Early decompressive craniectomy for malignant cerebral infarction

Meta-analysis and clinical decision algorithm

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Abstract

Background: Decompressive craniectomy (DC) is an aggressive life-saving surgical intervention for patients with malignant cerebral infarction (MCI). However, DC remains inconsistently and infrequently utilized, primarily due to enduring concern that increased survival occurs only at the cost of poor functional outcome. Our aim was to clarify the role of DC performed within 48 hours (early DC) for patients with MCI, including patients aged >60 years. **Methods:** We performed a meta-analysis of all available randomized controlled trials comparing early DC to best medical care for MCI. Studies were identified through literature searches of electronic databases including PubMed, EMBASE, and Scopus. We employed a Mantel-Haenszel fixed effects model to assess treatment effect on dichotomized modified Rankin Scale (mRS) outcomes at 12 months. **Results:** A total of 289 patients from 6 randomized controlled trials comparing early DC to best medical care were included. Early DC resulted in an increased rate of excellent outcomes, defined as mRS ≤ 2 (relative risk [RR] 2.81, 95% confidence interval [CI] 1.01–7.82, $p = 0.047$), and favorable outcomes, defined as mRS ≤ 3 (RR 2.06, 95% CI 1.25–3.40, $p = 0.005$). Early DC also increased the rate of survival with unfavorable outcomes, defined as mRS 4–5 (RR 3.03, 95% CI 1.98–4.65, $p < 0.001$). **Conclusions:** Early DC increases the rate of excellent outcomes, i.e., functional independence, in addition to favorable and unfavorable outcomes; however, these findings must be interpreted within the context of patients' goals of care. We have developed a clinical decision algorithm that incorporates goals of care, which may guide consideration of early DC for MCI in clinical practice. *Neurol Clin Pract* 2016;6:433–443

Malignant cerebral infarction (MCI) refers to large-volume ischemic strokes involving the middle cerebral artery territory, which are complicated by life-threatening cerebral edema.¹ Managed medically, MCI carries a mortality rate of 80%.^{1,2} Decompressive craniectomy (DC), the surgical removal of a portion

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[W]e performed a meta-analysis of all available RCTs comparing 12-month functional outcomes in adult MCI patients treated with early DC vs best medical care.

of the skull allowing outward herniation of infarcted brain tissue, may reduce MCI mortality to ~20%.²⁻⁴ Both nonrandomized and randomized controlled trials (RCTs) suggest that DC is most effective within 48 hours of stroke onset (early DC),^{2,3,5,6} but despite decreased mortality, survivors often have poor functional outcomes secondary to stroke severity.^{2,7}

In 2007, a landmark interim pooled analysis of 3 RCTs demonstrated improved functional outcomes, defined as modified Rankin Scale (mRS) scores 0–3, for MCI patients treated with early DC.⁶ However, this morbidity benefit was not present upon completion of the trials^{5,8,9}; nor has it been demonstrated in subsequent RCTs,^{10,11} which employed a less stringent definition of acceptable functional outcome (mRS 0–4) with poor generalizability.^{12–17} Consequently, there is enduring concern that early DC increases survival only at the cost of poor quality of life.^{8,9,12,15} Lack of clarity is evidenced by wide variations in clinical practice with infrequent and inconsistent utilization of early DC for MCI patients in the United States and other countries.^{15,18–20}

In light of these considerations, we performed a meta-analysis of all available RCTs comparing 12-month functional outcomes in adult MCI patients treated with early DC vs best medical care. Our aim was to generate more robust outcome data to better inform clinical decision-making.

METHODS

Literature search

Studies were identified through electronic database searches of PubMed, EMBASE, Scopus, and Cochrane Library. Conference presentations were identified in PubMed, BIOSIS Previews, Proceedings, and EMBASE. The search was developed and conducted by L.M.H. For full details of our literature search, see appendix e-1 at Neurology.org/cp. We performed our final literature search on January 9, 2015.

Study selection and data extraction

We determined a priori to include all RCTs of early DC for MCI in patients ≥18 years of age that reported functional outcomes at 12 months. Early DC was defined as enrollment with the intent to perform DC within 48 hours from stroke onset; this definition was derived from clinical trial data demonstrating increased treatment effect within this time period.^{2,3,5,6} Cohort studies and case series were not eligible due to high risk of bias.

All retrieved RCTs were reviewed independently by 2 authors (C.D.S. and B.J.M.). Quality control and risk of bias were assessed using a 7-point scoring system recommended by the Cochrane Collaboration.²¹ Accordingly, studies were assigned an overall risk of bias score: low, unclear, or high. Two authors (C.D.S. and B.J.M.) independently abstracted patient ages (dichotomized: ≤60 years or >60 years) and mRS scores at 12 months from each eligible trial. Patient ages from Slezins et al.²³ were obtained via correspondence with the author. Any discrepancies between the authors were resolved by review and consensus.

Statistical analysis

All 6 trials reported mRS scores at 12 months. We defined outcomes as excellent (mRS 0–2), favorable (mRS 0–3), or survival with unfavorable outcome (mRS 4–5) in best accordance with both clinical convention and public perception.^{6,12–15,17} Under this stratification,

Supplemental Data

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excellent outcomes (mRS 0–2) represent patients with only mild disability and preserved functional independence; favorable outcomes (mRS 0–3) represent patients with preserved functional independence, plus moderately disabled nonindependent patients who retain the ability to ambulate unassisted; unfavorable outcomes (mRS 4–5) comprise surviving patients who are unable to ambulate unassisted or attend to their own bodily needs, plus patients who are bedbound, requiring constant nursing care.

To assess treatment effect, we employed a Mantel-Haenszel fixed-effects model for its statistical properties when handling infrequent outcomes and small sample sizes, and in order to report our findings in terms of relative risk (RR).²² All studies that met our inclusion criteria were included in the primary analysis. In order to assess the robustness of our findings, we conducted a prespecified sensitivity analysis excluding any studies assigned an unclear or high risk of bias rating. Heterogeneity between studies was investigated by calculating I^2 . Clinically significant heterogeneity requiring further investigation was conservatively defined as $I^2 > 40\%$.²² We assessed publication bias and small study effects visually through funnel plots and statistically via Begg and Egger tests. Statistical significance was predefined as an α level <0.05 . A preplanned quantitative subgroup analysis of outcomes for patients older than 60 years was undertaken to explore the effect of age on treatment outcomes. All statistical analyses were conducted using STATA 13.1 (StataCorp, College Station, TX). The analysis plan was approved by the University of Pittsburgh Institutional Review Board. The study protocol was not published a priori.

RESULTS

Study selection and study characteristics

In total, we identified 1,229 nonduplicate articles. After screening each article for eligibility, we reviewed 7 full-text publications (figure 1). Six RCTs comprising 289 patients met our inclusion criteria: 4 completed trials of early DC, the published preliminary results from a trial of early DC, and a subgroup analysis comprised of patients randomized within 48 hours from Hemicraniectomy After Middle Cerebral Artery Infarction With Life-threatening Edema Trial (HAMLET), a DC trial which enrolled patients up to 96 hours from onset (table).^{5,10,11,23–25} One study was excluded, Hemicraniectomy and Durotomy Upon Deterioration From Infarction-Related Swelling Trial (HeADDFIRST), which enrolled patients up to 96 hours from onset and, notably, intentionally delayed DC until patients had severe clinical or radiographic deterioration.²⁶

Inclusion criteria for the individual trials were similar, with exception of the prespecified age ranges (table). Baseline patient characteristics of the treatment groups were well-matched with exception of Jüttler et al.²⁵ and Slezins et al.,²³ which reported higher mean NIH Stroke Scale scores in the medically managed group. Slezins et al.²³ also reported a lower mean age in the patients undergoing DC.

Risk of bias for independent studies

The 4 completed RCTs of early DC, Jüttler et al.,²⁵ Vahedi et al.,²⁴ Zhao et al.,¹¹ and Jüttler et al.,¹⁰ received a low risk of bias rating. Slezins et al.²³ is a brief preliminary report that does not comprehensively detail study methodology. Hofmeijer et al.⁵ reported a post hoc analysis of 39 patients enrolled in HAMLET within 48 hours of stroke onset, but did not report baseline patient characteristics or whether their initial randomization stratification was maintained in this subgroup.^{5,27} Secondary to these concerns, Slezins et al.²³ and Hofmeijer et al.⁵ both received an unclear risk of bias rating. A full risk of bias rating table is included in figure e-1.

Primary analysis and sensitivity analysis

At 12 months, patients with MCI who were treated with early DC had an increased rate of excellent outcomes, defined as mRS 0–2 (RR 2.81, 95% confidence interval [CI] 1.01–7.82, $p = 0.047$), and favorable outcomes, defined as mRS 0–3 (RR 2.06, 95% CI 1.25–3.40, $p = 0.005$).

Figure 1 Literature review flowchart

DC = decompressive craniectomy.

Treatment with early DC was also associated with an increased number of survivors with unfavorable functional outcome, defined as mRS 4–5 (RR 3.03, 95% CI 1.98–4.65, $p < 0.001$) (figure 2). There was an absolute risk increase (ARI) of 6.6% for excellent functional outcome with early DC, which corresponds to a number needed to treat (NNT) of 15.2. For favorable outcome, the ARI was 15.0% and NNT 6.7, whereas for unfavorable functional outcome ARI was 29.5% and NNT 3.4. There was no clinical heterogeneity in any of the analyses ($I^2 = 0$ –7.2% for primary outcome analyses) or evidence of publication bias or small study effects.

In our sensitivity analysis, the magnitude of treatment effect and statistical significance of early DC remained fundamentally unaltered across all outcome measures. Excellent outcomes (RR 3.84, 95% CI 1.01–14.52, $p = 0.048$), favorable outcomes (RR 2.01, 95% CI 1.12–3.59, $p = 0.019$), and unfavorable outcomes (RR 2.71, 95% CI 1.74–4.20, $p < 0.001$) were increased by early DC. There was no clinical heterogeneity ($I^2 = 0\%$ for all sensitivity analyses). For excellent functional outcomes, ARI was 7.6% and NNT 13.2, for favorable functional outcomes ARI was 14.0% and NNT 7.1, and for unfavorable outcomes ARI was 26.9% and NNT 3.7.

Subgroup analysis: Patients older than 60 years

Three RCTs of MCI included patients older than 60 years, with a total of 66 patients randomized to early DC and 83 to best medical care.^{10,11,23} Twelve-month outcomes were assessed quantitatively rather than by meta-analysis due to the limited number of trials. In contrast to younger patients, no older patients attained an excellent outcome (mRS 0–2) irrespective of treatment arm, and markedly fewer patients reached mRS 3. A total of 7.6% of older patients

It should be noted that age is a key determinant of functional outcome.

who underwent early DC achieved mRS 3 compared with 3.6% of older patients who received best medical care, corresponding to an ARI of 4.0% and NNT 25.0 for favorable outcomes. For unfavorable outcomes, ARI was 32.5% and NNT 3.1. A total of 75.9% of older patients in the medical treatment arm died in comparison with 39.4% of older patients who underwent early DC, absolute risk reduction 36.5% and NNT 2.7 to prevent mortality (figure 3).

DISCUSSION

Our meta-analysis demonstrates that early DC increases excellent outcomes, i.e., functional independence (mRS 0–2), and favorable outcomes (mRS 0–3) in patients with MCI. Better functional outcomes in early DC patients are likely not only due to preventing lethal brain herniation, but also improving cerebral hemodynamics, thereby limiting secondary injury and increasing potential for long-term recovery.^{28,29} However, we also found that early DC in MCI increases the risk of survival with unfavorable functional outcome (mRS 4–5). These somewhat paradoxical findings, in which both favorable and unfavorable functional outcomes are increased, are driven by the large reduction in MCI-related mortality in patients treated with early DC.^{5,6,10,11}

Nevertheless, our findings clarify and guide decision-making for MCI patients who are considered good candidates for early DC. Goals of care are driven primarily by (1) maximizing functional outcome or survival, (2) minimizing the likelihood of survival with disability, or (3) quality of life. As we have demonstrated, if the priority is to maximize functional outcome or survival, patients should undergo early DC. Conversely, due to stroke severity, MCI patients who wish to avoid survival with considerable disability should be managed medically and, when

Table Study inclusion characteristics

Study	No. of participants	Age, (y)	DC timing, (h)	Baseline mRS	Clinical and radiographic definitions of MCI
Jüttler 2014 ¹⁰	109	>60	<48	≤1	NIHSS >14 (nondominant) or >19 (dominant) >66% infarction MCA territory
Zhao 2012 ¹¹	47	18–80	<48	≤2	Eye and motor GCS ≤9 >66% infarction MCA territory
Slezins 2012 ^{23,a}	24	18–81	<48	≤1	NIHSS >15 >50% infarction MCA territory or DWI volume >145 cm ³
Hofmeijer 2009 ⁵	39	18–60	<48 ^b	≤1	NIHSS >15 (nondominant) or >20 (dominant) >66% infarction MCA territory
Vahedi 2007 ²⁴	38	18–55	<30	≤1	NIHSS >15 >50% infarction MCA territory or DWI volume >145 cm ³
Jüttler 2007 ²⁵	32	18–60	<36	≤1	NIHSS >18 (nondominant) or >20 (dominant) >66% infarction MCA territory

Abbreviations: DC = decompressive craniectomy; GCS = Glasgow Coma Scale; mRS = modified Rankin Scale; MCI = malignant cerebral infarction; MCA = middle cerebral artery; DWI = diffusion-weighted imaging; NIHSS = NIH Stroke Scale.

^aPreliminary publication.

^bPost hoc subgroup analysis of the original trial, which enrolled patients up to 96 hours from MCI onset.

Figure 2 Functional outcomes for patients treated with early decompressive craniectomy (DC) vs best medical care

(A) Excellent outcomes. (B) Favorable outcomes. (C) Unfavorable outcomes. CI = confidence interval; mRS = modified Rankin Scale; RR = relative risk.

appropriate, referred to palliative care. Finally, quality of life determinations following early DC may be derived from the pooled functional outcomes of all 6 RCTs and further refined by age to account for differences between younger and older patients (figure 3). For example, an otherwise healthy 50-year-old MCI patient who finds mRS 0–3 acceptable and mRS 4–5 unacceptable has a 43% chance of good quality of life, a 35% chance of poor quality of life, and a 22% chance of death 12 months after early DC. If that same patient found mRS 0–4 acceptable, the probabilities shift to a 69% chance of good quality of life, a 9% chance of poor quality of life, and a 22% chance of death. This clinical decision algorithm is illustrated in figure 4.

It should be noted that age is a key determinant of functional outcome. Goals of care for MCI patients older than 60 years must take into account the low likelihood of attaining an

Figure 3 Modified Rankin Scale (mRS) score shift analysis at 12 months

(A) All ages. (B) Age ≤60 years. (C) Age >60 years. Percentages may not sum to 100 because of rounding. Early DC = decompressive craniectomy performed within 48 hours; medical = best medical care. ^a The mRS is a validated functional outcome scale commonly used in clinical stroke trials. Scores are defined as 0, no symptoms; 1, no significant disability, able to carry out all usual activities despite some symptoms; 2, slight disability, remains independent, but unable to carry out all previous activities; 3, moderate disability, requires some assistance, but able to walk unassisted; 4, moderately severe disability, unable to attend to own bodily needs or walk unassisted; 5, severe disability, bedridden, requiring constant nursing attention; 6, dead.³² ^b No patients attained mRS score 0 or 1 due to stroke severity.

mRS score ≤3 following early DC. In fact, while only a small number of patients achieved mRS 2 (2% in the medical arm compared to 8.6% in the DC arm), none of them were older than 60 years. On the other hand, the large mortality benefit from DC persists for patients over age 60 years; therefore families and clinicians must weigh the survival benefit against the possibility of considerable neurologic disability and functional dependence. Additional prognostic considerations should include preexisting radiographic and neurologic signs of herniation and total infarct volume.^{7,23} There is no evidence that laterality (dominant vs nondominant hemispheric infarction) affects long-term outcome, although severe language deficits may be considered unacceptable quality of life.^{30,31}

This meta-analysis has multiple limitations. The first limitation relates to our definitions of excellent (mRS 0–2), favorable (mRS 0–3), and survival with unfavorable (mRS 4–5) functional outcomes. The mRS is a widely used, validated functional outcome scale that measures a person's degree of disability or dependence.³² At extremes of the mRS spectrum, there is general consensus that scores 0–2 represent good outcomes and scores 5–6 represent poor outcomes.^{12–15} mRS 3 is usually regarded as favorable, but perception of mRS 4 (which

Figure 4 Clinical decision algorithm for consideration of early decompressive craniectomy (DC) in malignant cerebral infarction (MCI)

Early DC = DC performed within 48 hours; mRS = modified Rankin Scale. ^a Twelve-month outcomes.

represents moderately severe disability with the inability to attend to one's bodily needs or walk unassisted) varies widely.^{12–16} Our own stratification was informed by multiple independent studies of physicians, nurses, and the general public in which 6%–38% of respondents considered mRS 4 a quality of life worth living.^{12,13,15,16} Nonetheless, retrospective studies have shown that most MCI patients who have undergone DC have a reasonable quality of life and are satisfied with their treatment, even those with an mRS of 4,^{33–35} creating an inherent difficulty in defining acceptable outcomes. Therefore, our findings should not be applied rigidly, but rather serve as a framework for clinical decision-making based upon individual patient and family goals of care. Although the most common interpretations of acceptable and unacceptable outcome are presented in figure 4, these probabilities can simply be recalculated to reflect alternative valuations of mRS outcome strata when necessary.

A second limitation is that there are only 6 RCTs of early DC eligible for our analysis and each trial was relatively small. We could have expanded the number of eligible patients by including DC trials that enrolled patients past 48 hours; however, there is sufficient evidence to suggest that patients treated later experience a different clinical course.^{5,26} We prespecified exclusion of patients undergoing late DC in order to maintain a pure sample population, which is reflected in the consistency of treatment effect across our studies as calculated by I^2 . For similar reasons, we excluded nonrandomized trials, whose results are potentially subject to substantial bias.

Another limitation is the timing of our outcome assessment. Although existing data support the use of 12-month functional outcomes rather than earlier time points, it is recognized that some patients continue to regain function after 1 year, which could lead to an underestimation of treatment effect.^{27,36} Only one RCT of DC has reported outcomes past 12 months.²⁷

When making outcome assessments, some of the studies attempted to blind the assessors to treatment assignment,^{6,11} while others did not.^{10,23,25} A further limitation is that the dichotomization of mRS outcomes leads to a loss of information and less precise valuations. For example, defining unfavorable outcome as mRS 4 and 5 does not account for the fact that mRS 4 is both more frequent and more desirable than mRS 5. Finally, the RCTs included in our meta-analysis restricted eligibility to patients who were otherwise healthy and functionally independent at baseline. Therefore our results cannot be generalized to MCI patients with notable medical comorbidities or those who were previously functionally dependent; however, such patients are less commonly considered for DC in clinical practice.

Strengths of our study include consistency in the magnitude of treatment effect and statistical significance observed across the primary analysis and sensitivity analysis. Additionally, our data were derived entirely from RCTs with an overall low risk of bias. We did not find any evidence of heterogeneity of treatment effect, publication bias, or small study effects. Unlike previous publications, we address the effect of early DC on achieving functional independence and also include the largest reported cohort of randomized MCI patients older than 60 years. Most importantly, despite multiple RCTs and previously published meta-analyses,^{8,37,38} early DC for MCI remains inconsistently and infrequently utilized.^{12,13,18–20}

Our specific aim was to generate outcome data with direct clinical applicability. Our study design and clinical decision algorithm incorporates individual patient or surrogate decision-maker perceptions regarding quality of life and therefore may be applied on a case-by-case basis when considering early DC for patients with MCI.

Our meta-analysis demonstrates that early DC improves excellent outcomes, defined as functional independence, at 12 months for patients with MCI. Additionally, early DC for MCI led to increased survival with both favorable and unfavorable functional outcomes at 12 months—a finding dependent upon the patient's valuation of mRS outcome strata. Our findings and clinical decision algorithm add clarity to the role of early DC in MCI and may help guide management of patients considered good candidates for decompressive surgery.

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AUTHOR CONTRIBUTIONS

C. Streib: study concept and design, data extraction, statistical analysis/interpretation of the data, drafting/revising the manuscript. L. Hartman: study concept and design, developed and conducted literature search. B. Molyneaux: study concept and design, data extraction, statistical analysis/interpretation of the data, drafting/revising the manuscript.

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