Malignant Middle Cerebral Artery (MCA) Infarction : How to Manage Now ?

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Abstract

Background: Malignant middle cerebral artery (MCA) infarction is a devastating clinical entity affecting about 10% of stroke patients. Decompressive craniectomy has been found to reduce mortality rates and improve outcome in patients. Key factors associated with favorable outcome include younger age and early surgical treatment. There is ongoing debate as to whether surgery should be routinely performed, considering the very high rates of disability and functional dependence in elderly survivors. Further data on what is the best management in older age, how to provide the best comprehensive neurological and medical care, and how to inform families facing complex decisions on surgical intervention in deteriorating patients have been still required.

Methods: A retrospective case review study was conducted to compare patients treated with medical therapy and decompressive surgery for malignant MCA infarction in Chumphon Ket Udomsakdi Province Hospital over a period of 3 years (from January 2012 and September 2014). Outcome was assessed in terms of mortality rate at 30 days, Glasgow Outcome Score (GOS) on discharge, and modified Rankin scale (mRS) at 6 months.

Results: No significant difference was seen between patients treated with medical therapy and decompressive surgery in mortality rate reduction, GOS at discharge, and mRS at 6 months. Mortality rate of medical therapy was 35.7% compared to 30.7% in patients treated with surgery. Good functional outcome based on mRS was seen in 60.8% of patients receiving medical treatment, comparing to 46.2% of patients treated with surgery. Even the results were not met significantly association by statistic calculation, it seem that patients with age > 50 years derived good outcome from medical treatment and the patients with age ≤ 50 years derived better outcome from surgical treatment. Factors associated with good outcome in medical therapy included pre-treated CT midline shift less than 10 mm ($P < 0.05$) and GCS of 10-13 ($P < 0.05$). Dominant hemisphere involvement and hemorrhagic transformation were not significantly associated with functional outcome.

Conclusion: Malignant MCA infarction is a critical condition that warrant immediate, specialized neurointensive care and often neurosurgical intervention. Early medical therapy should be considered in patients who continue to deteriorate neurologically. Elderly patients may benefit greatly from such an approach, and although disabled, they may be functionally independent. Age is an important factor to consider in patient selection for surgery. Appropriate patients are relatively young, in the first five decades of life.

Background

Middle cerebral artery (MCA) infarction is a clinical entity affecting up to 10% of all patients diagnosed with ischemic stroke. It is defined as an infarction involving an area encompassing at least two thirds of that supplied by the MCA.[1] The development of a space-occupying hemispheric infarction occurs in a subset of patients with ischemic stroke. Massive brain edema and herniation, a condition known as malignant MCA infarction. Severe swelling increases intracranial pressure (ICP) and leads to progressive brainstem dysfunction. It is a life-threatening condition with a high mortality rate. Intensive medical therapy have so far been ineffective, with reported mortality rates being as high as 80% despite optimum medical management.[2,5] A space-occupying mass effect develops rapidly and predictably over the initial 5 days after presentation. The initial presenting features include symptoms and signs of MCA occlusion, such as hemiparesis, hemiplegia, gaze preferences, and altered consciousness.[3] Decompressive craniectomy with duroplasty has been proposed as a treatment option for large hemispheric infarctions with cerebral edema.[4] Based on the rationale of treatment that the temporary removal of a part of the skull would create space to allow swollen brain (edematous tissue) to expand outside the cranium, thereby allowing for normalization of intracranial pressure, preventing brain tissue herniation, and preserving cerebral blood flow to prevent secondary brain damage.[5] The procedure can be performed in every neurosurgical center. However, in the past decompressive craniectomy for malignant middle MCA infarction has long been controversial, various nonrandomized trials and reports have been published. Previous retrospective and uncontrolled case series have suggested that decompressive hemicraniectomy can significantly reduce mortality to 20-30% compared to conservative treatment. But various unresolved issues remained in these early trials, which included timing of surgery, age limit, the limits of acceptable outcome and patient selection. This evidence has now been confirmed by the data of prospective randomised studies. Results from three European randomized controlled trials for decompressive craniectomy in malignant MCA territory infarction, the DECIMAL[6], HAMLET[7] and DESTINY[8] trials, published in 2007, demonstrated a significant reduction in mortality rates and improvement in functional outcome in younger patients early treated with decompressive craniectomy as compared to medical therapy. Key factors associated with favorable outcome include younger age and early surgical treatment. After the publication of these three trials, the utilization of hemicraniectomy for acute ischemic stroke in the United States has increased significantly especially in urban teaching hospitals from 0.05% of stroke discharges in 2001 to 0.30% of stroke discharges in 2009.[9] However, there is ongoing debate to whether surgery should be routinely performed, considering the very high rates of disability and functional dependence in survivors. The meta-analysis of the three trials suggested that the treatment significantly reduces the death rate but also increases the rate of severe disability and no evidence that hemicraniectomy was more beneficial than best medical treatment on the basis of the primary outcome.[10] Presently, these randomised-controlled trials were difficult to conduct, because of ethical considerations due to high mortality in control groups. However, there are still uncertainties surrounding the optimal management of patients with malignant MCA infarction. Guidelines are needed on how to manage, how to provide the best comprehensive neurological

and medical care, and how to best inform families facing complex decisions on surgical intervention in deteriorating patients. This was only a non-randomised-controlled study which was conducted to compare the difference in outcome in terms of mortality rate at 30 days and functional outcome at discharge and 6 months following decompressive craniectomy for treatment of malignant MCA infarction and medical treatment, as well as to study the association of factors influencing outcome in both groups.

Methods

A retrospective case review of patients diagnosed with malignant MCA territory infarction admitted to the neurosurgery department of Chumphon Khet Udomsakdi Province Hospital between January 2012 and September 2014 was performed. Data were collected from patients' medical records, surgical records, and radiological images. A total of 41 patients between the ages of 33 and 87 years were included in this study. Malignant MCA territory infarction was defined as an infarction of at least two-thirds of MCA territory with evidence of space-occupying edema and mass effect on non-contrasted computed tomographic (CT) imaging of the brain. Pretreatment clinical evaluation was based on the Glasgow Coma Scale (GCS). All patients had at least one scan done within 24 h of stroke onset. A repeat scan was done within the following 24-72 h, or the patients had early clinical changing.

Surgical treatment consisted of standardized decompressive craniectomy with fascio-duroplasty. To be successful, decompression must be extensive, targeting a bone flap measuring 14 cm from front to back, and extending 1 to 2 cm lateral to the midline sagittal suture to the floor of the middle cranial fossa at the level of the coronal suture. An augmentation duraplasty is mandatory.[10]

Conservative treatment: So far, no mode of conservative treatment in malignant MCA infarction has been proven to be effective or superior to another. As a result, treatment options may vary between institutions.

1. Osmotherapy: osmotherapy may be started at any time point after randomisation. The use of mannitol (20%, 100 ml or 0•5-1•0 g/kg every 4-6 h, maximum 2•5 g/kg/day), glycerol (10%, 250 ml, three to four times per day), Dosage depends on serum osmolality, which should not much more than 320 mOsm or urine sp.> 1.040.

2. Intubation and mechanical ventilation: patients should be intubated at a GCS score <8, when there are any signs of respiratory insufficiency (arterial pO_2<60 mmHg and/or pCO_2>48 mmHg), reduced swallowing or coughing reflexes, or when the airway is compromised.

3. Hyperventilation: the use of hyperventilation is discouraged in the early phase of treatment. In the case of further neurological deterioration and/or uncontrolled increase in ICP, hyperventilation may be started as an ultima ratio. It is advised to monitor venous oxygenation with jugular bulb oxymetry and to maintain saturation above 50%. Arterial pCO_2 may be reduced to 28-32 mmHg.

4. Blood pressure control: blood pressure is controlled according to the latest recommendations of the treatment of acute ischaemic stroke. An exception is made in patients after decompressive surgery. Blood pressure during the first 8 h after surgery is kept at 140-160 mmHg to avoid severe bleedings.

5. Positioning: flat head positioning is recommended. In patients at risk for aspiration or pneumonia, or after intubation, elevation of the head of 15-

30° is recommended.

6. Body core temperature: normothermia is recommended. Elevated body temperature is treated as soon as it exceeds 37-5°C. (Use antipyretics, external cooling)

7. Blood glucose level: blood glucose level should not exceed 140 mg/dl (8 mmol/l), with a target level of 80-110 mg/dl using insulin if necessary. Hypoglycaemia is treated with infusion of 10% or 20% glucose solution.

Those receiving medical therapy included in the previous conservative treatment guideline without any surgery. After patients diagnosed with malignant MCA territory infarction was consulted from medical staff, all patients would be transferred from medical ward to the neurosurgery intensive care unit. Serial computed tomography with measurement of midline and septum pellucidum shift. Time course and outcome were analyzed with regard to the clinical findings on admission and at follow-up. Outcome measured was assessed based on mortality rate at 30 days, Glasgow Outcome Score (GOS) on discharge, and the functional status of surviving patients was assessed using modified Rankin scale (mRS) at 6 months.

Chi-square test were used to determine significant differences in outcome based on mortality rate at 30 days, GOS at discharge, and mRS at 6 months between patients treated with surgery and medical treatment, as well as to determine significant difference in factors influencing outcome in patients treated with surgery and medical treatment group. The GOS was dichotomized as unfavorable outcome (GOS 4 and 5) and favorable outcome (GOS ≤3), and the mRS as good outcome (mRS ≤3) and poor outcome (mRS 4-6). Patients with a GCS score of 6 and below or those with evidence of absent brain stem reflexes were excluded from this study.

Variables with P values less than 0.05 and clinically relevant variables (P > 0.05) were subjected to multivariable logistic regression analysis to determine independent associative factors for long term outcome based on mRS at 6 months.

Result

A total of 41 patients with malignant MCA territory infarction during the study period were included in this study. The age range was between 33 and 87 years. Non-dominant hemisphere was involved in 17 patients (41.4%), while dominant hemisphere involvement was seen in 24 patients (58.6%). A total of 13 patients (32%) which mean (±SD) age was 54.5 (±14.4) years were treated with surgery. While 28 patients (68%) which mean (±SD) age was 64.8 (±13.1) years were managed with medical therapy. Majority of the patients (62%) had a GCS score of between 6 and 9 before surgery. Most time between stroke onset and surgery was more than 24 h. No significant difference was seen between patients treated with decompressive surgery and those treated with medical therapy in terms of mortality rate at 30 days, GOS at discharge, and mRS at 6 months. [Table 2] Patients treated with surgery had a mortality rate of 30.7%, as compared to 35,7% in patients treated with medical therapy (P> 0.05). Favorable outcome based on GOS at discharge was noted in 57.2% of the patients treated with medical treatment, as compared to 38.5% of the patients treated with surgery but they were not significantly associated (P >0.05). Good outcome based on dichotomized mRS (mRS <4) was seen in 60.8% of patients receiving medical treatment at 6 months, respectively comparing to 46.2% of patients treated with surgery at 6 months were not significantly

Table 1 Comparison of outcome in patients with malignant MCA territory infarction treated with surgery and medical therapy

Outcome measure	Surgery (n=13) N (%)	Medical (n=28) N (%)	P value
Mortality rate at 30 days			
Alive	9 (69.3%)	18 (64.3%)	> 0.05
Death	4 (30.7%)	10 (35.7%)	χ^2 = 0.09
GOS at discharge			
Unfavorable	8 (61.5%)	12 (42.8%)	> 0.05
Favorable	5 (38.5%)	16 (57.2%)	χ^2 = 1.21
mRS at 6 months			
Poor outcome	7 (53.8%)	11 (39.2%)	> 0.05
Good outcome	6 (46.2%)	17 (60.8%)	χ^2 = 0.26

χ^2=Chi-square value. GOS: Glasgow outcome score (dichotomized), mRS: Modified rankin scale (dichotomized)s

Table 2 Factors influencing outcome at 6 months in patients treated with surgery

Factors	N =13	Good outcome (%)	Poor outcome (%) (mRS 4–5 or death)	P value
Age (mean) (yrs)				
≤ 50	6	4 (66%)	2 (34%)	> 0.05
> 50	7	2 (28%)	5 (72%)	χ^2 = 1.87
Site of infarction				
Left	4	3 (75%)	1 (25%)	> 0.05
Right	9	4 (45%)	5 (55%)	χ^2 = 3.03
Midline shift(mm)				
≤ 10	7	5 (71%)	2 (29%)	> 0.05
> 10	6	2 (33%)	4 (67%)	χ^2 = 1.32
Pre-op GCS				
GCS 10-13	5	4 (80%)	1 (20%)	> 0.05
GCS 6-9	8	3 (37%)	5 (63%)	χ^2 = 2.21
Surgery interval				
≤ 24 h	2	0	2 (100%)	> 0.05
> 24 h	11	7 (64%)	4 (36%)	χ^2 = 2.74
Hemorrhagic transformation	1	0	1 (100%)	

associated (P > 0.05). In patients treated with surgery, no factors were associated significantly with good outcome at 6 months [Table 2] such as age, dominant hemisphere involvement, midline shift, preoperative GCS, time interval to surgery and postoperative complication of hemorrhagic transformation (P > 0.05). In

Table 3 Factors influencing outcome at 6 months in patients treated with medical treatment

Factors	n =28	Good outcome (%)	Poor outcome (%) (mRS 4–5 or death)	P value
Age (mean) (yrs)				
≤ 50	5	2 (40%)	3 (60%)	> 0.05
> 50	23	15 (65%)	8 (35%)	χ^2 = 1.08
Site of infarction				
Left	20	11 (55%)	9 (45%)	0.95
Right	8	6 (75%)	2 (25%)	χ^2 = 0.003
Midline shift (mm)				
≤ 10	17	16	1	< 0.001
> 10	11	1	10(D)	χ^2 = 19.63
Pre-treated GCS				
GCS 10-13	17	16	1	< 0.001
GCS 6-9	11	1	10(D)	χ^2 = 19.63
Hemorrhagic transformation	4	2	2	

n = the number of patients χ^2 = Chi-square value

patients treated with medical treatment, the factors significantly associated with good outcome at 6 months [Table 3] were midline shift less than 10 mm ($P < 0.001$) and preoperative GCS of 10-13 ($P < 0.001$). Age, dominant hemisphere involvement and postoperative complication of hemorrhagic transformation were not significantly associated with outcome at 6 months ($P > 0.05$).

Discussion

Decompressive craniectomy was not routinely performed in our hospital and many cases underwent medical treatment more often than surgical treatment. Decompressive craniectomy achieves good functional outcome in young patients with good preoperative GCS score and favorable radiological findings. Even the results did not reach significantly association by statistic calculation, it seem that patients with age > 50 years derived good outcome from medical treatment and the patients with age ≤ 50 years derived better outcome from surgical treatment. Three of five poor outcome cases with age > 50 years died from acute myocardial infarction after surgery. Our study could not explain the beneficial role of decompressive craniectomy over the medical treatment in reducing mortality rate and improving functional outcome in patients with malignant MCA territory infarction like the most previous study. As seen on study, good result could be met when we selected appropriate patients to start early medical treatment. We found that medical treatment had been yet the treatment of choice for malignant MCA infarction. Decompressive hemicraniectomy in older patients was less often used and performed later. Because most of cases had multiple underlying diseases and caregiver refused surgical treatment. Reasons for later intervention may be the belief that older patients may less likely proceed to herniation due to more compensating intracranial space, i.e. lower average brain volumes and

greater CSF space. Conversely, younger patients who do not have suffered the effects of cerebral atrophy may deteriorate faster, and present with a lower GCS score, are not proper to use medical treatment. Naturally, the prognosis of complete middle cerebral artery territory stroke is very poor and the course of deterioration varies between 2 and 5 days. The cause of death is trans-tentorial herniation with subsequent brain death. Herniation occurs as an end point in 80% of untreated patients.[11] Clinical signs that signify deterioration in swollen supratentorial hemispheric ischemic stroke include new or further impairment of consciousness, cerebral ptosis, and changes in pupillary size.[12] Despite well-defined clinical and neuroimaging (CT scan) diagnostic criteria, malignant MCA infarction might be missed in the first day of stroke onset. Diagnosis and treatment had often been delayed until CT scan was repeated after clinical deterioration of the patients. Identification of patients at high risk for brain swelling should include clinical and neuroimaging data. CT scan should be daily repeated in the first few days in all clinically suspected large infarction patients. After diagnosis was confirmed, all cases should be early consulted to neurosurgeon for attention. Admission to a unit with neurological monitoring capabilities is needed. These patients are best admitted to intensive care or stroke units attended by skilled and experienced physicians. Medical treatments should be started instantly even clinical and CT finding had changed or not. The goal of hyperosmolar therapy is to increase the serum osmolarity to approximately 315-320 mOsm/L. Glycerol or mannitol is used routinely to reduce ICP. In more severe cases and when mannitol fails, diuretic may be administered. Hyperventilation also helps reduce ICP effectively for a short time only. Corresponding to this study, good outcome was met if we started the medical treatment before midline shift more than 10 mm. on CT and GCS > 9. Pre-treated GCS score and midline shift on CT were found to be significantly associated with patient outcome at 6 months. And this factor may explain the comparable outcomes observed in the previous study. Patient's health status, co-morbidities, neurological condition on presentation and extent of infarction, social and employment situation, as well as patient's and family expectations should be taken into account in treatment decisions. Dominant hemisphere infarction was significantly associated with unfavorable outcome at 6 months follow-up in medical group. The patients and their caregivers need to be comprehensively informed about the long-term consequences of the acceptable degree of disability, the importance of aphasia and the possibility of worse prior to surgery.

Conclusion

Malignant MCA infarction is a critical condition that warrants immediate, specialized neurointensive care and often neurosurgical intervention. Despite high mortality and morbidity, decompressive craniectomy is a necessary option in many patients to prevent cerebral herniation for maximizing the potential of survival. Decompressive craniectomy should be considered in patients who continue to deteriorate neurologically. Selected patients may benefit greatly from such an approach, and although disabled, they may be functionally independent.[12] Thus, the indication for surgery is a great extent still dependent on the individual situation of the patient and the experience of the treating physicians. There is uncertainty about the efficacy of decompressive craniectomy in older patients. Age is an important factor to consider in patient selection for surgery. Peri-operative complication from cardiovas-

cular disease in older group must be concerned. Appropriate patients are relatively young, in the first five decades of life. Lethargy combined with midline shift on neuroimaging is an appropriate trigger to consider and discuss surgical intervention. Malignant MCA infarction, most of cases are old age patients and refused surgical treatment cases by caregiver. Medical treatment had been still proved as the treatment of choice. Good result could be met if proper medical treatment was started in early time. Factors that predicted outcome are total scores of baseline GCS at the time of treatment and significant edematous effect after infarction.

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