Nationwide survey of decompressive hemicraniectomy for malignant middle cerebral artery infarction in Japan

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Key words: Nationwide survey, Decompressive hemicraniectomy, Malignant middle cerebral artery infarction, Mortality, Functional outcomes, Elderly patients

Abbreviations and Acronyms:
CT: Computed tomography
DHC: Decompressive hemicraniectomy
GCS: Glasgow coma scale
MCA: Middle cerebral artery
ICA: Internal carotid artery
IQR: Interquartile range
MR: Magnetic resonance
mRS: Modified Rankin scale
NIHSS: National institutes of health stroke scale
RCT: Randomized controlled trial

Heading: Decompressive hemicraniectomy in Japan
OBJECTIVE:
Decompressive hemicraniectomy (DHC) for malignant middle cerebral artery (MCA) infarction has been shown to reduce mortality and improve functional outcomes in young adults; however, there is currently debate regarding how routinely such surgery should be performed in the clinical setting, considering the very high rate of disability and functional dependence among survivors. We herein report the current status of the frequency of and indications for DHC for malignant MCA infarction in Japan.

METHODS:
We retrospectively studied of cohort cases of DHC for malignant MCA infarction treated at pivotal teaching neurosurgical departments in Japan between January 2011 and December 2011. Information was obtained regarding patient characteristics, radiological features and outcomes during follow-up. The endpoints included 30-day mortality rate and functional outcomes, as measured according to the modified Rankin scale (mRS) score at three months.

RESULTS:
Three hundred and fifty-five patients underwent DHC at 259 neurosurgical departments who replied to the survey, corresponding to a rate of 8.7% of the 4,092 candidates with malignant MCA infarction, the latter being equivalent to 8.5% of patients with acute ischemic stroke identified during the same period. Among the patients undergoing DHC, the mean age was 67.0 years, and those ≥60 years of age comprised 80.2% of all DHC patients. The most frequently used modality for vascular imaging was magnetic resonance angiography (77.2%). DHC was generally performed between 24-48 hours after onset (38.9%), with 36.9% of patients undergoing surgery at ≥48 hours. At the time of surgery, 26.1% of the patients had a Glasgow coma scale (GCS) score of ≤6. Pre-surgical
midbrain compression was noted in 52.1% of the patients. The 30-day mortality after DHC was 18.6%, and factors affecting death were a GCS score of ≤6 (OR 1.88, 95% CI 1.05-3.32, P=0.03) and midbrain compression (OR 2.28, 95% CI 1.31-4.09, P=0.005). According to the multivariate analysis, only midbrain compression was an independent risk factor (OR 2.12, 95% CI 1.16-3.95, P=0.01) for 30-day mortality. Modified Rankin scale scores at three months were available in 175 patients (49.3%), only 5.2% of whom exhibited a favorable functional outcome (mRS score ≤3). Meanwhile, 22.9% of the patients had an mRS score of 4, 26.9% had an mRS score of 5 and 45.1% were found to have died.

CONCLUSIONS:
In the present study, less than one-tenth of candidates with malignant MCA infarction in Japan underwent decompressive surgery, and the vast majority of patients were elderly. Age was not found to be an independent factor for immediate mortality in this study, and performing surgery in the elderly may be justified based on additional evidence of functional improvements.

INTRODUCTION
Malignant middle cerebral artery (MCA) infarction is characterized by the development of life-threatening space-occupying cerebral edema complicating large MCA infarction and is widely used as a category for subgrouping stroke patients (6, 11, 14, 20, 25). Despite the scarcity of scientific evidence indicating its benefits in such patients, the use of decompressive hemicraniectomy (DHC) is well established and the frequency of this procedure has gradually increased (1, 11). Recent European randomized controlled trials (RCTs) have demonstrated that the use of DHC in cases of malignant MCA infarction reduces mortality and improves functional outcomes in young adults (10, 12, 22, 23). However, the application of decompressive surgery has not been fully characterized
with respect to how routinely it should be performed in the clinical setting, considering the very high rate of disability and functional dependence among survivors (6, 17, 20, 25).

In order to clarify the current status of such decompressive surgery in Japan, we surveyed patients who underwent DHC in 2011 using a questionnaire distributed to pivotal training neurosurgical departments. We herein report the present status of this treatment in Japan and compare the published literature on immediate outcomes after DHC in order to evaluate the efficacy of early decompressive surgery.

METHODS

In 2011, there were 556 pivotal teaching departments of neurosurgery containing at least three members of the Japanese Society of Neurosurgery in Japan. We sent each of these departments questionnaires in February 2012, including letters of request for participation, survey slips and a request for reports of the following between January 2011 and December 2011; the number of patients with acute ischemic stroke; the number of patients having undergone DHC for malignant MCA infarction, excluding cases of subarachnoid hemorrhage, intracerebral hemorrhage, head trauma and cerebellar infarction; the number of patients not treated with DHC for malignant MCA infarction; reasons for not performing DHC; demographics of the patients treated with DHC, such as age, National institutes of health stroke scale (NIHSS) score on admission, the level of consciousness before surgery, timing of surgery, modality of vascular imaging, pre-surgical radiological findings on computed tomography (CT) or magnetic resonance (MR) imaging, 30-day mortality and functional outcomes as determined according to the modified Rankin scale (mRS) score at three months after DHC.

The clinical diagnosis of malignant MCA infarction was made according to the definition used in recent RCTs (22): 1) clinical signs of
large MCA territory infarction with an NIHSS score of >18 and a level of consciousness of ≥1 on item 1a of the NIHSS either on admission or after secondary deterioration; 2) the presence of large space-occupying MCA infarcts on follow-up MR imaging or CT of at least half of the MCA territory with compression of ventricles or midline shift; and 3) the lack of other obvious causes of neurological deterioration. The timing of the initiation of DHC depended on the department, i.e. regardless of the presence of signs of clinical cerebral herniation, such as papillary dilatation, or hemorrhagic infarction, as shown in the radiological findings.

Factors affecting the 30-day mortality rate after DHC were statistically analyzed with logistic regression models using the JMP 9.0 software program (SAS Institute Inc., Cary, North Caroline, USA), and the odds ratio (OR) and 95% confidence interval (CI) were obtained. Variables were considered for the multivariable models if their univariate P value was less than 0.20. Statistical significance was accepted at a P value of <0.05.

RESULTS

Among the 556 neurosurgical departments, 259 replied, for a response rate of 46.6%, and a total of 48,369 acute ischemic stroke patients were identified, with a median number of 151 and an interquartile range (IQR) of 55-271, between January 2011 and December 2011 (Figure 1). There were 3,737 patients with malignant MCA infarction who did not undergo DHC in these departments, ranging from 0 to 148, with a median number of 9 (IQR 3-17). Reasons for not performing DHC, as indicated by family members, included an advanced age (72%), concern regarding the efficacy of the procedure (65%) and the presence of infarction in the dominant hemisphere (33%), with overlapping results.

Demographics of the patients undergoing surgery
A total of 355 patients (59% male, 41% female) treated with DHC for malignant MCA infarction were reported among 259 neurosurgical departments, ranging from 0 to 14, with a median number of 1 (IQR 0-2) (Figure 2). Therefore, a total of 4,092 patients with malignant MCA infarction (8.5%) among 48,369 patients with acute ischemic stroke identified during the same period were considered candidates for DHC, only 8.7% of whom underwent surgery. Among the patients undergoing DHC, the mean age ± standard deviation (SD) was 67.0 ± 11.5 years, with a median 69 of years (IQR 61-75), and those ≥60 years of age comprised 80.2% of all DHC patients (Figure 3). The NIHSS score on admission ranged from 0 to 38, with a median value of 18 (IQR 14-22) (Figure 4). A total of 257 patients had right-sided infarction (73.0%), 203 patients had ipsilateral internal carotid artery (ICA) occlusion (57.2%), 213 patients had arterial fibrillation (60.0%), 90 patients underwent the intravenous injection of tissue plasminogen activator (t-PA) (25.4%) and 56 patients received endovascular treatment (15.8%). The primary modality of vascular imaging was as follows; MR angiography=77.2%, conventional angiography=18.6%, CT angiography=16.9%, ultrasound sonography=7.0%, with overlapping results.

**Time to surgery from symptom onset**

DHC was generally performed (38.9%) between 24-48 hours after symptom onset (Figure 5). In addition, 131 patients (36.9%) underwent surgery ≥48 hours of onset. At the time of surgery, 194 patients (54.7%) exhibited a Glasgow coma scale (GCS) score of ≤6 with or without signs of clinical herniation. Pre-surgical compression of the midbrain was observed on CT or MR images in 185 patients (52.1%).

**30-day mortality and functional outcomes at three months**
Sixty-six of the 355 patients died within 30 days of DHC (18.6%). According to the univariate analysis, factors associated with death after DHC included a GCS score of ≤6 (OR 1.88, 95%CI 1.05-3.32, P=0.03) and midbrain compression on CT/MR imaging (OR 2.28, 95%CI 1.31-4.09, P=0.005) (Table 1). The presence of atrial fibrillation was found to be inversely correlated with mortality (OR 0.53, 95% CI 0.30-0.93, P=0.03). According to the multivariate analysis, only midbrain compression was an independent risk factor (OR 2.12, 95% CI 1.16-3.95, P=0.01) for 30-day mortality after DHC.

Modified Rankin scale (mRS) scores at three month were available in 175 patients (49.3%); only 5.2% of the patients achieved a favorable functional outcome (mRS score ≤3), whereas 22.9% had an mRS score of 4, 26.9% had an mRS score of 5 and 45.1% were found to have died.

DISCUSSION

Frequency of decompressive hemicraniectomy in Japan

In this study, we obtained data regarding DHC performed in 2011 at pivotal training neurosurgical departments in Japan. A total of 355 cases of DHC among 48,369 cases of acute ischemic stroke were reported, suggesting that 0.73% of acute ischemic patients underwent DHC at these departments. The prevalence of DHC is somewhat higher than the adjusted prevalence of 0.51% observed in acute ischemic stroke patients, based on the Diagnosis Procedure Combination data provided by the Ministry of Health, Labour and Welfare of Japan, which reported 632 decompressive craniectomy procedures (code 1492) among 123,427 patients with acute ischemic stroke (code 010060) between July 2010 and May 2011 in Japan.
Regardless of the problems associated with this procedure, such as complications, including cerebellar infarction, and excluding fee-for-service payments, these data are trustworthy and the present data approximated these findings. On the other hand, the incidence of malignant MCA infarction in the present study was 8.5% among acute ischemic stroke patients, and only 8.7% of patients considered to be candidates underwent decompressive surgery during the same period.

In a nationwide study in the US, only 0.07% of acute ischemic stroke patients were reported to have received decompressive surgery in 2005-2008 (2); however the frequency of DHC increased linearly by 21% per year, regardless of the additive effects after publication of the pooled analysis for DHC in 2007. In another report (8), urban teaching hospitals were considered to be responsible for the increase in the frequency of DHC from 0.05% in 2001 to 0.3% in 2009 among a US nationwide inpatient sample. In addition, trends in increased utilization were found to be greatest among younger patients (age<45 years) and males (8). The relatively high frequency of DHC in Japan may be due, at least in part, to the ready availability of MR imaging, thus facilitating the prediction of malignancy of MCA infarction, as the usefulness of MR imaging performed within six hours of onset in predicting progression to malignant MCA infarction has been reported, in contrast to the NIHSS score on admission, which fails to predict such progression (21). In a report from the Czech Republic, the procedure remained underutilized, as less than 10% of those who required decompression underwent surgery, with a frequency similar to our results (7).

**Characteristics of patients undergoing decompressive hemicraniectomy**

Among the patients undergoing DHC in this study, the median NIHSS score on admission was 18 (IQR 14-22), the condition exhibited a right-side predominance (73.0%) and the presence of ipsilateral ICA
occlusion was detected in 57.2% of patients, although these were not found to be independent factors affecting the 30-day mortality. Interestingly, the occurrence of atrial fibrillation (60.0%) was found to be inversely correlated with mortality, although this finding did not reach statistical significance in the multivariate analysis. The administration of intravenous thrombolysis and/or endovascular treatment also did not affect immediate mortality after DHC. In this study, 18.6% of the patients died within 30 days after undergoing DHC, and only 5.2% of patients exhibited a favorable functional outcome (mRS score ≤3) at three months after DHC.

Published reports suggest that a poor outcome may be attributable to the presence of herniation, a low preoperative level of consciousness and the involvement of multiple vascular territories in ischemic stroke patients (6, 10, 15, 20). In a meta-analysis of three RCTs, DHC performed within 48 hours of ictus reduced the mortality rate from 71% to 22% and doubled the probability of a favorable functional outcome (mRS ≤3) at one year after surgery (22). Because we only evaluated 30-day mortality, we cannot compare our findings with these data. In addition, the present subjects included many elderly patients (median age: 69), and 36.9% of the patients underwent surgery ≥48 hours after symptom onset, which do not correspond to the inclusion criteria used in recent RCTs (22).

**Time limitations**

Brain edema following MCA territorial infarction often peaks 48 hours after symptom onset, and the use of delayed surgery (48-96 hours) in recent RCTs has not been demonstrated to reduce mortality, although these studies were limited by a small number of patients (10). On the other hand, the efficacy of immediate surgery within 24 hours does not differ from that of surgery performed with 24-48 hours in terms of the likelihood of a functional recovery after the procedure (22). In the present study, DHC was generally performed (38.9%) between 24-48 hours of onset, and 36.9% of the patients underwent surgery ≥48 hours after symptom onset. The timing
of surgery was not found to be an independent factor affecting 30-day mortality, whereas a trend was observed toward decreased mortality, although it did not reach statistical significance (P=0.07). Patients in which brain edema develops after 48 hours may be more tolerant to the same degree of ischemic insult due to the presence of a preexisting or developing collateral circulation than those in whom such symptoms emerge before 48 hours, and additional predictors should be elucidated in future studies.

**Age limitations**

Another concern is whether performing decompression surgery in elderly patients with malignant MCA infarction can be used to reduce mortality and improve functional outcomes, as it has been shown that elderly patients have a statistically higher rate of mortality and poor functional outcomes after DHC than young patients (5, 9). As to in-hospital mortality, the rate observed among elderly patients after this procedure may be higher (24), while other studies have reported that age as well as sex, thrombolysis, and the occurrence of stroke-related complications, such as aspiration pneumonia, do not affect in-hospital mortality, although the patients undergoing DHC (mean age: 55.6 years) in these studies exhibited a higher rate (32.1%) of mortality than conservatively treated acute ischemic stroke patients (4). In a systematic review incorporating a wide range in age and hours from ictus to surgery, an age over 60 years (P<0.05) as well as additional cerebral artery involvement and a greater midline shift preoperatively were found to be independent factors affecting 30-day mortality after DHC (15). In the present study, it is interesting to note that the most frequent reason for not performing DHC, as indicated by family members, was an advanced age, while patients ≥60 years of age comprised 80.2% of all DHC patients (median: 69, IQR: 61-75). In addition, we did not find any evidence of a higher immediate mortality rate among elderly patients after DHC for malignant MCA infarction. Because elderly patients (aged >60) were excluded in recent RCTs (12, 22, 23), the indications for
performing this procedure in elderly subjects have not been justified, and the underutilization of DHC is a current problem (11, 17). Whether the application of DHC in the management of malignant MCA infarction in elderly patients is meaningful or equivalent to that observed in young adults should be evaluated, and new RCTs are currently underway (13, 16, 26).

**Study Limitations**

There are several limitations associated with the present study. First, because the data for small hospitals with two or fewer neurosurgeons were not included, the actual frequency of DHC could not be assessed. In addition, the information for the patients with acute ischemic stroke in this study was obtained in combination with the departments of neurology and neurosurgery; therefore, the results are representative, at least regarding the trends in the frequency of and indications for DHC for malignant MCA infarction in Japan. Second, the characteristics of the patients treated with and without DHC were not directly compared. In addition, the mortality of patients was calculated only at one month after DHC, and the functional outcomes at three months in survivors were not statistically evaluated. Among elderly patients, who comprised the majority of subjects in this study, the greatest concern is regarding a functional recovery, while hemispheric dominance does not affect mortality (11, 22). DHC increases the probability of achieving an mRS score of 4 at one year, although whether this indicates a favorable outcome has not reached a consensus (18, 22), as patients with non-speech dominant hemispheric infarction treated with DHC are possibly at high risk of depression and severe cognitive impairment (19). In this study, as a large number of patients were lost to follow-up after being transferred from each department, we were unable to obtain results regarding functional assessments at six months after DHC in order to provide data comparable to those reported in recent RCTs (12, 22, 23). The non-significant mortality observed at one month after DHC in the
elderly may be attributable to the selected definition of this concept. Nevertheless, we believe that our study clearly outlines the current status of DHC in the acute stage of malignant MCA infarction in Japan and indicates ongoing problems, especially with respect to the application of this procedure in the elderly.

**CONCLUSIONS**

The present study demonstrated the current status of DHC for malignant MCA infarction in Japan. Only 8.5% of candidates with malignant MCA infarction underwent decompressive surgery, and the vast majority of patients were ≥60 years of age. DHC was found to be underutilized and performed mostly in patients not meeting eligibility criteria for the procedure based on that reported in recent RCTs (12, 22, 23). Although age was not found to be an independent factor for immediate mortality in this study, performing surgery in the elderly may be justified by additional evidence regarding the ability to obtain functional improvements, considering the high rate of physical disability observed among survivors. Further studies are required to determine the proper utilization of such procedures by evaluating appropriate quality-of-life measurements and functional outcome parameters.

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*Conflict of interest statement: The authors declare that the article content was composed in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.*
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Legends

Figure 1
Distribution of the Number of Patients with Acute Ischemic Stroke at Each Neurosurgical Department

Figure 2
Distribution of the Number of Patients Undergoing Decompressive Hemicraniectomy for Malignant Middle Cerebral Artery Infarction
DHC, decompressive hemicraniectomy

Figure 3
Age Distribution of the Patients Undergoing Decompressive Hemicraniectomy

Figure 4
National Institutes of Health Stroke Scale Score on Admission in the Patients Undergoing Decompressive Hemicraniectomy
NIHSS, National institutes of health stroke scale

Figure 5
Time to Decompressive Hemicraniectomy from Symptom Onset
DHC, decompressive hemicraniectomy

Table 1
Factors Affecting the 30-day Mortality Rate after Decompressive Hemicraniectomy for Malignant Middle Cerebral Artery Infarction
According to the Univariate and Multivariate Analyses
OR, odds ratio; CI, confidence interval; ICA, internal carotid artery; t-PA, tissue plasminogen activator; NIHSS, National institutes of health stroke scale; GCS, Glasgow coma scale
Figure 1

Number of acute ischemic patients

Number of departments
Figure 2: The figure shows a box plot and a histogram representing the distribution of number of patients undergoing DHC among different departments. The x-axis represents the number of patients undergoing DHC, while the y-axis represents the number of departments. The box plot and histogram provide insights into the variability and central tendency of the data.
Figure 5

- Time to DHC from symptom onset
- Number of patients
- 0-3, 3-6, 6-12, 12-24, 24-48, 48-72, 72-
<table>
<thead>
<tr>
<th>Variables</th>
<th>Univariate Analysis</th>
<th>Multivariate Analysis</th>
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<td>Sex, M vs. F</td>
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<td>Infarcted side, R vs. L</td>
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<td>Atrial fibrillation</td>
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<td>Use of t-PA</td>
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<td>Surgery ≥48 hours of onset</td>
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<td>Midbrain compression</td>
<td>2.28 (1.31-4.09)</td>
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Table 1