MANAGEMENT OF MALIGNANT MIDDLE CEREBRAL ARTERY INFARCTION

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ABSTRACT

Malignant middle cerebral artery (MCA) infarcts occur in a small subset of patients with ischaemic strokes and lead to high levels of disability and mortality. Over the last 10 years, surgical interventions, in the form of decompressive craniectomies, have become more popular. There is insufficient evidence to support current medical treatments including mannitol, glycerol, steroids, hypertonic saline, and therapeutic hypothermia. Several randomised controlled trials of early decompressive craniectomies in younger patients have shown a significant improvement in functional outcomes and mortality. Questions still need answering regarding the timing of this surgery, long-term survival benefits, and age thresholds. In this review article we will discuss the evidence and uncertainties surrounding the management of malignant MCA infarcts.

Keywords: Malignant cerebral infarction, decompressive craniectomy, imaging, outcomes.

INTRODUCTION

Malignant middle cerebral artery (MCA) infarcts occur in about 8% of ischaemic strokes.[1] They are the most devastating form of acute stroke and lead to a mortality of around 80%.[2,3] This is due to the complete infarction of the MCA leading to acute brain swelling, elevated intracranial pressure (ICP), and brain herniation over 5 days.[2] It constitutes a distinct clinical picture also referred to as 'brain oedema in stroke',[4] 'cerebral infarction with swelling',[5] 'massive MCA infarction',[6] and 'space-occupying MCA infarction'.[7] Severe neurological deficits are seen more commonly than in other types of infarcts, including hemiplegia, hemisensory loss, hemianopia, global aphasia, pupillary abnormalities, and a decreased level of consciousness over 24-48 hours.[1]

Imaging is used for diagnosis and, along with the clinical presentation, can help in predicting the malignant course of the disease.[8] Risk factors for developing fatal brain swelling include a National Institutes of Health Stroke Scale (NIHSS) score ≥20 for left hemisphere infarcts or ≥15 for right hemisphere infarcts, nausea and vomiting, and >50% MCA territory hypodensity on computed tomography (CT) images.[8] Other CT parameters that have been shown to predict a fatal outcome are anteroseptal shift >5 mm, pineal shift >2 mm, and hydrocephalus.[9] Magnetic resonance imaging (MRI) with diffusion weighting (lesion volume >82 cm^3), perfusion imaging, and angiography within 6 hours of symptom onset have also been demonstrated to predict a malignant course.[10,11] Proton emission tomography, used to calculate cerebral blood flow (CBF) and the volume of ischaemic core, and neuromonitoring are new approaches that may be beneficial but which require more investigation.[12]

Over the last few years there has been uncertainty over the optimal management of patients presenting with brain swelling after a cerebral infarction.[5] Despite optimal medical management, outcomes have remained poor.[2,13] Between 2007 and 2009, three prospective randomised controlled trials (RCTs) showed an improvement in functional outcome and mortality with surgical decompression compared with medical management.[14-16] This has led to updated Scottish Intercollegiate Guidelines Network (Guideline

No. 108 December 2008) and National Institute for Health and Care Excellence (CG68 July 2008) guidelines recommending surgical intervention in certain patient groups. In this review article we discuss the evidence behind different treatment strategies used in the management of malignant MCA infarcts and where the future lies.

MEDICAL MANAGEMENT

Patients with large MCA infarcts should be cared for in a specialist neuro-intensive care unit.[7] Elective intubation may be needed to facilitate monitoring and treatment. In one case series from 2000, 24% of patients needed mechanical ventilation due to a decreased level of consciousness, heart insufficiency, and pneumonia, particularly if the infarct exceeded two-thirds of the MCA territory.[17] A cohort study evaluated the use of ICP monitoring in 48 patients with acute ischaemic stroke and elevated ICP.[18] They concluded that ICP monitoring can predict clinical outcomes in large hemispheric infarctions, but it was not useful in guiding management and they felt it did not have a positive influence on outcomes.

Mannitol

Mannitol is an osmotic diuretic that pulls water across the blood—brain barrier (BBB) out of the interstitium and intercellular spaces. It also causes a reduction in cerebral blood volume due to vasoconstriction. These effects lead to a consequent reduction in ICP and are therefore used to control cerebral oedema.[19] There are worries that if the BBB is not intact then mannitol can cross and lead to a 'rebound' intracranial hypertension when water is drawn back into the cerebral tissue.[20] In an observational study of 805 stroke patients, no effect or harm could be attributed to mannitol.[21] Other observational studies have shown that mannitol causes a reduction in ICP over 4 hours, but they do not comment on long-term outcomes.[22] A Cochrane review in 2007 identified only three small RCTs with 226 participants comparing mannitol with placebo or open control.[23] They concluded that there is not enough evidence to support the routine use of mannitol in acute strokes.

Hypertonic Saline

Hypertonic saline has been used as an alternative to mannitol to reduce cerebral oedema. It is thought to be more favourable as it is completely excluded from the BBB and expands the intravascular volume, which increases the cerebral perfusion pressure (CPP).[24] There are fears that unrestricted use may lead to severe hypernatraemia, but this has rarely been seen in clinical practice.[24] Only small case series evaluating the use of hypertonic saline in acute strokes exist. One included eight patients and showed that it led to a reduction of elevated ICP over 4 hours in 22 episodes.[25] Another case series evaluated nine patients and showed that hypertonic saline decreased ICP more rapidly than mannitol but was not as effective at increasing CPP.[22] There is no clinical trial that addresses the effect of hypertonic saline on functional outcomes.

Glycerol

Glycerol is a sugar that has also been used as an osmotic agent in large MCA infarcts. It has been shown to increase CBF and can be used as an alternative source of energy in the ischaemic brain.[26] Due to this metabolism, there is thought to be less risk of glycerol causing a rebound intracranial hypertension once it crosses the BBB.[27] Zuliani et al.[28] published a cohort study of 442 patients over 65 years of age with severe ischaemic strokes and showed there was no reduction in short-term mortality risk when they received intravenous (IV) glycerol. In 2004, a Cochrane review identified 11 randomised trials reviewing the use of IV glycerol in acute strokes.[29] They concluded that there was a lack of evidence of any improvement in long-term survival and that they would not support its routine use.

Corticosteroids

Theoretically, steroids have been shown to have a role in decreasing cytotoxic and vasogenic oedema.[30] However, there are multiple well-known adverse effects including hyperglycaemia and increased risk of infections.[27] One cohort study found concurrent treatment with steroids plus mannitol or glycerol worsened the short-term mortality risk from acute strokes in older patients.[28] A Cochrane review from 2002 identified seven randomised trials comparing corticosteroids with placebo or control in ischaemic strokes.[31] Treatment did not improve functional outcomes and they did not recommend its routine use.

Glyburide

Glyburide, a sulphonylurea used in diabetes management, is a new IV anti-oedema therapy that has undergone case—control trials.[32] It is

showing potential to improve clinical outcomes in malignant infarcts and further research is awaited.

Body Positioning

Moderate head elevation at 15-30° is routine practice in the management of elevated ICP due to the positive results of studies performed in patients with traumatic brain injuries.[33] Schwarz et al.[34] prospectively evaluated 43 ICP monitoring sessions in 18 patients with MCA infarcts without an ICP crisis. They found that CPP was maximal in the horizontal position despite the ICP being highest at this point. A systematic review and meta-analysis of observational studies published in 2014 included four studies and 57 patients.[35] The authors concluded that cerebral blood mean flow velocity was significantly increased on the side affected when in a horizontal or 15° position compared with 30°. This is currently undergoing randomised evaluation as to its effect on clinical outcomes (the HeadPoST study).

Hypothermia

Hypothermia is thought to have a neuroprotective effect by reducing cerebral metabolic rate, stabilising the BBB, reducing free radical formation, and decreasing brain oedema.[36] There are concerns regarding rebound intracranial hypertension during the re-warming period leading to cerebral herniation and death.[37] The evidence supporting its use in malignant MCA infarcts is restricted to observational studies at temperatures <33°C.[37,38] These studies have also shown high numbers of pulmonary infections and clinically relevant side-effects such as shivering. The number of patients involved and the quality of the trials available means that there is insufficient evidence to recommend its use. A randomised trial is awaited to assess the optimum timing, depth, incidence of complications, and method of cooling for therapeutic hypothermia in acute ischaemic strokes.[39]

SURGICAL MANAGEMENT

Prior to 2002 there were no RCTs comparing the surgical and medical management of malignant MCA infarcts. A Cochrane review published over this period identified only observational studies, case series, and single case reports.[40] The authors felt there was not enough significant evidence to support the use of decompressive surgery and further trials needed to be conducted. In 2007, Vahedi et al.[16] published the results of the first of three multicentre RCTs involving patients with malignant MCA infarcts (DECIMAL trial, Table 1). They compared functional outcomes with and without decompressive surgery using the modified Rankin Scale (mRS). Patients recruited were 18-55 years of age and with an infarct volume of >145 cm^3 on diffusion-weighted MRI. Surgery had to be carried out no later than 30 hours after treatment onset (range was 7-43 hours) and all patients received standard medical therapy according to published guidelines. The trial was prematurely stopped after the enrolment of 38 patients because the interim data showed a considerable difference in mortality between the two groups. The proportion of patients with an mRS score ≤3 at 1-year follow-up was 50% in the surgery group compared with 22.2% in the group receiving medical management alone (p=0.1). In a subgroup analysis, younger patients had a more favourable outcome. There was a 52.8% reduction of death in the surgical group (p<0.0001).

Another multicentre RCT included patients aged 18-60 years with malignant MCA infarcts (DESTINY trial, Table 1).[14] The infarcts were confirmed as more than two-thirds of the MCA territory on CT and with an NIHSS score >20 for lesions on the dominant hemisphere and >18 for lesions on the non-dominant hemisphere. The study randomised patients to either surgical and conservative treatment or conservative management alone. Surgery was conducted within the first 36 hours after symptom onset. The trial was stopped after 32 patients were recruited due to a statistically significant reduction in mortality in the surgical group (p=0.02). There was an improvement in the number of patients with an mRS score ≤3 after 12 months in the surgical arm but this was not statistically significant (p=0.23).

The third significant multicentre RCT in this area was published in 2009 by Hofmeijer et al. (HAMLET trial, Table 1).[15] Patients were aged 18-60 years and within 4 days of symptom onset from a large MCA infarct. This was confirmed as more than two-thirds of the MCA territory on CT and an NIHSS score ≥16 for right-sided lesions and ≥21 for left-sided lesions. They received either medical management alone, given at the discretion of the treating physician, or medical management and surgical treatment. The trial was ended after 64 patients were recruited because it was unlikely to show a statistically significant result in the primary outcome (mRS score). It did, however, show a reduction in case fatality with the surgical intervention.

Table 1: Summary of the three pooled randomised controlled trials comparing conservative management with medical management in patients with malignant middle cerebral artery infarcts.

Trial	Age range, years	Number of patients	Imaging criteria	Eligibility	Primary outcome	Secondary outcome
DECIMAL	18-55	38	CT: >50% MCA territory MRI DWI: >145 cm^3	Symptom onset <30 h	mRS score ≤3 at 6 months: p=0.18	Mortality at 1 year: p<0.0001
DESTINY	18-60	32	CT: ≥66% MCA territory	Symptom onset <36 h	mRS score ≤3 at 6 months: p=0.23	Mortality at 1 year: p=0.03
HAMLET	18-60	64	CT: ≥66% MCA territory	Symptom onset <96 h	mRS score ≤3 at 6 months: p=0.13	Mortality at 1 year: p=0.002

CT: computed tomography; MRI: magnetic resonance imaging; MCA: middle cerebral artery; DWI: diffusion-weighted imaging; mRS: modified Rankin Scale.

To obtain sufficient data to reliably estimate the effect of surgical decompression, the results of these three trials were pooled.[41] The main difference between the studies was the time allowed from the onset of symptoms to surgery, and so the pooled analysis adopted a maximum time window of 48 hours. This resulted in a total of 93 patients, with 51 randomised to surgical treatment and 42 to conservative management. At 12 months, more patients in the surgical group had an mRS score ≤4 (absolute risk reduction [ARR]: 51%, number needed to treat [NNT]: 2), an mRS score ≤3 (ARR: 23%, NNT: 4), and survived (ARR: 50%, NNT: 2). The probability of survival was shown to increase from 28-80%. The authors concluded that, in patients aged <60 years with malignant MCA infarcts, decompressive surgery undertaken within the first 48 hours reduces mortality and increases the number of patients with a favourable functional outcome.

In 2012, a Cochrane review aimed to examine the effects of decompressive surgery on survival and long-term disability in patients with massive acute ischaemic strokes.[42] They found only the three mentioned RCTs including 134 patients aged <60 years. Their analysis revealed that surgical decompression resulted in a reduced risk of death or severe disability (mRS score >4) at 12 months but there was no difference when using an mRS score >3. They felt that survival may be at the expense of substantial disability and that surgery should only be offered when it can be assumed that it is in the best interests of the patient. In addition, all of the trials were stopped early and an overestimation of the size of the effect could not be excluded. A 2014 meta-analysis with a total of 14 studies and 747 patients also concluded that early surgery (<48 hours) significantly decreased mortality.[43] This included a larger number of studies than previously analysed and found that there was a significant improvement in functional outcomes with mRS scores ≤3, which contradicted previous publications.

Older Patients

The results from the studies described above leave a large degree of uncertainty regarding how to manage patients >60 years of age and with a malignant MCA infarct. In 2009, Arac et al.[44] published a review of the available evidence involving outcomes in older patients receiving a decompressive craniectomy after a large MCA infarct. They included 19 studies totalling 273 patients, of which 73 were >60 years of age. The mortality rate was significantly worse for the older patients (51.2% versus 20.8%, p<0.0001). Furthermore, the older patients who survived had significantly higher rates of poor outcomes using an mRS score >3 and Barthel Index of <60. They concluded that age should be an important factor in patient selection for surgery. However, the data they obtained were largely from case series and retrospective studies, therefore requiring cautious interpretation of the results.

In 2014, an RCT enrolled 112 patients >60 years of age to receive either conservative or surgical management within 48 hours.[45] They found that hemicraniectomies resulted in a significantly greater proportion of patients surviving without a severe disability after 6 months (mRS score ≤4, p=0.004). However, there were no patients with an mRS score

of 0-2, with the majority having an mRS score of 4-5. They concluded that surgical management in older patients increases survival without a severe disability, but a majority of the patients will require assistance with most bodily needs.

An RCT recruiting patients up to 80 years of age was terminated after 47 patients were enrolled due to a significant reduction in poor outcomes (mRS score >4) in the surgical group.[46] They found a similar trend in a subgroup analysis of patients aged >60 years. However, such patients seemed to be at higher risk of developing a moderately severe disability (mRS score of 4). They felt that age should not be a contraindication to surgery and that the decision should be made on an individualised basis. In the 2014 meta-analysis described above, the authors investigated the association between age and functional outcome.[43] They found that surgery significantly reduces mortality in adults >60 years of age. However, the proportion of patients who had a poor functional outcome was significantly greater than the proportion in the younger patient group.

CONCLUSIONS AND THE FUTURE

Evidence supporting the medical management of patients with large MCA infarcts is clearly lacking. There are no convincing data regarding the use of mannitol, hypertonic saline, or glycerol in improving long-term outcomes, and there is the possibility that steroids may worsen mortality. The monitoring of ICP can guide management but has not been shown to have a positive impact on patient outcomes. Horizontal or 15° body positioning may increase CBF, but we are unsure if this has a beneficial effect regarding morbidity and await the results of further trials. The use of therapeutic hypothermia is not recommended and high-quality evidence is still needed, but there are promising results from observational studies.

In contrast, there is a growing library of evidence to support the surgical management of these patients. A pooling of three RCTs and a recent meta-analysis have shown both a significant reduction in mortality and improved functional outcomes (mRS score ≤4) when patients <60 years of age are treated with a decompressive craniectomy within 48 hours of symptom onset.[41,43] An mRS score of 4 means that a patient is unable to attend to their own needs without assistance, or walk unaided. The 2012 Cochrane review highlighted concerns regarding increased survival of these patients at the expense of disability.[42]

There is still uncertainty regarding how to manage older patients, and although surgery does reduce mortality in those aged 60 years and over it appears to be a predictor of a worse neurological outcome. Larger RCTs are needed to reach a consensus on management in this group. However, the future still holds many questions that need answering. There are considerable gaps in our knowledge regarding medical management strategies, including temperature modulation and head positioning. There may be the possibility of new drugs, such as glyburide, to reduce brain oedema, which will make surgical interventions redundant. Decompressive craniectomies appear to be the way forward but more clarity is needed regarding the timing, long-term outcomes in survivors, and potential age limits, so that we can answer whether we are saving the lives of patients who are then left with a significant disability, high caregiver burden, and a poor quality of life.

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