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Critical Care Neurology

Managing Malignant Cerebral Infarction

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Opinion statement

Managing patients with malignant cerebral infarction remains one of the foremost challenges in medicine. These patients are at high risk for progressive neurologic deterioration and death due to malignant cerebral edema, and they are best cared for in the intensive care unit of a comprehensive stroke center. Careful initial assessment of neurologic function and of findings on MRI, coupled with frequent reassessment of clinical and radiologic findings using CT or MRI are mandatory to promote the prompt initiation of treatments that will ensure the best outcome in these patients. Significant deterioration in either neurologic function or radiologic findings or both demand timely treatment using the best medical management, which may include osmotherapy (mannitol or hypertonic saline), endotracheal intubation, and mechanical ventilation. Under appropriate circumstances, decompressive craniectomy may be warranted to improve outcome or to prevent death.

Introduction

The term "malignant" was first used by Hacke et al. [1] to characterize the complete infarction of the middle cerebral artery (MCA) territory accompanied by space-occupying mass effect that develops during the first 5 days after presentation and that is associated with about 80% mortality. Malignant evolution of an infarct is consistently related to the volume of ischemic brain. Malignant cerebral infarction (MCI) usually denotes a large MCA infarction, with or without involvement of the ipsilateral anterior and posterior cerebral artery territories, that presents with acute brain swelling in the first 48 h after stroke, resulting in elevated intracranial pressure (ICP) or brain herniation. Ischemia that affects more than two thirds of the MCA territory predicts the development of MCI with a sensitivity of 91% and specificity of 94% [2, Class II]. Patients with more than 50% MCA involvement have a high risk of malignant evolution.

Space-occupying brain edema is the most important cause of death and disability in MCI. In addition to the extensive amount of necrotic brain tissue involved, other causes of poor neurologic outcome include severe postischemic edema that causes cerebral herniation, progressive brainstem dysfunction, and high ICP.

There is consensus regarding the poor outcome of these patients and the need to refer them to a comprehensive stroke center [3, 4, Class I], but criteria for admission to the intensive care unit (ICU) and recommendations for optimal monitoring and medical treatment vary widely. Most available evidence is based on expert opinion and consensus conferences (Class IV evidence). This article reviews treatment options for managing malignant cerebral edema after MCI and provides a practical algorithm that may be helpful in arriving at a decision about proceeding to decompressive craniectomy (DC).

Predicting malignant evolution

Early CT signs of ischemia may be quite subtle, and the detection of infarction in an unenhanced CT scan has wide interobserver and intraobserver variability. MRI or perfusion CT is superior for defining infarction size and predicting malignant evolution. Diffusion and perfusion MRI aid the prediction of malignant evolution as early as 6 h after symptom onset, with high specificity and a high positive and negative predictive value [5]. A volume of affected brain in diffusion MRI above 82 mL was the most powerful predictor of malignant evolution, with a high specificity (0.98) but rather low sensitivity (0.52) [5, Class II]. In this study, the volume of the affected brain observed in perfusion MRI was not an independent predictor of malignant evolution. A threshold of 145 mL or above has the maximum reported sensitivity (100%) and specificity (94%) [6, 7], but protocols for malignant infarction should be implemented at volumes of 72 to 82 mL (or perhaps even somewhat less) in the diffusion MRI, because these volumes can be associated with poor outcome [5, 8, Class II]. To compensate for the low specificity of the 72–82 mL threshold, a noncontrast CT scan obtained about 6 h after symptom onset may aid in identifying patients with smaller initial lesions on diffusion-weighted imaging (DWI) who are at risk for malignant evolution [5].

Treatment

Medical therapy

Osmotherapy: management strategy

- Both mannitol and hypertonic saline are first-line medical treatment options for cerebral edema in MCI, but surprisingly few clinical trials have been performed to study their impact on clinical outcome.
- Prophylactic osmotherapy should generally be avoided. Preclinical data suggest that prophylactic osmotherapy may increase infarct volume or midline shift [9].

- Patients exhibiting signs and symptoms of mass effect, such as diminished level of arousal or nausea and vomiting, are appropriate candidates for osmotherapy. In such cases, the use of osmotherapy should prompt a re-evaluation of infarct volume by neuroimaging, either CT or MRI. Trials in which DC demonstrated benefit often included patients with very large infarct volumes, such as DWI volume of 145 cm^3 or greater [7]. In patients with neurologic deterioration but smaller infarct volumes, it is possible that osmotherapy may make surgery unnecessary. In such instances, the temporal pace of both infarct growth and neurologic deterioration should be considered. In patients who are being considered for DC (see below), osmotherapy should not delay or take the place of DC; rather, it should be administered concurrently with preparations for surgery.
- **Mannitol** administration in the setting of symptomatic brain edema should be weight-based, 1 g/kg intravenously, repeated every 4 to 6 h [10]. Because mannitol acts as a diuretic, major complications include hypovolemia and hypotension. Strict fluid goals and volume replacement are essential. Impaired mannitol clearance may manifest as nephrotoxicity. Common practice includes repeating measurements of serum osmolarity and withholding repeat doses of mannitol when osmolarity exceeds 320 mOsm. Monitoring the osmole gap may be a more sensitive method for discerning mannitol clearance [11]. The gap of interest is the difference between the measured osmolarity and the calculated osmolarity, computed as follows:

$$\text{Calculated osmolarity} = 1.86(\text{Na} + \text{K}) + \text{glucose}/18 + \text{BUN}/2.8$$

- **Hypertonic saline** avoids the diuretic effect of mannitol and is also effective at reducing brain water. Various concentrations are used clinically, up to 30-mL boluses of 23.4% saline. Rapid increases in sodium in this context do not appear to cause other neurologic complications that one may fear with the large increases in sodium observed with rapid correction of hyponatremia [12]. Sodium levels up to 160 mmol/L may be acceptable, beyond which persistent hypernatremia may lead to worsening delirium, seizures, and overall poor outcome.
- Hypertonic saline has a higher reflection coefficient than mannitol, and this difference may allow hypertonic saline to extract water from both the injured and uninjured brain [13]. There are no definitive data to promote the use of one osmotic agent over another.

Other medical treatments

- **Corticosteroids** have been evaluated in several types of cerebral injury, including cerebral infarction. A large meta-analysis found no benefit to the use of corticosteroids in ischemic stroke (or intracere-

bral hemorrhage) [14], and their use is not recommended.

- **Barbiturates**, including pentobarbital, have been evaluated in ischemic stroke. They are effective in reducing ICP by lowering the cerebral metabolic rate, and they may have neuroprotective qualities as free radical scavengers [15]. Barbiturate use is often complicated by hypotension and sedation, however, as well as an increased risk of infection. The ability to follow the neurologic examination is lost. There have been no randomized studies of barbiturates in cerebral infarction, but their use is not recommended.
- **Hyperventilation** reduces ICP by reducing cerebral blood volume. Carbon dioxide is a potent cerebral vasodilator, so vasoconstriction is induced by decreasing pCO_2. The effect is almost immediate, reducing ICP typically within minutes. However, the effect is short-lived, and cerebral infarction volume may be worsened [16, 17]. There is also a risk of rebound vasodilatation and worsening ICP when the pCO_2 returns to normal [18]. Hyperventilation should be used as a temporizing measure while awaiting more definitive treatment for an acutely herniating patient.
- **Temperature modulation** is an important consideration in patients with MCI. After controlling for severity of illness, diagnosis, age, and complications, increased body temperature has been found to be strongly associated with an increased length of ICU and hospital stay, as well as higher mortality and worse overall outcome [19]. Increased excitotoxicity, cell depolarization, enzymatic dysfunction, and blood-brain barrier breakdown can all lead to increased cerebral edema and larger infarct volumes [20, 21]. Maintaining normothermia is a reasonable objective in patients with MCI.
- Early clinical-phase studies have demonstrated promise for induced **hypothermia**, but large-scale randomized trials are yet to be completed [22]. The optimal duration of induced hypothermia, and the incidence of potential complications such as infection, arrhythmias, and coagulopathy have not been determined. Better rewarming strategies must be developed, as prior studies have shown that rebound edema and fatal herniation are potential complications of this therapy [23]. At present, induced hypothermia remains investigational.

Monitoring intracranial pressure

General considerations

- ICP monitoring is not a standard of care in MCI. It is used routinely only in traumatic brain injury (TBI), in which robust evidence favors monitoring of all patients with a severe TBI and abnormal CT scan [24, Class II]. In MCI, there is no supporting evidence that ICP monitoring improves outcome or facilitates medical treatment. Despite this limitation, most treatments for MCI are aimed at direct or indirect signs of raised ICP.

- Some studies have suggested that patients with MCI can show neurologic worsening or even die despite normal ICP values, casting doubt on whether ICP monitoring alone is adequate for decision-making in the care of patients with MCI [25, 26•, 27].
- A prospective study in which ICP was monitored in MCI showed that ICP was below 25 mm Hg at the time of inserting the probe in 74% of patients and above 25 mm Hg in 26%. All patients with an initial ICP above 35 mm Hg died [27]. The main limitation of this study was the use of extradural devices that led to artifactually high ICP readings; these are not recommended for managing acutely brain-injured patients [28]. In a recent prospective study of patients with MCI, in which an intraparenchymal probe was inserted in the infarcted hemisphere, ICP values were 20 mm Hg or less in 69% of the patients, even though all of these patients showed a midline shift of 5 mm or more, signs of uncal herniation, or cistern effacement on CT scans [26•].

Methods of monitoring

- The Brain Trauma Foundation (BTF) guidelines [28] are the only published guidelines that address this issue. These guidelines recommend the use of a ventricular catheter connected to an external strain gauge as the most "accurate, low-cost, and reliable method of monitoring ICP" [28, Class I]. ICP monitoring through fiberoptic or microstrain gauge devices placed at the tip of ventricular catheters "provide similar benefits, but at a higher cost" [28]. Intraparenchymal ICP devices are very reliable and have a very low risk of drift. Extradural, subdural, and subarachnoid probes are not recommended because they lack reliability. ICP measurements obtained in the epidural space systematically overestimate the true ICP value and should not be used to make treatment decisions in MCI [29, Class I].

Clinical scenarios and probe insertion

- Contraindications for ICP monitoring are related to any type of coagulopathy that can increase the risk of developing hematomas, the most important cause of morbidity in ICP monitoring. In patients being treated with intravenous (IV) recombinant tissue plasminogen activator (rtPA), blood coagulation screening must be performed before inserting the ICP monitor.
- There are two clinical scenarios for monitoring ICP in MCI patients: 1) patients admitted to the ICU in whom medical management is the first line of treatment; 2) patients who are awaiting DC or have undergone DC. In the first group, ICP monitoring may be useful in guiding medical treatments aimed at reducing ICP (mannitol, hypertonic saline, hyperventilation, etc.). ICP thresholds to initiate therapies or to indicate DC in patients with high ICP have not been

established, and as noted, ICP alone is not a good predictor of clinical progression, as some patients may suffer neurologic deterioration and death despite normal ICP [25, 26•]. As a result, ICP monitoring is uncommon in practice.

- ICP monitoring is generally even less useful in the second group of patients. However, some patients may have elevated ICP for some days after DC, and hemorrhagic conversion can occur after DC. ICP monitoring may be helpful in managing these problems.
- When using a ventriculostomy to monitor ICP, withdrawing CSF to reduce ICP is controversial, as CSF withdrawal can increase brain shift [25, Class IV]. If intraparenchymal probes are used, the ICP sensor must be placed in the ischemic hemisphere to avoid underestimating ICP. As shown in different studies in TBI patients with mass lesions or a midline shift, supratentorial interhemispheric ICP gradients can exceed 15 mm Hg [30]. These findings have also been confirmed in ischemic stroke [27].
- If ICP monitoring is used, it should be used in conjunction with sequential CT scans. We recommend performing a CT scan every 24 h in patients with normal ICP. With any elevation of ICP, when other causes have been ruled out (fever, neck positioning, inappropriate ventilator settings, etc.), a CT scan should be performed immediately to rule out any increase in mass effect or hemorrhagic transformation of the ischemic tissue.

Surgery: Decompressive craniectomy

General considerations

- No guidelines from evidence-based medicine have been established for DC in the context of MCI. The recommendations contained in the 2007 American Heart Association guidelines for DC in stroke [3] were written before the publication of the results of three relevant European multicenter randomized clinical trials (DESTINY, DECIMAL, and HAMLET) [31]. In 2007, the results of a pooled analysis of the three randomized clinical trials with similar inclusion criteria and primary outcome measures, including favorable and unfavorable outcomes as determined by the modified Rankin Scale (mRS), showed a significant reduction in 1-year mortality. Mortality was 29% in patients who underwent DC, compared with 78% in the control group. The number of patients needed to treat to avoid one death in this study was only two. In patients 60 years of age or younger, DC within 48 h of malignant stroke significantly reduced mortality, compared with best medical treatment. The distribution of the mRS at 1 year was also significantly different: mRS of 4 or less was achieved by 75% of the patients in the DC group, versus only 24% in the nonoperative group [31]. Therefore, DC significantly reduces mortality in MCI (Class I). The European Stroke Organisation (ESO) guidelines for the management of ischemic stroke (published in 2008) recommend DC within 48 h after symptom onset in patients up to 60 years of age with evolving MCI [4, Class I].

- Surgical decompression improves survival but increases the proportion of patients with significant disability. One continuing controversy involves the identification of an mRS or other outcome measure that should be considered as a "favorable outcome." The mRS is a crude scale for measuring outcome and is strongly biased toward motor performance. Subanalysis of large cohorts with more robust measures of quality of life (QoL) that include patients' values and preferences should be included as this debate continues [32]. Regarding QoL, the personal account of Larack [33•] merits careful consideration, as it remarks on the complex issues of QoL and the importance of rehabilitation in the final outcome after MCI.
- Current clinical practice with regard to DC is highly variable. Some centers may wait until herniation occurs before proceeding to DC, whereas others may proceed to DC within 24 h, based on infarct size alone, before appreciable swelling has occurred. The first approach likely leads to excessively poor outcomes and the second approach likely leads to unnecessary surgery.
- The management strategy presented below, which is based on available published data [34, 35, Class I] as well as general neurosurgical opinion (Class IV), was developed as a practical approach to the problem and attempts to incorporate clinical as well as radiologic information into the decision-making process. It is acknowledged that several specific details (namely, the specific time designated for the "reference CT" and "reference exam," and the specific values for midline shift and Glasgow Coma Scale [GCS]), which serve to trigger certain events, may need to be revised as experience is gained.

Variables to consider

- **Age.** Under the appropriate circumstances, patients age 60 years or younger should be strongly considered for DC, as outcome may be improved [34, 35, 36]. Patients older than 60 years also may be considered, as mortality may be improved, but outcomes are generally less favorable [34, 35, 37].
- **Infarct size.** Trials in which DC demonstrated benefit included patients with very large infarct volumes. A threshold of 145 mL or above has the maximum reported sensitivity (100%) and specificity (94%) [6, 7], but protocols for malignant infarction should be implemented at volumes of 72–82 mL (or perhaps even somewhat less) in the diffusion MRI, because these volumes can be associated with poor outcome [5, 8, Class II].
- **Hemisphere.** Whether the involved hemisphere is dominant or nondominant is sometimes considered to be an important factor in decision-making regarding DC. However, anecdotal evidence suggests that at least some patients with dominant-hemisphere involvement are pleased to have had their lives saved [33•, 38]. The side of the infarct should probably not enter into decision-making [39].

- **Medical management.** There is no evidence to support the practice of prophylactic DC. Generally, treatment should progress to DC after "the best medical management" has been administered for a long enough period to determine whether medical management alone, without DC, will be sufficient. Patients may have variable brain swelling or adequate compliance, so that edema may be of limited clinical consequence; unnecessary surgery in such patients should be avoided because DC and subsequent cranioplasty are not without risk [40].
- **Time zero.** For the purposes of this algorithm, "time zero" is the "time last known at baseline" (TLN@B) with regard to neurologic status.
- **Timing of DC.** No controlled trial adequately addresses the timing of DC in humans.
  - Life-threatening edema in humans is difficult to predict on the first day after stroke [41]. Experience suggests that humans seldom "get into trouble" during the first 24 h.
  - Preclinical data in rats suggest that decompression within 24 h leads to more favorable outcome, but life-threatening brain swelling in rats occurs much more quickly than in humans (12–24 h vs 2–3 days) [1, 42, 43].
  - Review of uncontrolled trials (see Schirmer et al. [38]) suggests better outcomes if DC is performed within 24 h, but these reports almost certainly include patients who may not have needed surgery.
  - DC within 48 h of stroke likely improves outcome; the benefit of DC after 48 h is uncertain, although mortality may be reduced [35].
  - Thus, absent controlled trials, the interval between 24 and 48 h seems appropriate for decision-making. The algorithm below incorporates the concept that in patients with ischemia alone (no space-occupying hemorrhage), an initial decision regarding DC can be deferred until about 36 h after TLK@B.
  - At about 36 h (defined as 36±4 h) after TLN@B, a "reference CT" and a "reference exam" should be obtained, which are used for subsequent decision-making regarding DC.

Strategy for initial management

- The best medical management to minimize elevations in ICP should be ongoing, including as appropriate:
- **For all patients:** 30 degree head-of-bed elevation and IV fluids to maintain euvolemia.
- **Individualized management,** at the discretion of the treating physician:
- *Osmotherapy*, to treat symptomatic edema with mass effect. Avoid prophylactic osmotherapy. Osmotherapy should be used preferentially to hyperventilation and while the patient is eucarbic.

- *If the patient is unconscious*, intubation and mechanical ventilation, with the goal of maintaining eucarbia (pCO_2, 35–40 mm Hg). Use hyperventilation (pCO_2, 25–35 mm Hg) only in the setting of transtentorial herniation; it should be limited to 30 min or less "on the way to the OR."
- *If the patient is intubated*, easily reversible mild sedation.

- Potential causes of neurologic deterioration other than elevated ICP should be investigated and eliminated or treated, including:
  - The use of sedatives or other medications that adversely impact mental status. (Barbiturate coma is not recommended.)
  - Metabolic disturbances.
  - Significant temperature elevation.
  - Inadequately treated infection.
  - Hydrocephalus.
- At about 36 h, a "reference CT" and a "reference exam" are obtained.
  - The reference CT is obtained regardless of the neurologic exam findings; subsequent CT scans are obtained every 24 h for surveillance or at the discretion of the physician, based on neurologic deterioration.
  - The reference exam, performed in conjunction with the reference CT, includes the Glasgow Coma Scale (GCS), which is repeated every hour.
- DC should generally be avoided until about 36 h after TLK@B, except under extraordinary circumstances.
  - Brain herniation at any time may prompt DC [44].
  - Significant neurologic deterioration at an earlier time may prompt a new CT scan, which may lead to DC.

Management strategy

- Any one of items 1 through 3 below is sufficient to proceed to DC; item 4 by itself may be deemed sufficient at the discretion of the physician.
  1. At any time, clinical herniation syndrome [44, 45].
  2. At about 36 h, reference GCS ≤8 and reference CT with midline shift of ≥8 mm [39, 43, 46, 47, 48].
  3. After about 36 h, neurologic deterioration when compared with the reference exam: two consecutive hourly exams after the reference exam that show worsening, including:
     - GCS drop of 1 point or more, including (but not limited to) no longer following verbal or cued commands, or no longer localizing to painful stimuli.
     - New pupillary abnormality, such as anisocoria.
     - Noticeably less brisk response to pain, preferably documented by two examiners.

4. After about 36 h, radiologic deterioration, shown by a CT scan performed after the reference CT (obtained either because of neurologic deterioration or simply for surveillance) showing 1) progression in midline shift of ≥2 mm compared with the reference CT, or 2) development of hemorrhagic transformation, or a significant increase in hemorrhagic transformation compared with any previous CT scan.

- There is no time limit for how late a decision to proceed to DC can be made. Neurologic or CT deterioration at any time beyond about 36 h after TLK@B may prompt DC.
- ICP monitoring is not mandated, for the reasons discussed above, but if ICP monitoring is used, ICP elevations of 20 mm Hg or more should weigh heavily toward proceeding to DC.
- Patients who meet the criteria for DC may decline to proceed to DC (at the discretion of the patient, the family or legally authorized representative, or the treating physicians).

Contraindications

- **Absolute:** 1) IV rtPA (Alteplase) administration less than 12 h before proposed start of surgery; 2) Premorbid bleeding disorder that is not readily correctable.
- **Relative:** Development of a PCA infarct signifying transtentorial herniation (indicating a poor prognosis).

Preparations and precautions

- Every effort should be made to start surgery within 3 h of the time when the decision for DC is made (unless IV rtPA has been used, in which case 12 h should elapse after its use).
- If the INR is 1.3 or higher, fresh frozen plasma or prothrombin complex concentrate, in addition to vitamin K, should be given before the start of surgery.
- If antiplatelet agents (clopidogrel, aspirin) have been administered within 7 days, platelets should be given at the start of surgery.
- If the hematocrit is less than 30%, packed red blood cells should be slowly transfused (25–50 mL/h) prior to the start of surgery.

Procedure

- A large, low, frontotemporoparietal craniectomy is required.
- The scalp flap is made using a large "question-mark" incision from the widow's peak, proceeding posteriorly toward the vertex, then curving inferiorly above the pinna and down to the zygoma.
- A large frontotemporoparietal bone flap with a diameter of 14 cm or more is removed [49]. The bone flap is positioned to avoid violating the frontal sinus, unless the frontal sinus is huge. The medial limit of the craniectomy is about 2 cm from the midline, and the posterior limit is

about 5 cm posterior to the external auditory canal. The temporal squama is resected down to the floor of the middle cranial fossa.

- A large dural opening with step-wise expansive duraplasty is preferred:
  - The cruciate opening described by Yao et al. [50] may be used but may limit decompression of the temporal lobe.
  - Alternatively, opening the dura parallel to the bony exposure of the middle fossa may give wider decompression of the temporal lobe.
- A subgaleal drain, placed to bulb suction, is used to prevent an accumulation of blood in the subgaleal space that could compromise the decompression.
- A two-layer scalp closure is preferred.
- Temporal lobectomy usually is not performed, and infarcted tissue usually is not resected. It is left to the discretion of the surgeon whether to resect necrotic tissue with hemorrhagic conversion.
- The best medical management to minimize elevations in ICP, as described above, should be continued.

Disclosure

No potential conflicts of interest relevant to this article were reported.

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- •• Of major importance

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A personal account of an academic anesthesiologist who survived the aggressive treatment of a left MCI. In this paper, the author reflects on the concept of QoL and of the importance of intensive rehabilitation after massive stroke. This paper supports reconsidering the strong bias doctors generally show regarding life and death decisions based on the presumed QoL of survivors.

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