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CLINICAL TRIAL REPORT

Early Decompressive Hemicraniectomy Following Malignant Ischemic Stroke: The Crucial Role of Timing

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Hofmeijer J, Kappelle LJ, Algra A, et al.: Surgical decompression for space-occupying cerebral infarction (the Hemicraniectomy After Middle Cerebral Artery infarction with Life-threatening Edema Trial [HAMLET]): a multicenter, open, randomized trial. *Lancet Neurol* 2009, 8:326–333.

Rating

••Of major importance.

Introduction

Malignant infarction of the middle cerebral artery (MCA) territory is a devastating form of stroke that carries a mortality rate as high as 80% and produces severe disability among survivors [1, 2]. Most patients who die within 1 week of malignant infarction suffer herniation caused by infarct-related edema [1, 2]. Medical therapies aimed at reducing edema have not been proven to reduce mortality or disability [3]. Decompressive hemicraniectomy with duraplasty may ameliorate the effects of infarct-related edema by accommodating tissue shifts and preventing herniation [4]. Although surgical decompression appears to improve mortality after malignant infarction, it is not clear that surgical treatment achieves clinically significant improvement in functional outcome [5]. Further, the optimal patient selection criteria for and timing of decompressive surgery have not been established.

Following the publication of numerous observational and prospective, uncontrolled studies of hemicraniectomy, three recent randomized controlled trials (RCTs) explored the impact of decompressive surgery on mortality and functional outcome after malignant stroke. DECIMAL (Decompressive Craniectomy in Malignant Middle Cerebral Artery Infarcts) randomly assigned 38 patients enrolled within 30 h of stroke to undergo surgery or medical management; DESTINY (Decompressive Surgery for the Treatment of Malignant Infarction of the Middle Cerebral Artery) enrolled 32 patients up to 36 h after stroke [6, 7]. Both studies demonstrated a reduction in death rates in the surgical arm; however, neither included a sufficiently large sample to allow conclusions regarding functional outcome. HAMLET (Hemicraniectomy After MCA Infarction With Life-Threatening Edema Trial), the third RCT of decompressive surgery, enrolled patients up to 96 h after stroke. A meta-analysis of the patients enrolled in DECIMAL and DESTINY, as well as the first 23 patients enrolled in HAMLET within 48 h of stroke, showed an increase in favorable functional outcome, defined as a modified Rankin scale (mRS) score of 0 to 3, in those treated with surgery [8]. DECIMAL and DESTINY had completed enrollment at the time of this analysis; HAMLET continued to enroll patients.

Following malignant ischemic stroke, the peak of edema and the greatest risk of herniation occur between 24 and 96 h after symptom onset [1]. To our knowledge, HAMLET is the largest RCT investigating the effect of surgical intervention on both mortality and functional outcome throughout this high-risk period.

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Aims

To assess the effect of decompressive surgery within 4 days of the onset of symptoms in patients with space-occupying hemispheric infarcts.

Methods

The authors enrolled 64 patients aged 18–60 years diagnosed with acute ischemic stroke in the MCA territory within 96 h of initiation of trial treatment. The study was conducted at six specialized centers in the Netherlands. Enrolled patients had ischemic changes on CT affecting two thirds or more of the MCA territory and formation of space-occupying edema. Patients with right-sided lesions were required to have a National Institutes of Health Stroke Scale (NIHSS) score≥16 and a Glasgow Coma Scale (GCS) score≤13; those with left-sided lesions were required to have an NIHSS score≥21 and a combined GCS motor and eye score≤9. Patients with holohemispheric stroke, decreased consciousness attributable to medication effects or metabolic derangements, bilateral fixed and dilated pupils, alteplase administration within 12 h, systemic bleeding disorder, premorbid functional limitation (mRS score > 1 or Barthel index score<95), life expectancy less than 3 years, or serious premorbid illness were excluded. Patients were randomly assigned to receive surgical intervention involving removal of a bone flap of at least 12 cm in diameter with duraplasty or optimal medical management; 32 patients were assigned to each arm. No patients crossed over between treatment assignments. Medical management was conducted in either a stroke unit or an intensive care unit (ICU) setting and was at the discretion of the attending physician. Guidelines were issued recommending the use of hyperosmolar therapy, invasive intracranial pressure (ICP) monitoring, sedation with propofol for mechanical ventilation or elevated ICP, blood pressure control with labetalol or nitroprusside for pressures higher than 220/120 mm Hg, use of catecholamines for hypotension or optimization of cerebral perfusion pressure, and maintenance of normothermia, normoglycemia, and normovolemia. The guidelines discouraged the use of prolonged hyperventilation and barbiturates. The primary outcome measure was mRS at 12 months, dichotomized into good (0–3) and poor (4–6). Secondary outcome measures included case fatality, Barthel index score, Montgomery and Asberg depression rating scale (MADRS) score, and two quality-of-life assessments: the Medical Outcomes Study 36-item short form (SF-36) and a 10-point visual analogue scale. The authors originally planned to enroll 112 patients; however, the data monitoring committee recommended that enrollment stop after an interim analysis found that no statistically significant difference likely would be seen in the primary outcome between treatment groups.

Results

Baseline characteristics of the treatment groups were similar, except that patients treated surgically were older and those treated medically were randomly assigned slightly later. Use of interventions other than the trial treatment may have differed between the two arms. Patients in the surgical arm were more frequently admitted to the ICU and more frequently received mechanical ventilation, sedation, and ICP monitoring. Patients in the medical arm were more frequently admitted to a stroke unit and more frequently received osmotherapy; no patients in the medical arm received ICP monitoring. No statistical analysis of these differences was reported. The primary outcome measure was identical in both treatment arms; 24 patients in each arm had an mRS score greater than 3 at 12 months. Severe disability, defined as an mRS score greater than 4, was not significantly different between the groups. Of the secondary outcomes, risk of death was significantly reduced in the surgical group (absolute risk reduction [ARR], 38%; P=0.002) and the physical summary of the SF-36 was higher among medically treated patients (mean difference, 8; P=0.02). The reduction in risk of death was unchanged after adjustment for age and time to randomization. The authors performed subgroup analyses of patients ≤50 years old, 51–60 years old, with aphasia, without aphasia, randomly assigned at less than 48 h, and randomly assigned at more than 48 h. No effect of surgical treatment was found in these subgroups, except in patients randomly assigned within 48 h of symptom onset. For these patients, risk of death (ARR, 59%; 95% CI, 33–84) and severe disability with an mRS score greater than 4 (ARR, 30%; 95% CI, 1–59) were reduced. The authors also reported the results of an updated meta-analysis of all patients enrolled in DECIMAL, DESTINY, and HAMLET who underwent decompressive surgery within 48 h. The updated meta-analysis includes data from 109 patients, 58 treated surgically and 51 medically. As in the previous analysis, the authors found a significant reduction in risk of death (ARR, 49.9%; 95% CI, 33.9–65.9) and severe disability, defined as a 12-month mRS score greater than 4 (ARR, 41.9%; 95% CI, 25.2–58.6). The authors reported a trend toward reduction in risk of poor outcome, defined as a 12-month mRS score greater than 3 (ARR, 16.3%; 95% CI, –0.1 to 33.1).

Discussion

The authors concluded that surgical decompression within 96 h of malignant MCA stroke did not reduce poor outcomes at 1 year, but that significant reduction in death or moderate-to-severe disability (mRS score>4) existed in patients randomly assigned within 48 h of stroke. The authors noted that the benefit of surgery was not as strong

in HAMLET as was reported in the previously published meta-analysis of patients treated within 48 h. They hypothesized that this difference may have been the result of a longer interval between symptom onset and surgical treatment in HAMLET (mean 31 h) than in DECIMAL (mean 16 h) and DESTINY (mean 24 h).

Comments

Malignant ischemic stroke remains a devastating disease with limited effective medical treatments. The life-sparing potential of surgical treatment has long been recognized, with case reports of successful decompression appearing as early as 1935 [9]. There also have been long-standing concerns that the procedure creates survivors with severe neurologic disability and very poor quality of life. Some clinicians have come to use decompressive surgery only as a rescue therapy in the face of impending transtentorial herniation in select patients. Retrospective analysis of this practice suggested that surgical decompression should be reserved for patients who are young and have single-vessel, nondominant hemisphere strokes [5, 10, 11]. Other clinicians, using surgical decompression before clinical signs of herniation and within the first 24 h after stroke, reported promising results in a comparison of consecutive case series [12]. Which patients should be considered for decompressive surgery and when such intervention should be undertaken remain unclear. RCTs such as DECIMAL and DESTINY were undertaken to determine whether early hemicraniectomy offers clinically meaningful improvement in functional outcome after malignant stroke. Both studies were small and underpowered to demonstrate differences in functional outcomes. HAMLET is important in that it adds significantly to evidence derived from RCTs regarding decompressive surgery.

With 64 patients enrolled, HAMLET is the largest RCT investigating decompressive hemicraniectomy in stroke. HAMLET recruited 39 of these patients within 48 h of stroke, representing approximately one third of the total patients studied in RCTs of early decompression. HAMLET also is the first study to collect extensive quality-of-life data in this patient population. The results of HAMLET must be viewed as largely negative. Although case fatality clearly was reduced in the surgical arm of the study, the two arms were no different with respect to functional outcome. Quality-of-life measures also were the same in the two groups, with the exception of one measure that marginally favored medical therapy. HAMLET does not confirm the long-held fear that decompressive surgery creates life without quality.

The HAMLET trial results also must be considered in the context of the other recent trials of decompressive surgery. In the expanded meta-analysis of patients pooled from DECIMAL, DESTINY, and HAMLET, surgery conferred a protective effect on risk of death or moderate to severe disability (mRS score>4) at 12 months. These results are not trivial. Patients with an mRS score of 4 or 5 may continue to enjoy meaningful interactions with their friends and family, although they likely will require 24-hour assistance indefinitely. Whether this represents an acceptable quality of life is highly subjective and will vary greatly depending on the values held by an individual patient. Larger clinical trials are needed to better characterize the effect of surgery on functional outcome and to permit meaningful analysis of sophisticated measures of quality of life.

The most important finding of HAMLET, however, is that the clinical benefits of hemicraniectomy are greatest when surgery is performed early. In that sense, HAMLET recapitulates the same lesson we understand to be true for all forms of acute stroke therapy: time equals brain, and earlier is always better.

Disclosures No potential conflicts of interest relevant to this article were reported.

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