Hemicraniectomy for Malignant Middle Cerebral Artery Infarction (HeMMI): A Randomized Controlled Clinical Trial of Decompressive Hemicraniectomy with Standardized Medical Care Versus Standardized Medical Care Alone

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ABSTRACT

Background. Malignant middle cerebral artery (MCA) infarction, in which space occupying cerebral edema causes rapid neurological deterioration and transtentorial herniation, has a poor prognosis, with mortality rates as high as 80%. Decompressive hemicraniectomy can be performed in order to reduce increasing intracranial pressure and prevent herniation and further ischemic damage. Observational research has suggested that hemicraniectomy can reduce mortality and improve functional outcome, but only a few small clinical trials have been conducted, so that the evidence base remains uncertain.

Methods. Single-center randomized controlled clinical trial comparing standardized medical care (SMC) alone versus SMC with decompressive hemicraniectomy (SMC+DH) in adults with malignant MCA infarction. Primary outcome: functional status at 6 months, with a modified Rankin Score (mRS) of ≥ 4 considered a poor outcome. Secondary outcomes: mRS ≥ 5, death.

Results. Follow-up was available for 24 of 29 recruited patients (82.76%; 13 SMC+DH, 11 SMC). No statistically significant differences in either functional status outcome or mortality were observed in either intention-to-treat or per-treatment analysis.

Conclusion. The HeMMI trial identified no statistically significant differences between either treatment and functional outcomes or mortality. However, consideration of all previous trials suggests that decompressive hemicraniectomy is associated with increased chances of survival at 6 months, but also an increased likelihood that surviving patients will be severely disabled. This should be explained carefully to patients or their legal guardians before treatment decisions are made.

Key Words: hemicraniectomy, decompressive surgery, malignant middle cerebral artery infarction

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Introduction

Significant cerebral edema can occur in around 10% of cerebral infarctions, usually by the second to fifth day post-ictus.[1-5] However, some patients become symptomatic from cerebral edema even earlier, presenting clinically with a severe hemispheric stroke syndrome: hemiplegia, forced eye and head deviation, and progressive deterioration of consciousness within the first 48 hours, subsequently progressing to overt signs of herniation in the next 2 days. The term "malignant" middle cerebral artery (MCA) territory infarction has been coined to describe this condition, which has a poor prognosis and fatality rates as high as 70-80%.[6,7]

With medical therapies aimed at reducing cerebral edema and the associated increase in intracranial pressure often proving ineffective, decompressive surgery has been practiced to directly reduce intracranial pressure, reverse brain shifts, improve cerebral perfusion and prevent further ischemic damage and mechanical compression of the brain.[8,9] Case reports, case series, and nonrandomized studies have suggested that hemicraniectomy improves survival, possibly more so when done early, before clinical signs of herniation are observed.[8-12] Some studies have also suggested that surgical decompression may improve functional outcomes.[9,11]

Several randomized trials have been conducted that have compared hemicraniectomy with standard medical care. The results of three European trials involving 134 patients have been published and meta-analyzed, most recently in a 2012 Cochrane Review.[11] The results suggested that surgical decompression significantly reduces mortality as compared to conservatively treated patients.[8,9,15,16] However, the effect of hemicraniectomy on functional outcome is less certain, with the concern being that improved survival may be at the expense of severe disability. The results of a multicenter randomized trial in the United States completed in 2003 have not been published in full or included in meta-analyses.[5,13] The results of a trial in Turkey remain unpublished.[14]

This paper reports the results of the Hemicraniectomy for Malignant Middle Cerebral Artery Infarction (HeMMI) trial, which compared decompressive hemicraniectomy combined with standard medical care with standard medical care alone at the Philippine General Hospital.

Methods

Study Design and Patient Eligibility

The HeMMI trial was a prospective, single-center, randomized, controlled clinical trial in patients with malignant MCA infarction. Patients were assigned to receive either the standardized medical treatment alone or surgery (decompressive hemicraniectomy with duraplasty) with standardized medical treatment.

All patients were recruited from a single center, the Philippine General Hospital. Patients between 18 and 65 years old who presented with clinical signs of infarction of the MCA territory and who arrived at the hospital within 72 hours of symptom onset were potentially eligible for inclusion.

Other inclusion criteria included a Glasgow coma score (GCS) of 6 to14 in patients with right MCA infarction or GCS 5 to 9 in patients with left MCA infarction (adjusted to account for effect on speech deficit on GCS scores), or GCS of 15 on arrival but subsequent neurological deterioration defined by a score of ≥1 on the level of consciousness item of the National Institutes of Health Stroke Scale (NIHSS); computed tomography (CT) scan showing ischemic changes of more than 50% of the MCA territory with or without involvement of other vascular territories; and written informed consent from the patient or a legal representative.

Exclusion criteria were previous disabling neurological disease, estimated premorbid modified Rankin Scale (mRS) score >2[15]; terminal illness; presence of serious medical comorbidities like end-stage renal failure and cardiac disease with severe hemodynamic compromise; infarction due to surgical complications or vasospasm; primary intracranial hemorrhage; coagulopathies; and high risk for surgery upon assessment by the medical team.

Randomization and Masking

Randomization was computer-generated, with each treatment assignment enclosed in sealed sequentially numbered envelopes. After confirming eligibility and obtaining informed consent, the envelope with the lowest number was opened upon patient enrollment. Treatment allocation sequence was concealed from study staff and the patient until the envelope was opened.

Standard Medical Therapy

All patients enrolled in either arm of the study received standardized medical therapy in an intensive care unit (ICU), which included elevation of the head of bed at 30° to promote venous drainage without compromising cerebral blood flow, intermittent hyperventilation administered when necessary to acutely address signs of increased intracranial pressure refractory to other measures, and intravenous mannitol to achieve a serum osmolarity of 300 to 320 mOsm while keeping patients euvolemic. Mean arterial pressure was maintained above 90 mmHg. Hemoglobin concentration was maintained above 90 g/L. Hyperglycemia, hyperthermia and hypotension were avoided or corrected when present. Patients randomized to the medical group who deteriorated further while under treatment were offered decompressive hemicraniectomy for ethical and compassionate reasons.

Surgical Procedure

Decompressive hemicraniectomy involved removal of a large bone flap at least 12 cm in diameter, including parts of the frontal, temporal, parietal and occipital bones, with further craniectomy to the floor of the temporal fossa. The dura was opened widely and duraplasty performed using periosteum and temporalis fascia. The bone flap was either stored in a subcutaneous pocket in the abdomen or placed in the bone bank. Cranioplasty was performed on an elective basis not earlier than 6 months from the initial surgery.

Data collection and Outcome Measures

The primary outcome measure was functional status at 6 months measured by the modified Rankin Score (mRS), dichotomized as a good status (mRS 0-3) or poor status (mRS 4-6). A score of mRS 0-3 indicates functional status ranging from no symptoms to "moderate disability" (requiring some help, but able to walk without assistance); mRS 4-6 indicates functional status ranging from "moderately severe disability" (unable to walk or to attend to own bodily needs without assistance) through to death. A cut off of mRS 3 was adopted a priori because the ability to walk independently, with or without the help of a device, was considered a favorable outcome.

Secondary outcomes were survival at 6 months and mRS scores dichotomized at mRS 0-4 and mRS 5-6 at 6 months: mRS 5-6 indicates functional status ranging from "severe disability" (bedridden, incontinent and requiring constant nursing care and attention) through to death. The latter outcome was considered because it was included in previous trial reports.[16-18]

Demographic data, laterality and etiology of infarction, presence of hypertension or diabetes, smoking status, GCS, NIHSS, and pre-stroke mRS were assessed at baseline. Follow-up assessments, including mRS, were at 7 days, 2 weeks, 1 month, 3 months, and 6 months post-stroke. The date and cause of death were recorded where appropriate.

Statistical Analysis

Based on previous studies suggesting that 20% of patients with malignant MCA infarction had poor outcome on standard treatment and the premise that decompressive hemicraniectomy will result in a 20% increase in the proportion of patients with good functional outcome at 6 months, the sample size required for a power of 80% and alpha of 0.05 was 28 per treatment arm.

Results for primary and secondary outcome measures are reported by intention-to-treat (ITT) and per-treatment. Distributions of baseline characteristics and dichotomized outcomes were compared between groups using t-tests and chi-squared tests as appropriate and distributions of the whole spectrum of functional outcome scores using Wilcoxon-Mann-Whitney U tests. Risk difference (absolute risk reduction) and 95% confidence intervals were calculated for all outcomes. The criterion for statistical significance was set at $p<0.05$. Analysis was conducted in IBM SPSS Version 20.[19]

Ethical considerations

Written informed consent was obtained from all patients or their legal representative. The study was approved by the Research Implementation and Dissemination Office Ethics Committee of the University of the Philippines College of Medicine and registered with the Internet Stroke Centre Clinical Trials Registry.[20] Prospective registration in an ICMJE-listed registry was not required as recruitment started prior to 1 July 2005. The trial was therefore registered retrospectively at www.clinicaltrials.gov.[21]

Results

Of 156 patients screened between January 2002 and December 2009, 29 were found to be eligible for inclusion and were invited to participate (Figure 1). Consent was obtained for all 29. Recruitment for the study was terminated due to slow recruitment combined with the publication of other decompression trial results and an associated recommendation that the results of all trials should be pooled.

Of the 29 patients enrolled, 13 patients were randomized to medical therapy alone and 16 patients to surgical decompression with medical therapy. Six-month follow-up was available for 24 of 29 patients (82.76%; 13 surgical, 11 medical). No statistically significant differences in baseline characteristics were observed between the two groups (Table 1). One patient from the surgery group did not undergo surgery because he developed an acute myocardial infarction before surgery and was deemed high risk. Three patients in the medical group underwent decompression as they deteriorated further despite best medical therapy. Only one patient in the medical group was randomized beyond 48 hours, while 2 patients in the surgery group underwent surgical decompression beyond 48 hours.

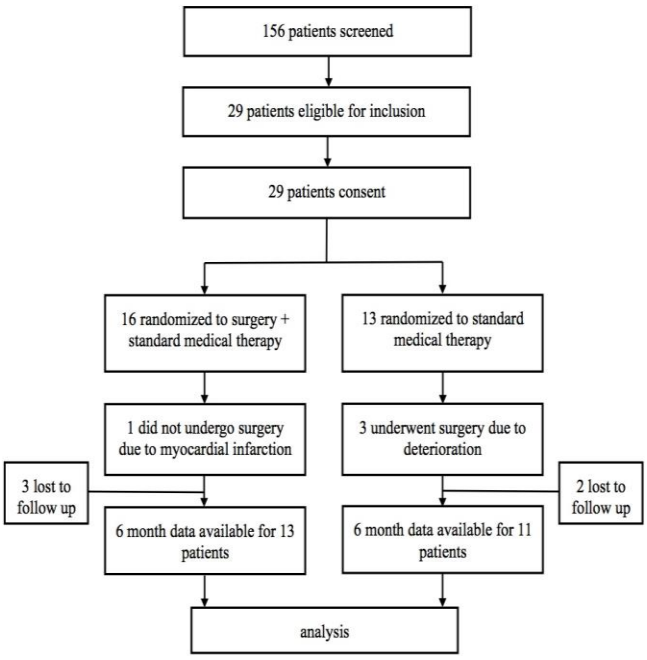

Figure 1. Disposition of patients enrolled in the study.

Table 1. Baseline characteristics of patients included in the HeMMI study

	Surgery	Medical	Total	
Number of participants	13	11	24	
Mean age (SD)	50.3 (9.5)	50.1 (7.0)	50.2 (8.3)	0.951‡
Male sex – n (%)	11 (85)	9 (82)	20 (83)	0.855†
Hypertension – n (%)	6 (46)	5 (46)	11 (46)	0.973†
Diabetes – n (%)	2 (15)	0 (0)	2 (8)	0.174‡
Smoker – n (%)	10 (77)	8 (73)	18 (75)	0.813†
NIHSS at randomization – mean (SD)	22.8 (4.7)	22.5 (6.1)	22.6 (5.3)	0.888‡
Hours from stroke onset to randomization - mean (SD)	7.9 (6.6)	10.2 (14.3)	9.0 (10.6)	0.604‡
Hours from stroke onset to surgery – mean (SD)	36.6 (19.7)	-	-	
GCS at randomization - mean (SD)	10.3 (2.4)	10.2 (2.7)	10.3 (2.5)	0.904‡
Etiology (n, %)				
Cardioembolic	4 (31)	6 (55)	10 (42)	0.379†
Atherosclerotic	1 (8)	0 (0)	1 (4)	
Cryptogenic	8 (62)	5 (46)	13 (54)	
Left hemisphere infarction – n (%)	8 (62)	5 (46)	13 (54)	0.431†

For the primary outcome measure based on ITT analysis, 23.1% of the surgical group and 38.4% of the medical group had a good functional outcome at 6 months (mRS 0-3) (Table 2). The difference was not significant, with an absolute risk reduction (ARR) of 13% (95% CI -23%, 50%). Analysis of distribution of the whole spectrum of mRS scores revealed no significant difference. When the favorable

outcome was extended to include a mRS score of 4, there was no statistically significant difference between groups in ITT analysis (ARR -015; 95% CI -41%, 39%). Analysis of the distribution of the whole spectrum of mRS scores also revealed no significant difference (p=0.910). Neither was the difference statistically significant if analysis was done on a per treatment basis.

Table 2. Primary and secondary outcomes in the HeMMI trial, by intention to treat and per treatment

Outcome at 6 months	Overall	Medical	Surgical	p-value
Intention to treat				
Number of patients	24	11	13	
Modified Rankin Scale				
mRS 0-3 (n, %)	7 (29.2%)	4 (38.4%)	3 (23.1%)	0.476[†]
mRS 0-4 (n, %)	11 (45.8%)	5 (45.5%)	6 (46.2%)	0.973[†]
mRS 6 (Dead) (n, %)	11 (45.8%)	6 (54.5%)	5 (38.5%)	0.431[†]
Per treatment				
Number of patients	24	9	15	
Modified Rankin Scale				
mRS 0-3 (n, %)	7 (29.2%)	3 (33.3%)	4 (26.7%)	0.728[†]
mRS 0-4 (n, %)	11 (45.8%)	4 (44.4%)	7 (46.7%)	0.916[†]
mRS 6 (Dead) (n, %)	11 (45.8%)	5 (55.6%)	6 (40.0%)	0.459[†]

ITT analysis showed a greater number of deaths in the medical group (n=6; 54.5%) compared with the surgical group (n=5; 38.5%), although the difference was not statistically significant (ARR –16%; 95% CI –56%, 23%). The difference was only slightly greater and also not statistically significant in per treatment analysis (55.6% versus 40.0%). If the two patients in the medical group who underwent decompressive hemicraniectomy and survived were considered as mortalities within their group (based on the assumption that they would have died without surgery), the difference between the groups would still not be statistically significant (ARR –34%; 95% CI –72%, 03%).

One patient who was allocated to the surgical group died within 72 hours of stroke onset due to an acute myocardial infarction. The other deaths occurred from 10 days to 2 months after stroke onset due to recurrent stroke or medical complications. Two patients had postoperative complications: an epidural hematoma which had to be evacuated and a superficial surgical site infection. Neither were considered to have altered eventual outcomes.

Discussion

The HeMMI trial detected no statistically significant association between treatment and its primary outcome, functional status at 6 months dichotomized at mRS 0-3 and mRS 4-6. This is in line with previous meta-analyses of 1-year outcomes of the three European trials.[16-18] Functional status, with mRS of 0-3 as the criterion for a good outcome, was the primary outcome of all three European trials.

In the HeMMI trial no statistically significant association was detected between either treatment when an mRS scores were dichotomized at 0-4 and 5-6. This is similar to one-year outcomes in the Dutch HAMLET study, but differs from those in DESTINY and DECIMAL and meta-analyses of all three, which observed an association between surgery and a reduced risk of severe disability or death.[16-18,22]

The decision to include functional status dichotomized as 0-4 and 5-6 as a secondary outcome in analysis for the HeMMI trial was based upon the reports of the European studies. The reports included this outcome in post hoc analyses and based their findings that hemicraniectomy is associated with improved functional status upon these.[16-18,22] The distinction between an mRS of 3 and an mRS of 4 is significant in terms of functional independence for the patient. A patient with an mRS of 3 requires some help, but is able to walk without assistance; an mRS of 4 indicates that the patient is unable to walk or to attend to their own bodily needs without assistance. Post hoc decisions to dichotomize functional status outcomes at mRS 0-4 and mRS 5-6 in published reports of the European studies have been criticized because moderately severe disability is included as a favorable outcome.[23]

Both individually and when meta-analyzed, the European trials detected an association between decompressive surgery and a reduced risk of mortality.[16-18,22] HeMMI found no association between surgery and improved survival. HeMMI's results relating to survival are similar to those in the Hemicraniectomy and Durotomy on Deterioration From Infarction-Related Swelling Trial (HeADDFIRST), a pilot multicenter randomized clinical trial in the United States in which 25 patients were randomized between 2000 and 2003 to either decompressive surgery or standardized medical care alone, with one subsequently withdrawn from the trial before treatment was initiated. As in the HeMMI trial, no significant difference was detected between treatment groups in terms of survival, with 4 deaths (40%) in the surgery group and 5 (37.5%) in the medical group at 6 months.[5,13]

Although decompressive hemicraniectomy may reduce the risk of death at 6 months, the likelihood of severe disability amongst survivors may be increased. Functional status of mRS 5 ("severe disability" - bedridden, incontinent and requiring constant nursing care and attention) at 6 months was observed only in surgical patients in the HeMMI, DECIMAL and HAMLET trials. Among all five trials, mRS 5 was observed in only three patients in the medical group (3.5% of all patients, 8.6% of survivors) and 11 (11.5% of all patients, 15.5% of survivors) in the surgical group. Although disappointing, this is not surprising since the main purpose of surgery is to reduce increased intracranial pressure and associated herniation and not to reverse the neurologic deficits incurred from the stroke. This is a factor of which patients or their relatives or legal guardians should be advised before a treatment choice is made.

Patient characteristics, inclusion criteria, features of decompressive surgery and the aims and methods of medical care were broadly similar in all trials. That said, some differences allow for consideration of reasons for differing results, although these can only be speculative.

That no improved survival was seen in HeMMI's surgical group may reflect a lower capacity to recover from major surgery as a result of the relatively older age of the trial's patients compared to those in the European trials, in which a survival benefit was observed. It seems intuitively reasonable that age may influence outcomes in hemicraniectomy. In the DECIMAL trial, a statistically significant association between surgery and improved functional outcome was observed only when the distribution of non-dichotomized mRS scores was compared between treatment groups, with a clear tendency towards better outcomes in younger patients detected. The lack of survival benefit in HeMMI may also be related to the effect of poorer general health status on capacity to recover: Philippine General Hospital is a government hospital that largely provides services to the less advantaged sectors of society, so that baseline general health status may be lower than would be found in private clinics or in hospitals in Western countries.

The size of area affected by infarction may influence outcomes, with a survival benefit observed only in the three trials that required greater area for eligibility. All five trials required that at least 50% of MCA area was affected by infarction in all patients. However, both DESTINY and HAMLET required that ≥ ⅔ of the MCA area was affected by infarction, while DECIMAL required ≥50%, but with an additional requirement of >145 cm on diffusion-weighted imaging.

Length of time from event to surgery has also been suggested as predictive of outcomes. Analysis of pooled data from DESTINY, DECIMAL and subgroups of HAMLET patients who underwent the procedure within 48 hours have concluded that early hemicraniectomy in particular is associated with most benefit.[17,22] More recently, mortality among those patients from these three trials who underwent the procedure within 48 hours has been compared with mortality for HAMLET patients who underwent the procedure later than 48 hours. While a significant reduction in risk of death was observed in the early hemicraniectomy patients, no significant reduction was seen in the patients who underwent surgery later. However, the 105 patients receiving early hemicraniectomy were compared with only 25 patients who were treated later, so that the analysis may be viewed with caution.[24]

Importantly, the criteria used to decide when, if ever, to perform hemicraniectomy might be considered. There was an important difference in the process of recruitment and randomization between HeADDFIRST and other published trials. Although HeADDFIRST's initial recruitment criteria were similar, only those patients in whom continued brain swelling to a predefined degree was observed (>4 mm of pineal shift or > 7.5 mm of anteroseptal shift observed by CT scan within 96 hours of stroke onset) subsequently became eligible for randomization. Only 26 patients progressed to meet the criteria for randomization; one was not randomized because the physician decided to limit treatment and another randomized to the surgical arm was withdrawn from the study on his wife's request. Notably, all 14 of those who did not develop the degree of brain swelling required for randomization for surgery survived at 21 days under the standardized medical care protocol, many of whom would have been randomized to surgical treatment in the other trials.[13]

The effect of optimal medical care may on occasions not have been sufficiently considered to date in research into the effectiveness of decompressive surgery. Only in HeADDFIRST, DESTINY and HeMMI did medical treatment of both medical and surgical patients follow protocols agreed to by all participating physicians, with all patients treated in ICUs and the proportions of patients who died in the medical arms of these trials were lower than in the other two European studies. In DECIMAL it was recommended that American and European guidelines for the management of stroke were followed and in HAMLET medical treatment was at the discretion of the attending physician. As a result, medical treatments may have been inconsistent between trial arms and individual patients. In both trials significant proportions of patients were not treated in ICUs, especially in the medical treatment arms.

Study limitations

The HeMMI study has weaknesses that must be acknowledged and taken into account when considering the results. Like all the trials that have been conducted on hemicraniectomy for malignant MCA infarction, HeMMI was stopped before it reached its predefined sample size, which may have undermined its potential to identify statistically significant effects. The trial design allowed the crossover of medical group patients who deteriorated to surgery, although analysis by treatment did not show different results. In addition, this was a single-center study, which can affect generalizability.

Conclusions

The HeMMI trial identified no statistically significant associations between either treatment and functional outcomes or mortality. However, consideration of all previous trials suggests that decompressive hemicraniectomy is associated with increased chances of survival at 6 months, but also an increased likelihood that surviving patients will be severely disabled. This should be explained carefully to patients or their legal guardians before treatment decisions are made.

Contributions of authors

Annabell Chua conceived and designed the study, was the principal investigator, oversaw data collection and contributed to drafting the paper. Brian S. Buckley conducted and interpreted statistical analyses, oversaw the production of the drafts and wrote the final draft. Marie Carmela M. Lapitan assisted in protocol development, data interpretation and writing of drafts. Dominic Jamora participated in the design of the study, data collection and contributed to drafting the paper. All authors approved the final draft.

Conflicts of interest

The authors have no conflicts of interest to declare.

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