Hemicraniectomy – An Overview of Current Status and Future Considerations

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Abstract

Space-occupying so-called 'malignant' middle cerebral artery infarction is – besides acute basilar artery occlusion – the most devastating form of ischaemic stroke. Until recently, there was no proven treatment. In 2007, results from randomised controlled trials were published providing evidence for the benefit of early hemicraniectomy with respect to mortality after three months. This article focuses on current treatment options for malignant ischaemic brain infarction, especially hemicraniectomy. Moreover, major unsolved problems and open questions regarding the disease are discussed, and a perspective is given on future clinical studies in this field.

Keywords

Decompressive surgery, hemicraniectomy, malignant middle cerebral artery infarction, brain oedema, space-occupying stroke

In 2006, results from randomised controlled trials were published regarding decompressive surgery for the treatment of space-occupying 'malignant' middle cerebral artery (MCA) infarctions. Each of these studies and the pooled analysis provided evidence for a benefit of early hemicraniectomy with respect to mortality after three months. This article focuses on hemicraniectomy as the current treatment of choice for malignant ischaemic brain infarction.

Complete MCA territory infarctions, occasionally with additional ischaemia of the anterior and posterior cerebral artery (ACA and PCA, respectively), are found in 1–10% of patients with supratentorial infarcts.[1] The term 'malignant MCA infarction' was introduced based on the commonly associated serious brain swelling, which usually manifests itself between the second and fifth day after stroke onset.[2] These massive cerebral infarctions are life-threatening events with a uniform natural course and an extremely poor prognosis.[3] The mass effect leads to an increased intracranial pressure (ICP) with further destruction of formerly healthy brain tissue, resulting in midline shifting and possible transtentorial or uncal herniation in the majority of patients (see *Figure 1*).[1,3] A rapid neurological deterioration with a case fatality rate of up to 80% despite maximal treatment was seen in about two-thirds of these patients.[4,5] Several medical treatment strategies, such as osmotic therapy, steroids, hyperventilation, barbiturates and buffers, have been proposed to reduce cerebral oedema formation and raised ICP, but so far none of these therapeutic strategies has been supported by adequate evidence of efficacy from experimental studies or randomised clinical trials and several reports suggest that these approaches are not only ineffective, but even detrimental.[6,7]

Hemicraniectomy
Findings from Experimental and Observational Studies

Hemicraniectomy for the treatment of space-occupying stroke is by no means new and dates back to as early as 1935.[8] Results from animal studies revealed that decompressive surgery was significantly associated with a reduction in mortality and infarct size and, moreover, improved regional blood flow and functional outcome.[9–11] These experimental findings are supported by data from clinical reports; meanwhile, there are many data available in the literature on hemicraniectomy for the treatment of malignant MCA infarction – between 1935 and 2007, 93 case reports and series of patients with malignant brain infarctions were published including a cumulative total of 1,834 patients. However, most of the reports were retrospective, including only few patients.[12,13] Before 2006, there were only a few prospective trials comparing decompressive surgery with conservative treatment, some of which used historical control groups, and most control groups consisted of patients who were older, suffered from more severe co-morbidity and were frequently affected by infarctions of the dominant hemisphere.[14–17]

Comparative data from non-randomised clinical studies reported that hemicraniectomy reduced in-hospital mortality from 60–100% (in controls) to 0–29% in surgically treated patients, and long-term mortality from 83–100% to 33%, respectively.[16,18] A systematic review performed by Gupta and colleges analysed all available data of 138 patients and described an overall mortality rate after hemicraniectomy of 24% after a period of seven to 21 months.[14] Various trials suggested that decompressive surgery reduces a poor outcome and increases favourable or independent functional outcome.[15,18–20] On the other hand, there are several studies that doubt these results, especially in patients with increased age and with additional infarction of the ACA or PCA

Figure 1: Natural Course of Malignant Middle Cerebral Artery Infarction
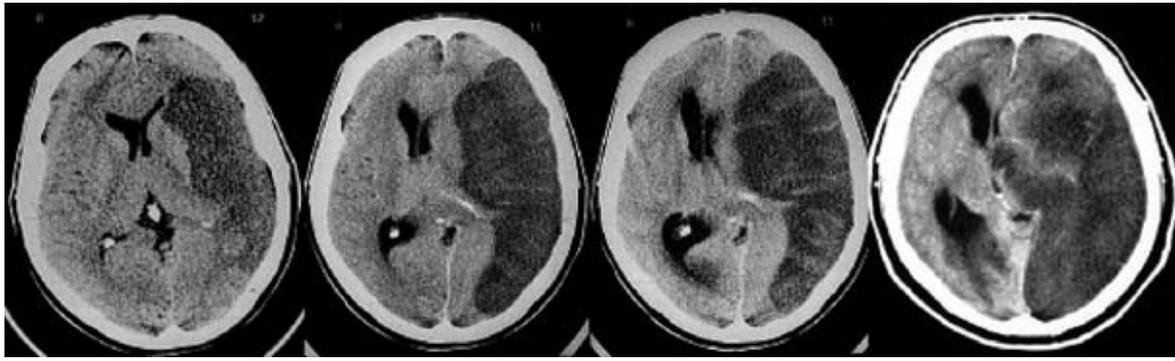
From left to right: cranial computed tomography (CT) scans on day two, three, four and five after symptom onset resulting in transtentorial herniation.

territory.[17,21,22] Other predictors that have been proposed to predict unfavourable outcome are pre-operative midline shift, low pre-operative Glasgow Coma Scale (GCS), presence of anisocoria, early clinical deterioration and internal carotid artery occlusion.[23] In the meta-analysis by Gupta et al., age was the only prognostic factor for poor outcome, whereas time to surgery, the presence of brainstem signs prior to surgery or additional infarction of the ACA or PCA territory were not associated with outcome.[14]

Surgical Techniques

The rationale of decompressive surgery is to remove a part of the neurocranium and to provide space to accommodate the swollen brain. It further aims to normalise intracranial pressure, to avoid ventricular compression, and to revert brain tissue shifts. Moreover, cerebral blood flow shall also be restored, which may allow a better perfusion and tissue oxygenation of still healthy brain to minimise infarct volume.[24,25] There are two different techniques: external (removal of the cranial vault and duraplasty) or internal (removal of non-viable, i.e. infarcted, tissue) decompression. The two techniques can be combined.[15,19]

Meanwhile, there is a broad consensus among neurosurgeons about the recommended procedure. External decompressive surgery consists of a large hemicraniectomy and a duraplasty: a large (reversed) question-mark-shaped skin incision based at the ear is made. A bone flap with a diameter of at least 12cm (including the frontal, parietal, temporal and parts of the occipital squama) is removed. Additional temporal bone is removed so that the floor of the middle cerebral fossa can be explored. The dura is then opened and an augmented dural patch, consisting of either homologous periost and/or temporal fascia, is inserted (the size may vary; usually, a patch of 15–20cm in length and 2.5–3.5cm in width is used). The dura is fixed at the margin of the craniotomy to prevent epidural bleeding. The temporal muscle and the skin flap are then re-approximated and secured. Ischaemic brain tissue is not usually resected. During this procedure a sensor for registration of intracranial pressure can also easily be inserted. In surviving patients, cranioplasty is performed after at least six weeks (usually six to 12 weeks) using the stored bone flap or an artificial bone flap.[26]

Randomised Controlled Studies

In 2006 and 2007, data from three randomised trials were published providing strong evidence for a dramatic reduction in mortality.[27–30] The trials were: DEcompressive Surgery for the Treatment of malignant INfarction of the middle cerebral arterY (DESTINY);

DEcompressive Craniectomy In MALignant middle cerebral artery infarcts (DECIMAL); and Hemicraniectomy After Middle cerebral artery infarction with Life-threatening Edema Trial (HAMLET).

DESTINY was an open, controlled, prospective, multicentre, randomised trial. Patients were randomised to either surgical plus conservative treatment or to conservative treatment alone. The maximum time from symptom onset to treatment start was 36 hours. All patients were treated in an intensive care unit (ICU) and were intubated and ventilated. DESTINY was based on a sequential design, taking mortality after 30 days as the first end-point, and randomisation was planned to go on until statistical significance for this end-point was reached. Thereafter, patient enrolment would be interrupted until the six-month functional outcome end-point (primary end-point) – modified Rankin Scale (mRS) dichotomised at a score of 0–3 versus 4–6 – had been collected. Depending on the observed difference in functional outcome, the final sample size would be recalculated for a second explorative trial stage. Secondary end-points included analysis of the mRS 0–4 versus 5–6 and the distribution of scores of the mRS at six months and at one year. After inclusion of 32 patients between February 2004 and October 2005, patient recruitment was stopped due to the statistically significant results of mortality: in the intention-to-treat analysis, two of 17 patients (11.8%) treated by hemicraniectomy had died, whereas seven of 15 patients (50.3%) who received maximum conservative treatment on the ICU alone had died after 30 days (p=0.02). Functional outcome data after 12 months are summarised in *Figure 2*: 47.1% of the patients in the surgical arm and 26.7% of the patients in the conservative arm reached an mRS of 0–3 (p=0.23), and 76.5% in the surgical arm versus 33.3% in the conservative arm reached an mRS of 0–4 (p=0.01). Analysis of the distribution of the mRS scores showed positive results in favour of surgery (p=0.04). After a sample size projection for the primary end-point suggested a number of 94 patients to be included in each arm, the trial was stopped.[29]

DECIMAL was another open, controlled, prospective, multicentre trial that also randomly assigned patients to either surgical plus conservative treatment or to conservative treatment alone. Among other criteria, an infarct volume on diffusion-weighted imaging (DWI) of at least $145cm^3$ qualified patients for inclusion. Hemicraniectomy had to be performed within 30 hours after symptom onset and within six hours after randomisation. The primary end-point in DECIMAL was functional outcome based on the score on the mRS, dichotomised 0–3 versus 4–6. A sequential design for this end-point

Figure 2: Functional Outcome After Conservative Treatment (A) and After Hemicraniectomy (B) in Patients with Malignant Middle Cerebral Artery Infarction

A. Functional outcome after 12 months – conservative treatment (mRS)

B. Functional outcome after 12 months – hemicraniectomy (mRS)
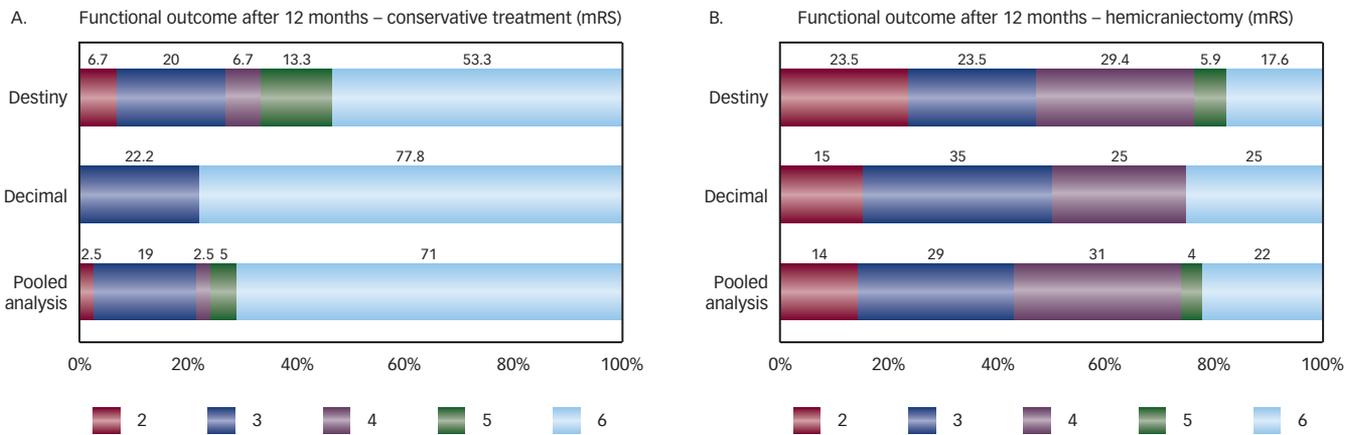
was chosen based on interim analyses after every four patients. Secondary end-points included survival and the score on the mRS at six and 12 months. Between December 2000 and November 2005, 38 patients were enrolled. Survival was significantly different between both groups: the mortality rate was five of 20 patients (25%) in the surgical treatment group and 14 of 18 patients (77.8%) in the conservative treatment group (p<0.0001). Functional outcome data after 12 months are summarised in *Figure 2*: 40.0% of patients in the surgical arm versus 22.2% of patients in the conservative arm reached an mRS of 0–3 (p=0.08).[27]

In 2007 the results of a prospectively planned pooled analysis of the three European randomised trials including all patients from DESTINY and DECIMAL and 23 patients from HAMLET receiving early hemicraniectomy within 48 hours was published.[27–30] For the pooled analysis, a maximum time window from stroke onset to randomisation of 45 hours and of 48 hours to treatment start was adopted. Outcome measures were the score on the mRS at one year, dichotomised into 0–4 and 5+6, as well as 0–3 and 4–6, and the case fatality rate at one year. All patients randomised in DECIMAL and DESTINY and 23 patients from HAMLET were eligible for the pooled analysis. Thus, a total of 93 patients were included, of whom 51 were randomised to decompressive surgery and 42 to conservative treatment. Results demonstrated that after decompressive surgery, more patients had an mRS ≤4 (75 versus 24%; p<0.0001), with a pooled absolute risk reduction (ARR) of 51% (95% confidence interval [CI] 34–69). In addition, more patients had an mRS ≤3 (43 versus 21%; p=0.014), with a pooled ARR of 23% (95% CI 5–41). The case fatality rate in the surgical group was 78% versus 29% in the conservative treatment group (p<0.0001) indicating a pooled ARR of 50% (95% CI 33–67) (see *Figure 2*). The resulting numbers needed to treat are two for survival with an mRS ≤4, four for survival with an mRS ≤3 and two for survival irrespective of outcome.[30]

Open Questions
Timing of Surgery – Early or Delayed
Debate remains with regard to the optimal time-point for decompressive hemicraniectomy. It has still not been clarified whether to operate as soon as possible, when the diagnosis of malignant MCA infarction has been made, or to wait for development of clinical deterioration, midline shift on brain imaging, increased intracranial pressure or signs of herniation. Malignant MCA infarction does not

necessarily result in fatal brain oedema. It seems important to identify those patients who are at risk of developing a malignant clinical course as soon as possible. Magnetic resonance imaging (MRI) features are likely to contribute to rapid diagnosis and prediction of fatal oedema formation; however, further studies and a more systematic evaluation are needed.[31,32] From our clinical experience we know that there are patients with large brain infarctions who rapidly develop fatal brain swelling. In these patients early decompressive surgery is probably the only life-saving procedure. On the other hand there are patients with massive infarctions but only mild brain swelling over a long period of time. Many of these patients never develop signs of herniation, and hemicraniectomy may not necessarily be mandatory. It is unclear which factors promote early and rapid brain swelling and which factors are protective. Experimental studies have suggested that free radicals, prostaglandins, arachidonic acid and leukotrienes may play a role, and reperfusion of already irreversibly damaged brain tissue may enhance oedema formation.[7,33]

Data from the literature are contradictory: Mori et al. retrospectively compared patients who had been treated before the onset of brain herniation with those who showed clinical and radiological signs of herniation. Mortality was markedly reduced from 17.2 to 4.8% after one month and from 27.6 to 19.1% after six months. Outcome at six months was also significantly improved by early intervention.[15] Another retrospective study by Woertgen and colleges investigated 48 patients and showed comparable results for mortality (early versus delayed surgery: 16 versus 39%), but not for outcome.[34]

These results were confirmed in two prospective studies: Schwab et al. demonstrated markedly decreased mortality in patients treated within 24 hours after symptom onset compared with 48 hours or later (16 versus 34%), as well as a significantly decreased duration of treatment in the ICU (7.4 versus 13.3 days) and a trend for improved clinical outcome after three months in favour of early hemicraniectomy.[19] These results were not supported by other case series: in a review by Gupta et al., including all individual patient data from the literature until 2004, neither the presence of brainstem signs nor the time from symptom onset to operation was associated with poor outcome or increased mortality rates.[14] Because of the results from DESTINY and DECIMAL, early hemicraniectomy is recommended as soon as the diagnosis of a malignant MCA infarction has been made.

Treatment of Patients with Dominant Hemispheric Infarction

Controversy remains with regard to the question of whether patients with malignant infarction of the dominant hemisphere should receive hemicraniectomy. The loss of ability to communicate in combination with severe hemiplegia was considered to be too disabling, and hemicraniectomy was often restricted to patients with a non-dominant hemispheric infarction. From the randomised trials and larger prospective case series there is currently no indication that patients with dominant malignant infarctions do not profit from treatment. Neither mortality nor functional outcome was associated with the hemisphere;[14,30] in fact, the handicap caused by aphasia may be balanced by the neuropsychological deficits from which patients with infarction of the non-dominant hemisphere suffer, i.e. severe attention deficits, apraxia and depression.[35,36] Moreover, the long-term aphasia in dominant malignant MCA infarction is rarely global.[20,34] So far there is no evidence that surgery should not be considered for patients with dominant hemisphere infarction.

Age Limit for Hemicraniectomy

Although the percentage of young patients with malignant MCA infarction is relatively high, more than 60% of patients are over 50 years of age and 40% are over 60 years of age.[1,16,37] There are several studies that indicate an unfavourable outcome in elder patients after hemicraniectomy, proposing an age limit between 50 and 60 years.[17,22,23] In the analysis from Gupta and colleges, age was the only prognostic factor for a poor outcome.[14] Interpretation of these findings is limited by the fact that in most of these studies older patients were operated significantly later and treated less aggressively than younger patients. The randomised trials do not contribute very much in this issue, because the upper age limit in the three European trials was 55–60 years. In the pooled analysis, there was no statistical difference for the primary end-point of mRS 0–4 versus 5 and 6 comparing patients older or younger than 50 years; however, the number of patients over 50 years of age was very small.[30] From the data available it is currently impossible to define an age limit after which decompressive surgery should not be performed.

Conclusion

The pooled analysis of the three randomised controlled trials on decompressive surgery for the treatment of malignant MCA infarction provided basic evidence for a significant reduction in mortality after hemicraniectomy. Nevertheless, there remain some clinical and ethical questions that need to be addressed in the future, especially regarding the time-point of surgery, the hemisphere affected and the age of the patient, combined with a parallel discussion about the outcome of the surviving patients and their quality of life. ■

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