Surgical Neurology International

OPEN ACCESS

For entire Editorial Board visit : http://www.surgicalneurologyint.com

Editor: **James I. Ausman,** MD, PhD University of California, Los Angeles, CA, USA

Editorial

Hemicraniectomy in the management of malignant middle cerebral artery infarction: Lessons from randomized, controlled trials

Dustin Hatefi, Brian Hirshman, Didier Leys[1], Jean-Paul Lejeune[1], Lawrence Marshall, Bob S. Carter, Ekkehard Kasper[2], Clark C. Chen

Division of Neurosurgery, University of California, San Diego, CA, [1]Department of Neurology and Neurosurgery, University of Lille North of France, Lille, France, [2]Division of Neurosurgery, Beth Israel Deaconess Medical Center, Boston, MA, USA

E-mail: Dustin Hatefi - dhatefi@ucsd.edu; Brian Hirshman - bhirshma@ucsd.edu; Didier Leys - didier.leys@univ-lille2.fr; Jean-Paul Lejeune - lejeune@chru-lille.fr; Lawrence Marshall - lfmarshall@ucsd.edu; Bob S. Carter - bobcarter@ucsd.edu; Ekkehard Kasper - ekasper@bidmc.harvard.edu
*Clark C. Chen - clarkchen@ucsd.edu
*Corresponding author

Received: 19 February 14 Accepted: 06 March 14 Published: 15 May 14

This article may be cited as:
Hatefi D, Hirshman B, Leys D, Lejeune J, Marshall L, Carter BS, *et al.* Hemicraniectomy in the management of malignant middle cerebral artery infarction: Lessons from randomized, controlled trials. Surg Neurol Int 2014;5:72.
Available FREE in open access from: http://www.surgicalneurologyint.com/text.asp?2014/5/1/72/132589

BACKGROUND

Territorial middle cerebral artery (MCA) infarcts are among the most devastating forms of ischemic cerebral disease.[5] It is associated with life-threatening cytotoxic edema, with mortality reported as high as 80%.[1] Patients suffering intractable intracranial hypertension secondary to malignant edema often undergo hemicraniecomty as a life-preserving measure. The efficacy of hemicraniectomy in this context is now documented by several randomized controlled studies (RCTs). The controversy that remains involves the functional status of the surviving patient, since territorial MCA infarcts are intrinsically associated with significant disability. Here we review the available RCT data, with the goal of addressing this controversy.

RANDOMIZED CONTROLLED TRIALS

At present, there have been seven published, RCTs evaluating hemicraniectomy as treatment for malignant MCA infarction.

The first study was termed "HeADDFIRST" (Hemicraniectomy and durotomy on deterioration from infarction-related swelling trial) and was only published as an abstract.[3] This study prospectively randomized 26 patients (ages 18-75) with MCA infarction >180 cc with midline shift >7 mm to either medical care + hemicraniectomy or medical care only. The study reported that hemicranicetomy reduced mortality from 46% to 27%. However, this reduction was not statistically significant due to the limited sample size. No data on functional outcome or timing of the surgical intervention were reported in this study.

The second RCT reported was a pooled analysis of one year outcome data from three European multicenter hemicraniectomy RCTs: The French DECIMAL (decompressive craniectomy in malignant MCA infarcts) trial, the German DESTINY (decompressive surgery for the treatment of malignant infarction of the MCA) trial, and the Dutch HAMLET (hemicraniectomy after MCA infarction with life-threatening edema trial). While the inclusion criteria and exclusion criteria of these three studies differed (see below), the clinical results from 93 patients fulfilling the following criteria were pooled: Age 18-60 years, NIHSS (National Institutes of Health Stroke Scale) >15, Infarct >50% of the MCA territory (or approximately >145 ccs), and randomization within 45 h of symptoms. Of note, patients with

Access this article online	
Quick Response Code:	Website: www.surgicalneurologyint.com
	DOI: 10.4103/2152-7806.132589

significant preexisting morbidities were excluded from this analysis (e.g. life expectancy <3 years). In this pooled analysis, hemicraniectomy was associated with a statistically significant reduction of mortality from 75% to 24%. The modified Rankin Scale (mRS,[4] Table 1) was used to assess functional outcome at the one-year follow-up. Of the surviving surgical patients, 5% had a mRS of 5; 40% had a mRS of 4; 38% had a mRS of 3; and 17% had a mRS of 2. Statistical analysis revealed that the proportion of patients with mRS≤3 was significantly increased in the surgery group (43%) relative to the medically managed group (21%).[9]

Seven months after the publication of the pooled result, the outcome of the German DESTINY trial and the French DECIMAL trials were separately published. The German DESTINY trial[7] prospectively randomized 32 patients (ages 18-60 years) with an MCA infarct >2/3 of the territory (or approximately 200 ccs), and NIHSS >18 (for nondominant hemisphere infarcts) or >20 (for dominant hemisphere infarcts). Surgical interventions were performed within 12-36 h of symptom onset. In this study, hemicraniectomy was associated with a statistically significant reduction of mortality from 88% to 47%. At the one-year follow-up, 7% of the surviving surgical patients had a mRS of 5; 35% had a mRS of 4; 29% had a mRS of 3; and 29% had a mRS of 2. Statistical analysis revealed that the proportion of patients with mRS≤3 was increased in the surgery group (47%) relative to the medically managed group (27%). However, this difference did not reach significance in this study.

The French DECIMAL trial[10] prospectively randomized 38 patients (ages 18-55) with an MCA infarct >50% of the territory (approximately 145 ccs), and NIHSS >16. Surgical interventions were performed within 36 h of symptom onset. Here, hemicraniectomy was associated with a statistically significant reduction of mortality from 78% to 25%. At the one-year follow-up assessment, 25% of the surviving surgical patients had a mRS of 5; 25% had a mRS of 4; 35% had a mRS of 3; and 15% had a mRS of 2. Statistical analysis revealed that the proportion of patients with mRS≤3 was increased in the surgery group (50%) relative to the medically managed group (22%). However, this difference also did not reach significance.

Table 1: Modified rankin scale

Score	Definition
0	No symptoms
1	No significant disability. Able to carry out all usual activities, despite some symptoms
2	Slight disability. Able to look after own affairs without assistance, but unable to carry out all previous activities
3	Moderate disability. Requires some help, but able to walk unassisted
4	Moderately severe disability. Unable to attend to own bodily needs without assistance, and unable to walk unassisted
5	Severe disability. Requires constant nursing care and attention, bedridden, incontinent
6	Dead

The Dutch HAMLET trial[6] prospectively randomized 64 patients (ages 18-60) with MCA infarcts >2/3 of the territory (approximately 200 ccs), and NIHSS >16 (nondominant hemisphere) or >21 (dominant hemisphere). Surgical interventions were performed within 96 h of symptom onset. In this trial, hemicraniectomy was associated with a statistically significant reduction of mortality from 59% to 22% ($P < 0.05$). At the one-year follow-up assessment, 24% of the surviving surgical patients had a mRS of 5; 44% had a mRS of 4; 28% had a mRS of 3; and 4% had a mRS of 2. Statistical analysis revealed that the proportion of patients with mRS≤3 was not significantly different between the surgery group relative to the medically managed group (28% versus 25%, respectively). Of note, symptoms of depression as assessed by the MADRS were higher among the surgical group (78%) compared with the medical group (58%).

There last two RCT that included patients age >60 years. The first study was reported by Zhao *et al.*[11] This is a Chinese RCT that randomized 47 patients (ages 18-80) with MCA infarcts >2/3 of the territory (approximately 200 ccs), and Glasgow Coma Scale scores (GCS) ≤ 9. In this study, >50% of the patients were aged >60. Patients with significant preexisting morbidities were excluded from the trial (e.g. baseline mRS>2). Surgical interventions were performed within 48 h of symptom onset. Hemicraniectomy was associated with a statistically significant reduction of mortality from 60.9% to 12.5% ($P = 0.001$). Similar to observations made in the HAMLET study, the proportion of patients with mRS<3 was not significantly different between the surgery group relative to the medically managed group (9% versus 21%, respectively). At one-year follow-up, 15% of the surviving surgical patients had a mRS of 5; 15% had a mRS of 4; 60% had a mRS of 3; and 10% had a mRS of 2. The one-year mRS for the surgical patients aged >60 years were: 15% with mRS of 5; 70% had a mRS of 4; and 15% had a mRS of 3. These results were significantly worse than the overall outcome.

The German DESTINY II trial[8] prospectively randomized 112 patients age >60 (median age of 70) with an MCA infarct >2/3 of the territory, and NIHSS >14 (for nondominant hemisphere infarcts) or >19 (for dominant hemisphere infarcts). Surgical interventions were performed within 48 h of symptom onset. In this study, hemicraniectomy was associated with a statistically significant reduction of mortality from 76% to 43%. At the one-year follow-up, <10% of the surviving

patients in either arm had a mRS<3. Severe depression was present in 80 to 100% of the survivors, irrespective of intervention.

A quantitative summary of the overall survival and mRS outcome after hemicraniectomy are as shown in Figures 1 and 2.

EXPERT OPINIONS

"The only good reason to doubt hemicraniectomy as a treatment for malignant infarcts in the increased proportion of patients with [severe disability]." Didier Leys and Jean-Paul Lejeune, University of Lille North of France

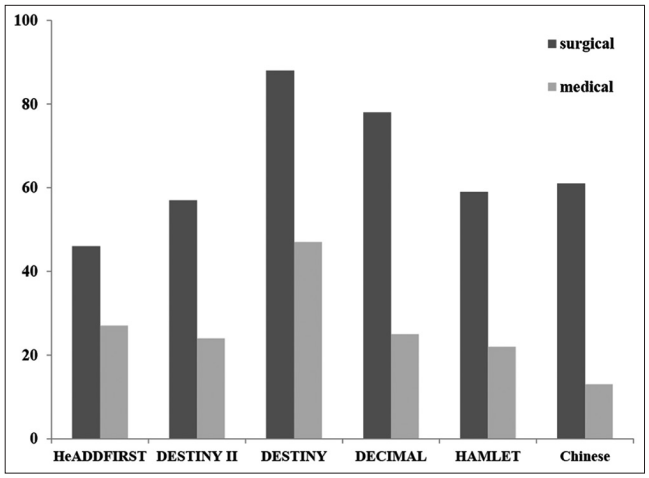

Figure 1: Effect of hemicraniectomy on overall survival for patients with territorial MCA infarcts. Comparison of overall survival in patients afflicted with territorial MCA infarcts who underwent medical management and surgical decompression in the six RCTs are shown. *Y* axis: overall survival

Given the RCT data, the only good reason to doubt hemicraniectomy as a treatment for malignant infarcts is the increased proportion of patients with a mRS 4 (i.e. these patients are unable to attend to their own bodily needs without assistance and are unable to walk unassisted) in patients who underwent the procedure. This is really an issue, but the question is whether we can refuse to offer decompressive surgery to a patient with a large MCA infarct, if there is a high probability of developing malignant infarct, when the treatment increased the probability of being fully independent from 2% to 14%, and of having no or minimal dependency from 21% to 43%? Even if hemicraniectomy for large MCA infarcts still leaves unanswered questions, it should be considered as an important step in the treatment of patients suffering from territorial MCA infarct.

The hemicraniectomy RCTs represent only one step in defining the optimal treatment for large MCA infarcts. There will likely be improvements in the future. First, for such a severe disorder, it is likely that one-year follow-up is too short to evaluate the outcome. There are reports of significant improvements after one year. Second, the selection of patients suitable for surgery will probably improve in the future. Third, registries of patients treated by hemicraniectomy will probably be useful to better identify the best candidates, exactly as we did with intravenous thrombolysis. Finally, more research is needed to better identify patients who should not be treated surgically, and to identify complementary strategies. We should bear in mind that improvements are made by small successive steps nowadays (e.g. in cancer), rarely by a single, important discovery that changes the world, as were

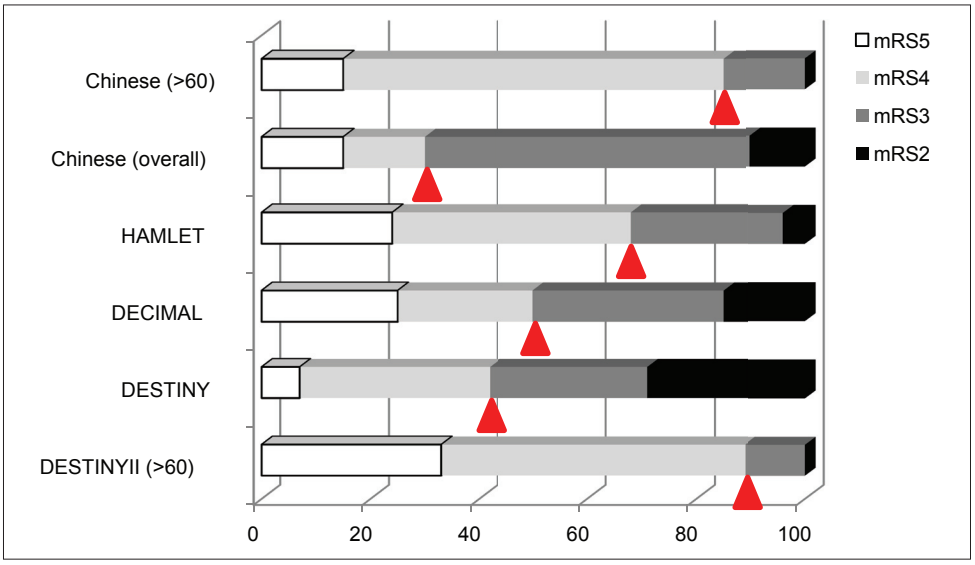

Figure 2: Functional outcome of patients surviving territorial MCA infarct after hemicraniectomy as measured by the modified Rankin Scale (mRS). Percent of patients with each mRS scale are shown on the *X*-axis. Red triangles indicate the demarcation of independent function based on mRS≥3. The mRS of patients >60 from Zhao et *al.*[11] and the overall outcome of other RCTs are shown

the discovery of antirabies vaccination or of penicillin.

"Despite its general applicability, mRS tells us nothing about some of the fundamental issues that most would consider to impact human dignity, such as bowel and bladder control." Lawrence Marshall, University of California, San Diego.

There are a number of observations that we can gleam from the hemicraniectomy RCTs. First, mortality and morbidity is clearly reduced by hemicraniectomy for patients under the age of 60. Given the variable inclusion criteria and the different time allowance in the trials, pooling the data would be frowned upon by statisticians. Nevertheless, what is encouraging is that hemicraniectomy moved certain patients up the continuum of better functional outcomes in all RCTs for patients under the age of 60. Conversely, hemicraniectomy should not be performed in patients aged >60 as there is no evidence of benefit. Second, there are suggestions that outcome after hemicraniectomy may be improved if the procedure is performed earlier. Of the three European trials, the most unfavorable outcome was observed in the HAMLET trial, where patients underwent DHC within 96 h of presentation.

What could be done better to improve the future hemicraniectomy RCT design? First we need uniform entry criteria. Critical variables to consider include patient age, infarct volume, time to procedure, clinical status (e.g. pupillary reactivity), and whether Intracranial pressure (ICP) monitoring was instituted. The last variable is of particular importance as it can be used to guide the timing of hemicraniectomy. Additionally, we need to use better measures of functional outcome than just the mRS. Despite its general applicability, mRS tells us nothing about some of the fundamental issues that most would consider to impact human dignity, such as bowel and bladder control.

Editorial Summary

Morbidity and mortality

Irrespective of age, all seven RCTs publications consistently demonstrated that decompressive hemicraniectomy decrease the mortality associated with malignant, territorial MCA infarct from 46-75% to 12-27%, with absolute mortality risk reduction of a half to a third. The picture for morbidity reduction was more mixed. While DECIMAL and DESTINY trials demonstrated that the likelihood of a survivor incurring deficit with mRS≥3 was reduced from approximate 50-25%, such reduction was not observed in the HAMLET, DESTINY II, or the Chinese study. The most notable difference between the latter studies and the former involved the age of the patient population and the timing of the decompression. The HAMLET study allowed randomization up to 96 h post-ictus, while the Chinese and the DESTINY II study involved patients aged >60. Thus, a reasonable interpretation of the data set is that decompressive hemicraniectomy may reduce morbidity in select patient populations. Irrespective of interpretation, the objective data show that patients who survive territorial infarct after decompressive craniectomy have an approximately 30-95% likelihood of living with significant disability characterized by mRS≥3.

Recommendations

The decision of choosing to live with a significant disability versus opting for comfort care when facing the consequences of a territorial MCA infarct is a highly personal one. In one extreme, some patients may opt for the chance to live irrespective of consequences. On the other end of the spectrum, some patients may rather choose to pass away peacefully if there is likelihood of a significant morbidity. Reasons against decompression may range from not wanting to be a financial burden to their family to not wanting to be remembered as someone who slowly wasted away to the unwillingness to cope with significant morbidity. Most patients fall in the spectrum of views defined by these two extreme poles. It is interesting to consider that when patients who suffered territorial infarct and survived after hemicraniectomy were posed the question of whether they would have undergone surgery if they had knowledge of their subsequent clinical course, only 50% of these patients reported that they would have opted for surgery.[2] In this context, perhaps the most important responsibility of the neurosurgeon is to thoughtfully review the available RCT data and past experiences with comparable patients with the affected family. If the family members were to elect to proceed with surgery, it is critical to establish reasonable expectations for the family in terms of functional recovery. The responsible surgeon should also be aware of his/her own biases on this issue during consultation.

The scenario of an elderly (aged >60) who presents with a territorial MCA infarct without an advance directive or health proxy is a particularly challenging one. On the one hand, independent studies (Chinese and DESTINY II) suggest that the likelihood of functional independence after decompression was <10%. As such, an argument can be made not to perform the surgery. On the other hand, death is irreversible. It is the practice of the senior editor of this article (CCC) to review the overall clinical condition of the patient with the intensive care specialists and neurologists as to determine surgical risk and likelihood of functional recovery. Discussions are then held with the family members or health proxy as to the appropriateness of the surgery.

REFERENCES

1. Berrouschot J, Bettin S, Köster J, Schneider D, Sterker M. Mortality of space-occupying ('malignant') middle cerebral artery infarction under conservative intensive care. Intensive Care Med 1998;24:620-3.

2. Buonanno F, Candia GJ, Carter BS, Ogilvy CS, Rosas HD . One-year outcome after decompressive surgery for massive nondominant hemispheric infarction. Neurosurgery 1997;40:1168-75; discussion 1175-6.
3. Frank J. Hemicraniectomy and duratomy upon deterioration from infarction related swelling trial (HeADDFIRST): First public presentation of the primary study findings. Neurology 2003;60 Suppl 1:A426.
4. Farrell B, Godwin J, Richards S, Warlow C. The United Kingdom transient ischaemic attack (UK-TIA) aspirin trial: final results. J Neurol Neurosurg Psychiatry 1991;54:1044-54.
5. De Georgia M, Hacke W, Horn M, Schwab S, Spranger M, von Kummer R. 'Malignant' middle cerebral artery territory infarction: Clinical course and prognostic signs. Arch Neurol 1996;53:309-15.
6. Algra A, Amelink GJ, Hofmeijer J, Kappelle LJ, van der Worp HB, van Gijn J, HAMLET investigators. Surgical decompression for space-occupying cerebral infarction (the Hemicraniectomy After Middle Cerebral Artery infarction with Life-threatening Edema Trial [HAMLET]): A multicentre, open, randomised trial. Lancet Neurol 2009;8:326-33.
7. Hennerici M, Jüttler E, Schmiedek P, Schwab S, Unterberg A, Woitzik J, *et al*. Decompressive surgery for the treatment of malignant infarction of the middle cerebral artery (DESTINY): A randomized, controlled trial. Stroke 2007;38:2518-25.
8. Amiri H, Bösel J, Jüttler E, Sakowitz OW, Unterberg A, Woitzik J, *et al*. Hemicraniectomy in older patients with extensive middle-cerebral-artery stroke. N Engl J Med 2014;370:1091-100.
9. Algra A, George B, Hofmeijer J, Juettler E, Vahedi K, Vicaut E, *et al*. Early decompressive surgery in malignant infarction of the middle cerebral artery: A pooled analysis of three randomised controlled trials. Lancet Neurol 2007;6:215-22.
10. Guichard JP, Kurtz A, Mateo J, Orabi M, Vahedi K, Vicaut E, *et al*. Sequential-design, multicenter, randomized, controlled trial of early decompressive craniectomy in malignant middle cerebral artery infarction (DECIMAL Trial). Stroke 2007;38:2506-17.
11. Su YY, Wang L, Zhang Y, Zhang YZ, Zhao J, Zhao R, *et al*. Decompressive hemicraniectomy in malignant middle cerebral artery infarct: a randomized controlled trial enrolling patients up to 80 years old. Neurocrit Care 2012;17:161-71.