

# Effects of early decompressive craniectomy on functional outcome of patients with malignant middle cerebral artery infarctions

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## Keywords

Middle Cerebral Artery; General Surgery; Brain Ischemia; Infarction; Mortality

## Abstract

**Background:** This study aimed to compare the functional outcome of patients with malignant middle cerebral artery (MCA) infarction who had undergone either early decompressive craniectomy (DC) or optimal medical therapy (OMT).

**Methods:** This study was conducted during a 2-year period in Golestan Hospital of Ahvaz, Iran. The selected patients with malignant MCA infarction who were admitted within 48 hours of presenting signs were included. The patients were randomly assigned to undergo either early DC (n = 12) or OMT (n = 12) in the neurosurgical intensive care unit (ICU). The functional outcomes in the subjects were evaluated with the Glasgow Outcome Scale (GOS) and the

National Institutes of Health Stroke Scale (NIHSS) at discharge, 6, and 12-month intervals.

**Results:** The patients who underwent DC had significantly higher GOS at discharge (P = 0.013), 6 (P = 0.022), and 12 (P = 0.042) months as compared to the medical therapy group. However, the NIHSS score did not show any significant difference between the two groups during the study. Likewise, DC was associated with lower mortality at 6 (P = 0.027) and 12 (P = 0.014) months; moreover, the lower mortality rate (P = 0.014), severe disability (P = 0.040), higher good recovery (P < 0.001), and moderate disability (P < 0.001) were observed after

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12 months of follow-up.

**Conclusion:** These findings suggest that early DC in patients with malignant MCA can decrease mortality and improve the functional outcome according to GOS criteria compared to medical therapy.

### Introduction

Malignant middle cerebral artery (MCA) infarction is a devastating state resulting from brain infarction or ischemia following occlusion of the proximal parts of the MCA (M1 or M2-MCA). This condition causes rapid neurological deterioration due to the effects of space-occupying cerebral edema about 24 to 72 hours after the onset of the symptoms.<sup>1</sup> The prognosis of the malignant MCA infarction is significantly poor despite maximal medical therapy.<sup>2</sup>

Decompressive craniectomy (DC) is currently considered the only available surgical treatment for patients with malignant MCA infarctions. The theory beyond this modality is the disruption of the vicious cycle between the cerebral edema and ischemia which leads to increased intracranial pressure (ICP) and reduced cerebral perfusion pressure (CPP), and consequently more ischemia and infarction in the penumbra.<sup>1</sup> Removing a large portion of bone flap followed by duraplasty results in decreased ICP and increased space for the swelling brain to occupy.<sup>3</sup> The role of DC in managing ischemic stroke and malignant MCA infarction has been a controversial subject over the past decade.<sup>4-6</sup> The current lines of evidence suggest that DC is accompanied by decreased mortality but increased disability in patients with malignant MCA infarctions.<sup>4,7</sup> Determination of the ideal timing for DC after the malignant MCA infarction remains the most important predictive factor. A recent meta-analysis demonstrated that early DC (within 24 hours of symptom onset) was associated with decreased mortality and better favorable functional outcome in subjects with malignant MCA infarctions.<sup>6</sup> However, the meta-analyses<sup>4-6</sup> are mostly based on prospective cohort studies, and the lack of randomized clinical trials affects the results and the level of evidence. The present study aimed to determine the effects of early DC on the functional outcome of patients with malignant MCA infarction compared to optimal medical therapy (OMT).

### Materials and Methods

**Study population:** This study was conducted from March 2015 to March 2017 in Golestan

Hospital, a tertiary healthcare center and stroke center affiliated to Ahvaz Jundishapur University of Medical Sciences, Ahvaz, Iran. The study protocol was also registered in the Iranian Registry of Clinical Trials (IRCT) ([www.irct.ir;IRCT201112018272N1](http://www.irct.ir;IRCT201112018272N1)). All included patients had the following criteria: 1) first-time MCA infarction age of 18-80 years (with and without the previous small lacunar infarctions), 2) the onset of the infarction less than 48 hours, 3) ischemic signs (hypodensity in MCA territory) on subsequent cerebral computed tomography (CT) scan involving at least 2/3 of the MCA territory without additional infarction in the territory of the anterior or posterior cerebral artery (ACA/PCA), 4) decreased consciousness,  $14 \geq$  Glasgow Coma Scale (GCS)  $> 6$ , and 5) no significant rise of ICP causing anisocoria. The exclusion criteria were as follows: 1) those who had a pre-stroke modified Rankin Scale (mRS) of  $\geq 2$ , 2) other causes of decreased level of consciousness such as intoxications and metabolic etiologies, 3) the presence of intracranial hemorrhage (ICH) or hemorrhagic transformation of the ischemic area, 4) comorbidities preventing the surgery from being conducted such as renal and hepatic failure, use of warfarin, and any coagulopathies, 5) contraindication of the general anesthesia and surgery, 6) pregnancy, and 7) any intracranial mass. We also removed any patients from the study if during the first 48 hours of infarction developed critically high ICP causing anisocoria or two-level decrease of GCS who underwent immediate DC.

All the recruited patients were initially assessed by a neurologist and a neurosurgeon and the eligibility criteria were assessed. Then, the patients were randomly assigned to the surgery group (undergoing early DC) and the medical group (receiving maximal medical therapy). All included patients provided written informed consent.

**Surgical procedure:** All the patients underwent surgery by the same surgeon and team. A standard fronto-parieto-temporal bone flap measuring approximately  $12 \times 15$  cm was removed using a craniotome. The dura was opened in a C-shape manner with a base over the superior sagittal sinus (SSS). The duraplasty was performed in a water-tight manner using a large pericranial fascia. The bone flap was placed within the abdominal wall for the subsequent cranioplasty. The patients were transferred to the intensive care unit (ICU) for postoperative care

and a brain CT scan was performed.

**Outcome measures and follow-up:** After completion of therapy in both groups and stabilization of patients, they were discharged from the hospital. All the patients were followed for 6 and 12 months and were visited in outpatient clinics. We recorded all-cause mortality after 6 and 12 months of follow-up. The outcome measures including the Glasgow Outcome Scale (GOS) and the National Institutes of Health Stroke Scale (NIHSS) were recorded in time points of 6 and 12 months and the functional outcome was recorded in both study groups.

The sample size of 12 patients in each group was calculated according to the type I error of  $\alpha = 0.05$  and power of 0.8. All the data were analyzed using SPSS software (version 20.0, IBM Corporation, Armonk, NY, USA). Data are presented as mean  $\pm$  standard deviation (SD) and proportions as appropriate. The proportions were compared using the chi-square test between the two study groups. The parametric variables with normal distribution were compared using an independent t-test between the two study groups. For parametric variables without normal distribution, Mann-Whitney U test was used. A two-sided P-value of less than 0.05 was considered statistically significant.

## Results

We screened a total number of 29 patients with malignant MCA infarction who were admitted to our center for eligibility. Five patients did not meet the inclusion criteria and were excluded and a total number of 24 patients were randomized to two study groups. All of the 24 patients finished the study. The baseline characteristics, neurological examination, and the functional outcome of the patients are summarized in table 1. There was no significant difference between the two groups regarding the baseline characteristics and comorbidities. The neurological examination on admission among the two groups was determined by GCS ( $P = 0.794$ ) and the NIHSS ( $P = 0.937$ ).

The patients were followed for 12 months, and the functional outcome, as well as all-cause mortality, was recorded. At the end of the study, 4 patients in the surgical group and 9 in the non-surgical group expired, which was a statistically significant difference. The results did not show a significant difference in NIHSS between the two groups during the hospital stay ( $P = 0.369$ ), at discharge ( $P = 0.723$ ), after 6 months ( $P = 0.707$ ),

and after 12 months ( $P = 0.834$ ). However, those who had undergone decompression surgery had significantly higher GOS at discharge ( $P = 0.013$ ), after 6 months ( $P = 0.022$ ), and after 12 months ( $P = 0.042$ ) (Table 1).

The percent of the persistent vegetative state was 16.6% in each group ( $P = 0.998$ ). Although severe disability was significantly fewer in the surgical group than the medical group ( $P = 0.040$ ), the results showed that moderate disability and good recovery were higher in the surgical group ( $P < 0.001$ ).

## Discussion

The optimal treatment of patients with malignant MCA infarction remains a dilemma to the neurologists and neurosurgeons. Although decompressive surgery has an important role in the therapy of these patients, there are many controversies regarding the exact timing of surgery and patient selection criteria to achieve a better outcome.

Appropriate timing of the decompression surgery in patients with malignant MCA infarction has been a challenging subject.<sup>3,4,7</sup> In these patients, the cerebral edema increases from the onset of the symptoms and reaches its peak by 3 to 5 days post injury.<sup>8,9</sup> Thus, secondary neuronal injury and worsening cerebral perfusion due to increased ICP may be prevented by early decompressive surgery. However, previous studies have used various time points, ranging from 24 to 48 hours.<sup>3,4,6,7,10,11</sup> The advantages of late surgery (beyond 48 hours of symptom onset) have been analyzed in a few studies.<sup>12,13</sup>

In the current study, we chose the time limit of 48 hours for surgery because this time point appears to represent the possible beginning of malignant edema that is often appreciable on brain imaging. Decompression at this stage might halt the cascade of increased edema, increased ICP, reduced cerebral perfusion, herniation, and poor outcome.<sup>8,9</sup>

Vahedi<sup>14</sup> analyzed prospectively the data from the three European trials evaluating the effect of early DC less than 48 hours (DECIMAL, DESTINY, and HAMLET). He showed a 50% decrement in mortality rate with surgical treatment. Our study results showed a 41.7% mortality reduction which is comparable to his results, despite the age difference, which in our study was 80 years (compared to 60 years in those 3 trials).

**Table 1.** Baseline characteristics, neurological examination, and the functional outcome of patients with malignant middle cerebral artery (MCA) infarction undergoing decompressive craniectomy (DC) (n = 12) or medical therapy (n = 12)

Variable	Surgery (n = 12)	Medical therapy (n = 12)	P
Age (year)	62.33 ± 9.16	63.17 ± 10.57	0.279
Gender			
Men	9 (75.0)	7 (58.3)	0.121
Women	3 (25.0)	5 (41.7)	
Side			
Right	5 (41.7)	6 (50.0)	0.157
Left	7 (58.3)	6 (50.0)	
Comorbidities			
HTN	8 (66.6)	7 (58.3)	0.781
DM	5 (41.7)	6 (50.0)	0.643
IHD	4 (33.3)	5 (41.7)	0.577
Smoking	4 (33.3)	3 (25.0)	0.123
Previous stroke	3 (25.0)	2 (16.6)	0.085
Hypercholesterolemia	2 (16.6)	1 (8.3)	0.067
Examination			
GCS (baseline)	8.58 ± 2.53	8.67 ± 1.37	0.794
NIHSS			
Baseline	20.17 ± 7.46	20.17 ± 9.37	0.937
During hospital stay	18.42 ± 8.73	21.83 ± 9.49	0.369
Discharge	8.15 ± 5.62	7.01 ± 8.48	0.723
6 months	7.12 ± 4.21	6.68 ± 4.71	0.707
12 months	6.53 ± 2.37	6.42 ± 3.24	0.834
GOS			
Discharge	2.83 ± 1.52	1.42 ± 0.99	0.013
6 months	3.32 ± 1.75	1.86 ± 1.42	0.022
12 months	3.59 ± 1.35	2.12 ± 1.54	0.042
Mortality			
6 months	1 (8.3)	3 (25.0)	0.027
12 months	3 (25.0)	6 (50.0)	0.014
GOS at 12 months			
PVS	2 (16.6)	2 (16.6)	0.998
Severe disability	1 (8.3)	3 (25.0)	0.040
Moderate disability	3 (25.0)	1 (8.3)	< 0.001
Good recovery	3 (25.0)	0 (0)	< 0.001

Data are presented as mean ± standard deviation (SD) and number and percentage

HTN: Hypertension; DM: Diabetes mellitus; IHD: Ischemic heart disease; NIHSS: National Institutes of Health Stroke Scale; GCS: Glasgow Coma Scale; GOS: Glasgow Outcome Scale; PVS: Persistent vegetative state

Most of the studies agree that surgery will reduce mortality, but not neurological disabilities. DECIMAL trials showed the advantage of a younger age to achieve a better functional outcome in the surgical group compared to older patients.<sup>15</sup> Therefore, the age and time of infarction onset to surgery are important factors associated with functional outcomes. Besides, Zhao et al. in a randomized clinical trial showed that DC significantly reduced mortality. Also, significantly fewer patients had an mRS score > 4 after surgery.<sup>16</sup> Recently, Paliwal et al. conducted a retrospective study and showed that the early decompressive surgery was an independent predictor of favorable functional outcome at 6 months.<sup>6</sup>

Due to the limited number of patients in our

study, mRS was not used for outcome assessment. According to some references, NIHSS is more sensitive when the sample size is not large.<sup>17</sup> Therefore, we measured the functional outcomes by NIHSS. We also considered using GOS as another outcome measure because of its reliability and ease of use.<sup>18</sup> We did not find any significant difference in NIHSS during hospitalization or on discharge between the two groups. However, we found that GOS was higher in patients who had undergone hemicraniectomy in comparison to the medical treatment group. We found that early DC (< 48 hours) is associated with an increased number of good recovery (GOS = 5) and moderate disability (GOS = 4), but not severe disability (GOS = 3 and 4) at 6 and 12 months after the

operation. The results of the current study recommend that early DC could improve the functional outcome and decrease the mortality of patients with malignant MCA infarction. It is following other previous reports in randomized clinical trials and cohort studies.<sup>6,10,16</sup>

The main limitation of our study is that results were based on small number of participants from a single center. This might have made the study underpowered in some subgroup analyses. However, we determined that the study had 80% power to detect at least a 5% difference between the primary endpoint of the study, which was mortality. Moreover, we did not evaluate the quality of life, symptoms of depression, or aphasia. These variables are valuable in the evaluation of prognosis.

### Conclusion

The current study demonstrated that early DC (< 48 hours) in comparison with OMT improved the functional outcome and decreased mortality in patients with malignant MCA infarction. Therefore, it seems that the surgery may be a superior protocol for these patients. However, the

results of this study should be confirmed by the large multi-center trials to increase the level of evidence. Also, it is worth considering how to judge what is the better outcome, for example, a mother surviving after decompressive surgery for left side MCA stroke, who otherwise would not survive without surgery. Although she may remain hemiplegic and aphasic, she is normally awake and alert and is emotionally happy and satisfied to see her children growing and having very good family support. Is it considered a bad outcome of surgery? And can anyone decide not to operate on this patient?

### Conflict of Interests

The authors declare no conflict of interest in this study.

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