was performed to answer this.

METHODS

Protocol and Registration

The PROSPERO systematic review registration number is CRD42018095962.

Eligibility Criteria and Search Strategy

The question to be answered was "In patients with malignant MCA stroke, is decompressive hemicraniectomy more effective than medical treatment alone in improving mortality and morbidity?" The length of follow-up varied between 3 and 12 months. A Medline and PubMed search was performed with the search terms "decompressive surgery," "craniectomy," "hemicraniectomy," "decompressive hemicraniectomy," and "middle cerebral artery," "MCA" "infarct,*" "stroke,*" "embolus," "emboli," "thrombosis," "occlusion," "infarction," and "middle cerebral artery stroke." The limitations included were English language and humans. There was no limitation on years.

Information Sources

RCTs, retrospective and prospective observational studies, case series, and reviews were identified (Figure 1). The last searched date was June 24, 2017. Databases used were Medline and PubMed. The studies considered were those with adult populations (above the age of 18) and those that compared surgically treated patients with conservatively treated patients. In all the studies reviewed, a DC and a duraplasty were performed. For the review of views on postoperative QoL, a literature search did not produce any results. The relevant articles were identified from the references of related articles. Study authors were not contacted to identify additional studies.

Study Selection

RCTs and retrospective and prospective observational studies were identified using the above search criteria. RCTs were included in the meta-analysis.

Data Collection Process

Data was extracted independently from reports. Data was not confirmed with investigators.

Data Items

Information collected included years of study, patient numbers with malignant MCA stroke, patient age group, time interval between symptom onset and surgery, percentage of dominant and nondominant hemisphere stroke, follow-up interval, survival rates in surgically versus medically treated patients, degree of disability in surgically versus medically treated patients, comorbidities, randomization method, type of preoperative and postoperative care, and study limitations. The most frequently used scores to assess outcome were the modified Rankin Scale (mRS) (Table 1) and the Barthel Index. For the randomized controlled trials, the timings of the operation ranged between 6 and 96 hours of stroke onset. Aspects that were not considered were the effects on the outcomes of size of the hemicraniectomy (for most studies the diameter was at least 12 cm), performing a temporal lobectomy, and the material used in duraplasty. Funding data was not collected.

Risk of Bias in Individual Studies

The Cochrane risk of bias tool was used for the RCTs. We looked for postallocation bias in studies. Specifically, we checked to see whether the dichotomy between favorable and unfavorable outcomes (mRS cutoff of 3 or 4) was changed from the "protocol" or "methods" to the "results." This is a problem as, although we know that it saves lives, if the dichotomy point is changed from 3 to 4, this reduces the extent of morbidity resulting from surgery. Also, we checked to see whether the time interval within which surgery was performed was changed from the "methods" to the "results." Additionally, we looked for selection, performance, detection, attrition, and reporting bias. The prospective reviews and retrospective reviews were assessed for bias using the Newcastle-Ottawa scale.

Summary Measures

The primary outcome measure was the mRS score at 1 year or 6 months. This was divided between favorable (0–4 or 0–3) and unfavorable (5 and death or 4–5) outcomes. Secondary outcome measures were the mortality rates at 1 year or 6 months, and a division of the mRS between 0 to 3 and 4 until death. In HAMLET and DECIMAL, to assess the effect of surgical treatment, absolute risk reductions and 95% confidence intervals were reported.[10,11] In DESTINY I and II and HeADDFIRST, odd ratios and 95% confidence intervals were used.[11,12] Zhao et al used absolute risk reduction, number needed to treat, and 95% confidence

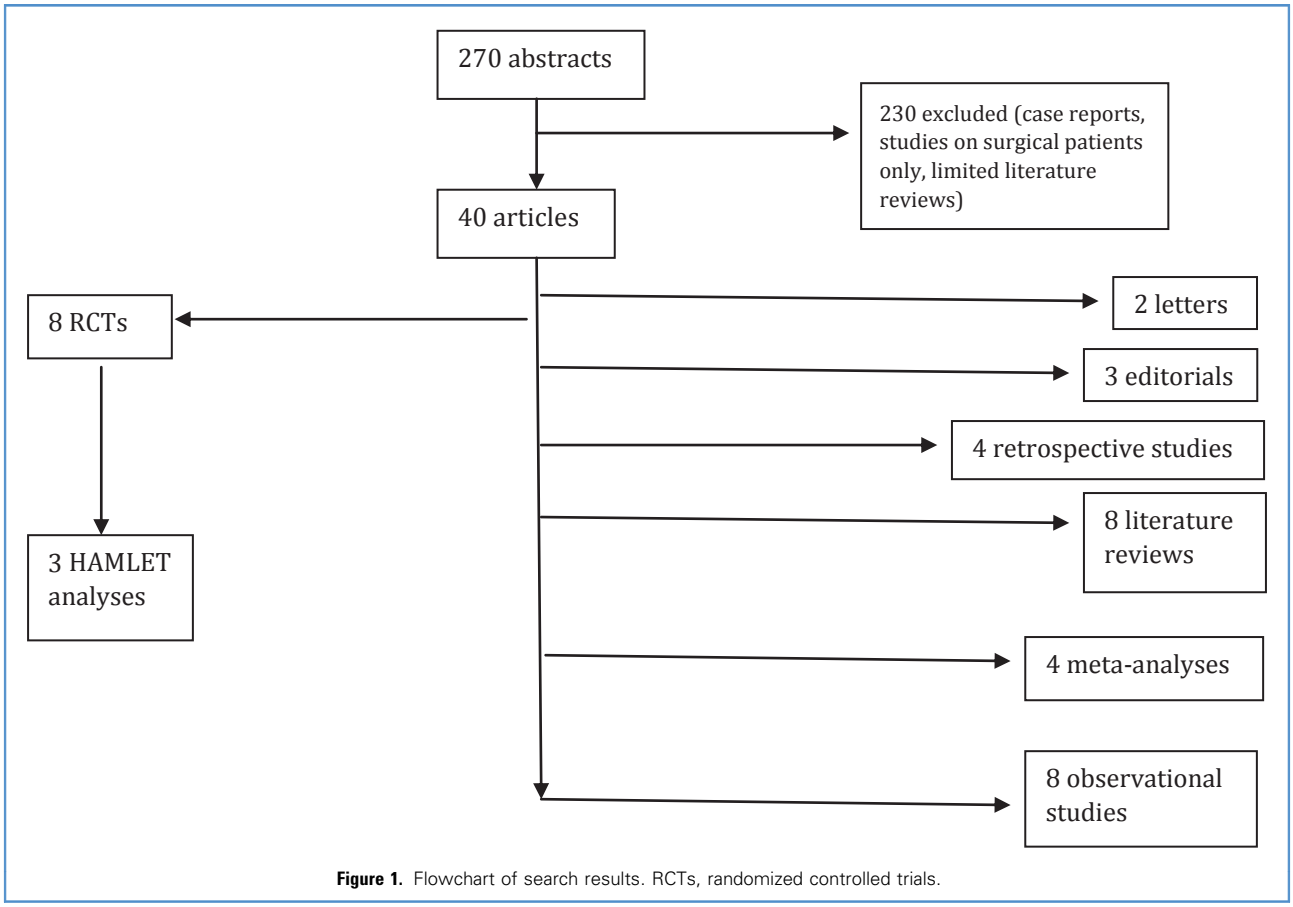

Figure 1. Flowchart of search results. RCTs, randomized controlled trials.

intervals.[13] This was unclear for Slezins et al.[14]

Summary of Results

The software R (R, version 3.5.0, The R Foundation for Statistical Computing, 2018) was used to perform the meta-analysis. Data were taken from full-text published articles using 6-month outcome data. mRS scores of 4 to 6 were compared in surgical and best medical therapy arms. Survival and death were compared in the same arms. A fixed-effects model was used for both meta-analyses. This was chosen (instead of random effects) because the outcome of surgery was invariably reduced mortality, and increased morbidity, with the extent of both varying depending on the study. Risk ratios were reported with the 95% confidence interval. There was insufficient data in the source material to allow for separate analyses of outcomes for patients above or below 60 years of age. Study heterogeneity was assessed using Levene's test.

Table 1. Modified Rankin Scale

Modified Rankin Scale (mRS)	
mRS 0	No symptoms
mRS 1	No significant disability; able to carry out all usual activities, despite some symptoms
mRS 2	Slight disability; able to look after own affairs without assistance, but unable to carry out all previous activities.
mRS 3	Moderate disability; requires some help, but able to walk unassisted.
mRS 4	Moderately severe disability; unable to attend to own bodily needs without assistance, and unable to walk unassisted.
mRS 5	Severe disability; requires constant nursing care and attention, bedridden, incontinent.
mRS 6	Dead

Risk of Bias Across Studies

Potential biasing factors that affected more than 1 trial were considered. This included age of patients, outcome measures, and capture of full treatment morbidity, including deferred cranioplasty.

RESULTS

Study Selection and Characteristics

A summary of the results of the major studies is presented below. Table 2 shows the results for 8 RCTs and 2 prospective and 3 retrospective observational studies.

The majority of studies reported improved survival for surgical patients. Some also showed reduced morbidity. However, in 4 studies, the great majority of survivors of surgery had severe levels of disability, with mRS scores $\geq$4.[10,11,15,20] Not all studies had directly comparable follow-up intervals: these ranged from 3 months to 1 year. There was insufficient information on causes of mortality to enable comparison of all 12 studies. However, in DESTINY II, the majority of surgical deaths were due to medical complications (15 of the 20 deaths), and the majority of medical deaths were due to herniation (34 of the 47 deaths). **Figure 1** shows a flowchart of search results. Studies that were not RCTs or observational studies were excluded.

Risk of Bias Within Studies

HAMLET changes the dichotomy point from between mRS 3 and 4 (as stated in the protocol), to between 4 and 5 in the "Results." Thus, it reduces the significance of morbidity as an outcome of DC. This post-hoc analysis should not be presented as a primary outcome. During data collection, HAMLET randomly sorted patients up to 96 hours from stroke onset. However, there was a post-hoc analysis limiting the trial data to those randomized within 48 hours. The authors state that this was due to other RCTs using 48 hours. There is performance bias, inasmuch as participants and personnel knew which intervention was assigned. There is no comment on reporting bias. It is not clear whether there is attrition bias.

In DECIMAL, DESTINY, DESTINY II, HeADDFIRST, HEMMI, Zhao et al., and Slezins et al, there is performance bias, inasmuch as participants and personnel knew which intervention they are assigned to. Reporting bias is not commented on. In DESTINY and DESTINY II, there is detection bias, inasmuch as the outcome assessor was not blinded to the intervention. DESTINY II also has attrition bias, with no comment on why patients were lost (in surgery, 49 patients reduced to 47; in medical, 63 patients reduced to 62). In HeADDFIRST, there is attrition bias where 1 patient was randomized to surgery but not operated on because his wife deemed it was not worth the excessive disability. In Slezins et al., there is attrition bias: 3 patients were randomized to surgery but were not included because the operation timing was 100 hours (instead of 48 hours) after stroke onset. One patient did not undergo surgery because there were no signs of raised ICP despite randomization to the surgery group. Blinding of the individuals who assessed the outcomes is not mentioned. In HEMMI, there was attrition bias with, from the surgical group, 1 patient not having surgery because of a myocardial infarction and 3 being lost to follow-up, and, from the medical group, 3 having surgery because of deterioration and 2 being lost to follow-up.

There was accidental allocation bias when DESTINY I's medical group had more dominant hemisphere strokes.

The prospective reviews by Rai et al. and Hao et al., and retrospective reviews by Holtkamp et al. and Yang et al., all had 8 stars on the Newcastle-Ottawa scale, which indicated that they were all high-quality studies.[18-21] The maximum score is 9.

Results of Individual Studies

The results are shown in **Table 2**. Further descriptions of the results are provided later in this text.

Synthesis of Results

Levene's test was attempted. However, because all absolute deviations were constant within each cell, Levene F statistics could not be calculated. The within-groups sum of squares was zero, indicating that there was no variance within groups and consequently no heterogeneity. The meta-analysis of results using a fixed-effects model is shown in **Figure 2** and **Figure 3**.

Risk of Bias Across Studies

The age of patients in most studies was younger than that in the overall stroke population. That means the results are not generally applicable. However, the systematic age bias is due to current beliefs about the relationship between age and efficacy of surgery. There is evidence to support these beliefs. No studies captured the morbidity of cranioplasty, which is significant from other series, particularly in the elderly. Studies account for motor function, but they do not cover cognitive function or depression, for example,[22] Including assessments for cognition (e.g., CAMCOG) and for depression (e.g., MADRS) would contribute to an overall improved understanding of functional outcome and the degree of long-term dependence. None of the studies report outcomes based on hemisphere dominance, so it is not possible to state categorically that infarction in a specific hemisphere would result in reduced morbidity. The QoL studies have a major limitation in the way the data are collected. Seeking patients' and caregivers' views after the operation results in a different viewpoint in favor of surgery.

Views on Quality of Life After Surgery

Twelve articles were identified on post-operative QoL. Surveys of healthcare professionals tend to find that most would prefer not to be kept alive with severe disability involving chronic impairment of consciousness.[23] Demertzi et al. distributed a survey among healthcare professionals at European conferences to determine end-of-life attitudes toward patients in chronic minimally conscious and vegetative states. They found that the majority did not wish to be kept alive in either a chronic minimally conscious state (67%) or a vegetative state (82%).[23]

However, surveys of those who have severe disability tend to find that they are happy to be alive.[24] Rahme et al performed a systematic literature review to assess the outcome of DC in malignant MCA stroke from the patient's perspective.[24] There were 382 patients, with 268 survivors (with a mean of 19 months follow-up data). Caregivers were also interviewed. Of the 192 survivors with QoL assessment, the average QoL reduction was 45%; 56% of 114 survivors had depression. Methods of assessment included a life satisfaction checklist (asking to choose between grades of satisfaction/dissatisfaction), asking whether "life was worth living," and retrospective agreement. For the latter, patients and caregivers were asked at the end of the follow-up period (with the outcome known) whether they would have consented again for surgery, and 76% of 209 survivors and caregivers were satisfied with life and would give their consent again for surgery. It is debatable how representative caregivers' answers are of the patients' wishes, and the number of caregivers participating is not mentioned. Ninety-five percent of relatives said they

Table 2. Comparison of Studies Assessing the Outcomes of Patients Having Decompressive Hemicraniectomy Against the Outcomes of Patients Being Treated Conservatively

Study	Year	No. of Patients	Age of Patients	Timing of Decompression	% Dominant Hemisphere (Surgical)	% Nondominant Hemisphere (Surgical)	% Dominant Hemisphere (Medical)	% Nondominant Hemisphere (Medical)	Survivor (Surgery) (%)	Survivor (Medical) (%)	mRS >3 (Surgery) (High Morbidity) (%)	mRS >3 (Medical) (High Morbidity) (%)	*P* Value
Randomized controlled trials													
DESTINY I Juttler et al.[11] (6 months)	2004–2005	32	18–60	12–36	53	47	73	27	82.40	46.70	42.90	42.90	0.04
DESTINY II Juttler et al.[12] (12 months)	2009–2012	112	>60	48	16	-	25	-	57.10	23.80	51	19	0.73
DECIMAL Vahedi et al.[15] (6 months)	2001–2005	38	18–55	7–43	-	-	-	-	75	22.20	10	16.70	0.18
HAMLET Hofmeijer et al.[10] (12 months)	2002–2007	64	≥60	3–96	-	-	-	-	78.10	40.60	53.10	15.60	1.00
HeADDFIRST Frank et al.[16] (6 months)	2000–2002	24	18–75	96	36	-	50	-	64.30	60	38.50	30	-
HEMMI Chua et al.[17] (6 months)	2002–2009	24	18–65	72	8	-	5	-	61.50	45.50	46.20	45.50	0.92
Zhao et al.[13] (6 months)	1996–2007	47	18–80	48	37.5	-	39.1	-	87.50	39.10	79.20	95.70	0.21
Slezins et al.[14] (6 months)	2009–2012	24	18–80	8–36	-	-	-	-	45.50	7.69	9.09		-
Prospective observational studies													
Hao et al.[18] (12 months)	2007–2011	219	≤60	48	71	-	53.2	-	61.30	37.80	29	26.10	0.006
Rai et al.[19] (12 months)	2010–2011	60	20–91	9–148	-	-	-	-	61.10	16.70	8.30d	16.70	0.025
Retrospective observational studies													
Holtkamp et al.[20] (3–9 months)	1998–1999	24	>55	13–130	-	-	-	-	66.70	16.70	66.70	16.70	-
Yang et al.[21] (3 months)	1996–2004	24	19–75	31–140	-	-	-	-	90	36	50	35.70	0.05

mRS, modified Rankin scale.

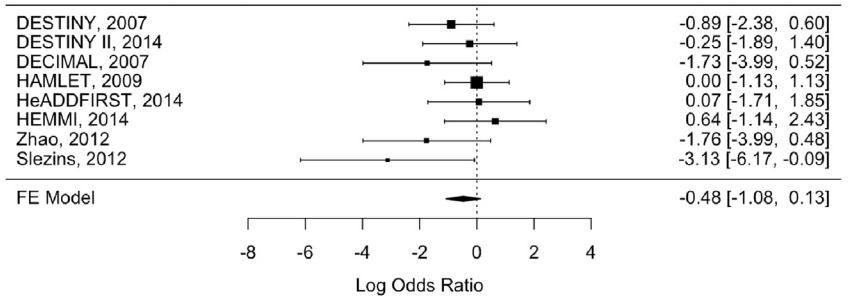

Figure 2. Poor (modified Rankin Scale [mRS] 4–6) versus good (mRS 1–3) outcomes.

would give consent again.[25] Foerch et al found that numbers of patients or caregivers, who in retrospect knowing the outcome would again choose DC, was nearly equally distributed. Nine patients answered "yes," 9 were against it, and 4 could not decide.[26]

Woertgen et al demonstrated that the overwhelming majority (81%) of patients or relatives would opt for surgery after they had undergone DC.[27] Benejam et al reported that when asked if they would undergo DC again with the same outcome, 79% of 29 patients said yes.[25] Carter et al showed a tendency toward favoring DC retrospectively, considering the patients' current recovery.[28] Six patients indicated yes, 3 indicated maybe, and 2 would not consider DC again.[28] Erban et al found that 14 patients retrospectively agreed with the decision to have DC, 3 indicated probable disapproval, and 6 retrospectively would definitely not approve of DC.[29] Leonhardt et al reported that 4 of 18 patients would not retrospectively agree to undergo DC again because of poor QoL.[30] Walz et al found that 11 of 12 stroke survivors and their relatives retrospectively approved of their decision to proceed with DC.[31] Weil et al. report that 7 patients (87.5%) were happy to be alive and to have had the DC, and 1 (12.5%) would not have consented to it for the same result. QoL may be affected by several variables, including severity of disability, the premorbid lifestyle, and the patient's personality and his or her relatives.[32]

Age and Decompression

The studies included in this review covered a spectrum of ages: between 18 and 91 years. Several studies had an upper age cutoff of 55 to 65 years. An editorial by Murthy suggests that DC in patients older than 60 years with malignant MCA infarction is associated with a survival benefit. However, available data suggest that most of these patients have disability scores of mRS 3 to 4.[7] Another editorial suggests an age limit for surgery of 60 years; these patients may be poor candidates for aggressive rehabilitation.[33]

Timing of Decompression

All the RCTs showed that the 2 groups (surgical and medical) had similar mean time intervals from stroke onset to recruitment (Table 3). The exact timing of hemicraniectomy has not been tested.[6,34] Forty-eight hours from time of injury appears to be a pragmatic cutoff. This could be due to reduced direct pressure on the brain and minimized secondary ischemia resulting from reduced blood flow by increased tissue pressure or arterial compression. A recent study demonstrated that early DC (within 48 hours) was associated with reduced discharge to a rehabilitation center and better outcomes. However, there was no difference in outcome in patients that did not have sustained herniation.[35]

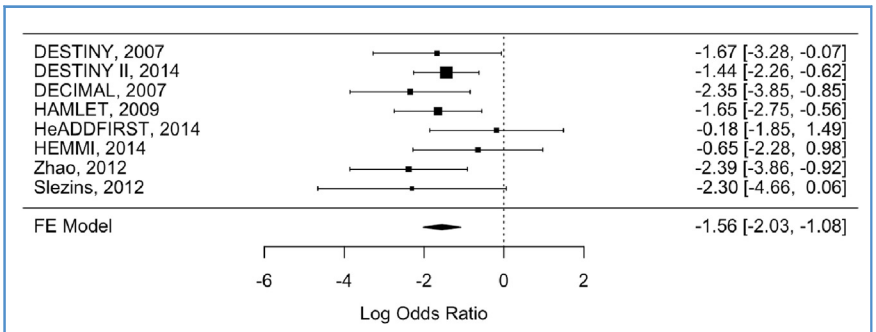

Figure 3. Surviving versus dead patients at 6 months. FE, fixed effects.

Quality of Life of Survivors

Quality of life was measured using the Barthel Index and mRS, with mRS being used more consistently. For the purpose of this review, patients were divided into 2 groups: favorable (mRS 1–3) and unfavorable (mRS >3). What follows is a summary of the proportion of patients in both groups of mRS scores, first for surgical patients, then for medical. Each study had different inclusion criteria as described above, which must be taken into account when the different results are compared.

The mRS scores for surgical patients varied between studies. In the DESTINY trial, 57.1% of them had mRS 1–3, and 42.9% had mRS >3.[11] In the DESTINY II trial, there were more surgical survivors with severe disability (6.1% with mRS 1–3, 51% with mRS>3).[12] In the DECIMAL trial, 50% had an mRS of 1–3.[15] The higher disability score of >3 was attributed to 10% of surgical patients. The HAMLET trial reported 25% with mRS 1–3.[10] There were more surgical patients with severe disability (mRS >3 in 53.1%). The HeADDFIRST trial had 30% with mRS 1–3 and 38.5% with mRS >3.[16] The HEMMI trial reported 23.1% with mRS 1–3.[17] An mRS >3 was assigned to more surgical (46.2%) patients. Hao et al, had fewer severely disabled surgical patients (71.3% with mRS 1–3, with 29% having mRS >3).[18] Rai et al. had more surgical patients with mRS 1–3 (52.8%) than mRS >3 (8.3%).[19] Holtkamp et al. had no patients with mRS 1–3.[20] Of the patients with mRS >3, 66.7% were surgical patients.

Table 3. Comparison of Time Intervals From Ictus to Treatment in Randomized Controlled Trials

	Range or Mean Time Interval (with SD Where Available) From Ictus to Treatment, Hours	
Study	**Surgery**	**Best Medical Treatment**
DECIMAL[15]	20.5 ± 8.3	-
DESTINY[11]	24.4 ± 6.9	23.8 ± 7.8
DESTINY II[12]	16–50	-
HAMLET[10]	(Ictus to randomization: 29–50)	(Ictus to randomization: 29–63)
HeADDFIRST[16]	(Ictus to randomization: 29.5–64.4)	(Ictus to randomization: 27.7–80.4)
HEMMI[17]	36.6 ± 19.7	-
Zhao et al.[13]	(Ictus to randomization: 23.6 ± 6.4)	(Ictus to randomization: 24.1 ± 6.4)
Slezins et al.[14]	8–36	(ictus to randomization: 6–34)

Yang et al. reported 40% of surgical survivors with mRS 1–3 and 50% with mRS >3.[21] Zhao et al. reported more surgical (79.2%) patients than medical patients with severe disability[13]; 8.33% had mRS 1–3. In the study by Slezins et al, surgical survivors were mostly of low (mRS 1–3) disability (45.5%),[14] and 9.09% were severely disabled, with mRS >3.

The mRS scores for medical patients also varied. In the DESTINY trial, 57.1% had mRS of 1–3 and 42.9% had mRS >3.[11] In the DESTINY II trial, there were more medical survivors with severe disability (4.8% with mRS 1–3, 19% with mRS >3).[12] In the DECIMAL trial, 5.6% had mRS of 1–3.[15] The higher disability score of >3 was attributed to 16.7% of medical patients. The HAMLET trial reported 25% with mRS 1–3 and 15.6% with mRS >3.[10] The HeADDFIRST trial had 30% with mRS 1–3 and 30% with mRS >3.[16] The HEMMI trial reported 36.4% with mRS 1–3.[17] An mRS>3 was assigned to 45.5%. In the study by Hao et al., 11.7% of medical patients had mRS 1–3 and 26.1% had mRS >3.[18] In Rai et al, all surviving medical patients were of severe disability (16.7%).[19] Holtkamp et al. had no patients with mRS 1–3.[20] Of the patients with mRS >3, 16.7% were medical patients. Yang et al. reported that all the medical survivors had severe disability (35.7%).[21] Zhao et al. reported fewer medical (95.7%) patients than surgical patients with severe disability[13]; 4.35% had mRS 1–3. Slezins et al reported no figures for the medical survivors.[14]

High rates of depression have been noted among survivors. In a review by Rahme et al, 56% of survivors were affected by depression, and in 25%, this was moderate or severe.[29]

DISCUSSION

Summary of Evidence

The available research base has established 2 facts unambiguously: 1) Decompressive craniectomy reduces mortality after malignant MCA infarction. 2) Most of those lives saved by craniectomy are accompanied by severe disability.

It is important to recognize that, though not explicitly mentioned, some of the studies may have captured morbidity data on any subsequent cranioplasty procedure. Literature reports pertaining to traumatic brain injury indicate that cranioplasty is associated with significant mortality rates (around 5%) and a complication rate of around 25%.[36] This consideration should be factored in during the evaluation of the relative merits of craniectomy as an adjunct to the treatment of malignant MCA infarction.

This finding leaves 2 areas where further inquiry is needed. The first is the ethical question of whether there is a level of disability below which life is not worth living; if so, what is this level? Some research has been done on this, as summarized in the Results section. The second area is the question whether the operation improves the likelihood of moderate disability or good recovery. Available data indicate a nonsignificant trend in this direction, but small improvements could easily be offset by the morbidity and mortality of cranioplasty operations, which many of these patients go on to have. A purely mechanistic analysis suggests that the operation is more likely to increase the rate of good recovery or moderate disability in younger patients. Young people have less cerebral atrophy; therefore, less brain swelling is able to provoke brain shift and a critical rise in intracranial pressure. This means that less extensive MCA infarcts can be life-threatening; therefore, the operation may preserve life in patients with less irreversible damage. The available data do tend to support this hypothesis, but they allow only for the fairly crude estimate of the difference between those over and under the age of 60.

In the context of severe traumatic brain injury, DC, as demonstrated in the DEcompressive CRAniectomy (DECRA) and RescueICP trials, has not been shown to improve patient outcomes.[37-39] Data from these trials show a similar effect of surgery, with reduced mortality but increased morbidity.

The meta-analysis by Alexander et al. includes 7 RCTs.[40] Our meta-analysis has an additional RCT, which is the HEMMI trial conducted in the Philippines. Their findings are similar to ours, with DC resulting in fewer mortalities but more morbidities. The largest increase was in patients with mRS 4. Unlike us, those authors used a random effects model for the meta-analysis. The GRADE method was used to assess the quality of evidence, which we have not done. Eligibility criteria for inclusion were determined by having separate groups of reviewers working in pairs and independently identifying and reviewing full texts of possible articles. That approach was unlike the approach this study, where this decision was made by the first author alone. Supervising authors confirmed the decision. Alexander et al., like us, used the Cochrane Risk of Bias tool.

Our meta-analysis differs from previous such studies. The differences from the

world of Alexander et al. are outlined above. We have included the HEMMI RCT. We have also included a review of caregivers' and patients' views on their QoL after DC, which has not been summarized before.

The implications for healthcare providers, users, and policy makers are that decision for surgery is to be made on an individual basis, with careful discussion between healthcare professionals, family, and, where possible, patients. Graphic displays of the data resulting from these studies will be useful aids to such discussions. Some patients present fully conscious with significant strokes that threaten to cause a deterioration in level of consciousness over the first 24 to 48 hours. The question of discussing surgery and gaining the patient's views during this lucid period should be given serious consideration.

Limitations

The RCTs available are small trials, which reduces the generalizability. There is a significant age effect, with the younger (below 60) age group having better outcomes than the older (above 60) group. An effective comparison could not be made between all studies because of the heterogeneity in patient populations and in the study designs. Most of the studies had a lower limit of age of 18 but had upper age limits that varied from 55 to 91 (**Table 1**). Three studies had an older patient population with a minimum age of 55 or 60.[12,15,20] Time to surgery and follow-up intervals were different. In the RCTs, time intervals before decompression ranged from 3 to 96 hours, with the maximum time interval in the observation studies being 148 hours (**Table 1**). Follow-up periods were mostly 6 months. Few studies had more useful 12-month intervals.[10,12,18,19] Not all studies gave details of what medical treatment involved. Only DECIMAL, DESTINY I and II, HAMLET, and Zhao included a detailed description of what standard medical treatment was provided.[10-13,15]

The outcomes scores (mRS and Barthel Index) do not measure functional levels fully; they account for motor function, but they do not cover cognitive function or depression, for example.[22] Including assessments for cognition (e.g., CAMCOG) and for depression (e.g., MADRS) would contribute to an overall improved understanding of functional outcome and the degree of long-term dependence. None of the studies report outcomes based on hemisphere dominance, so it is not possible to state categorically that infarction in a specific hemisphere would result in reduced morbidity.

There was some selection bias: in HAMLET, there were few patients with aphasia.[10] The QoL studies have a major limitation in the way the data were collected. Seeking patients' and caregivers' views after the operation has been performed results in a different viewpoint in favor of surgery.

CONCLUSION

Survival is high, but so is morbidity and cost. QoL studies show differing views between professionals, and survivors and family. Professionals do not consider DC worthwhile if severe disability occurs. Despite experiencing high rates of disability and depression, patients are happy that they underwent the operation.[24]

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