A Concise Guideline for the Management of Large Hemispheric Infarction in Taiwan: 2010 Update: A Guideline from the Taiwan Stroke Society

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Abstract-

In this report, we present comprehensive recommendations for the diagnosis and treatment of large hemispheric infarction (LHI). A systematic literature search was conducted until June 30, 2010. The American Heart Association Stroke Council's Levels of Evidence grading algorithm was used to grade each recommendation (Table 1). The guideline was revised after several official meetings with local experts, and was reviewed by 3 expert reviewers.

Early diagnosis of malignant large hemispheric infarction (MLHI) is critical. Studies have shown that using computed tomography (CT) or transcranial sonography to track midline shifting of the cerebrum and applying diffusion-weighted magnetic resonance imaging might contribute to the early recognition of MLHI.

Glycerol and mannitol should be administered only when a patient shows evidence of brain edema or mass effect. The effect of barbiturate coma on improving prognosis is inconclusive and requires close monitoring of the patient. Meanwhile, using steroids on patients with stroke is not recommended. The effect of hyperventilation on reducing intracranial pressure is rapid but short-lived, and is used only in emergency situations. The target levels of PaCO2 are 30-35 mmHg. Moderate hypothermia (32-34˚C) may be effective in controlling intracranial hypertension, but should be used cautiously along with rigorous monitoring.

Timely decompressive craniectomy can probably offer patients a better chance of survival and quality of life. Usually, surgery for MLHI is indicated in patients with clinical deterioration associated with a significant mass effect, as observed on neuroimaging. However, with a reliable indicator of MLHI, early decompressive craniectomy before clinical deterioration may further reduce mortality and lead to a better functional outcome.

Key Words: guideline, large hemispheric infarction, malignant large hemispheric infarction, decompressive craniectomy

Acta Neurol Taiwan 2010;19:296-302

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Received August 30, 2010. Revised September 28, 2010. Accepted November 20, 2010.

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Table 1. *Definition of Classes and Levels of Evidence Used in the American Heart Association (AHA) Stroke Council Recommendations*

Class I:	Conditions for which there are evidence and/or general agreement that the procedure or treatment is useful and effective
Class II:	Conditions for which there is conflicting evidence and/or a difference of opinion on the usefulness/efficacy of a procedure or treatment
Class IIa:	The weight of evidence or opinion is in favor of the procedure or treatment
Class IIb:	Usefulness/efficacy is less well established by evidence or opinion
Class III:	Conditions for which there is evidence and/or general agreement that the procedure or treatment is not useful/effective, and in some cases may be harmful
Therapeutic recommendation	
Level of Evidence A:	Data derived from multiple randomized clinical trials
Level of Evidence B:	Data derived from a single randomized trial or nonrandomized studies
Level of Evidence C:	Consensual opinion of experts
Diagnostic recommendation	
Level of Evidence A:	Data derived from multiple prospective cohort studies employing a reference standard applied by a masked evaluator
Level of Evidence B:	Data derived from a single grade A study or one or more case-control studies or studies employing a reference standard applied by an unmasked evaluator
Level of Evidence C:	Consensual opinion of experts

INTRODUCTION

Although large hemispheric infarction (LHI) accounts for only 3-15% of all ischemic strokes, it is the main cause of high mortality and severe disability occurring after ischemic strokes. LHI generally refers to an infarction that affects more than two-thirds of the middle cerebral artery (MCA) distribution area[1]. Malignant large hemispheric infarction (MLHI) refers to large infarctions with subsequent clinical deterioration that require further treatment in the intensive care unit[2]. While literature review reveals a wide range of LHI mortality rate (from 17-80%), MLHI accounts for a very high mortality rate: up to 80%[1-4]. The mortality and prognosis of LHI patients are largely related to the extent of infarction.

Diagnosis and monitoring

Clinically, patients with LHI may show a wide range of neurological deficits simultaneously such as hemiplegia, hemianesthesia, hemianopia, speech disturbance, and gaze deviation. Patients may also present with disturbed consciousness at the onset of the disease. In the acute stage, patients with LHI may deteriorate because of brain swelling, extension of the infarct, hemorrhagic infarctions, seizures, or other medical complications. Brain swelling following LHI is most common and severe in the first week after the insult. This may result in decreased levels of consciousness, dilated pupils, and absent light reflexes, indicating transtentorial herniation.

Every LHI patient should be subjected to one or more non-contrast computed tomography (CT) examinations. In addition to the initial exclusion of cerebral hemorrhage or other brain diseases, CT scanning can ascertain the extent of infarction and monitor the subsequent brain swelling. Furthermore, it is also very helpful in predicting the prognosis and choosing treatment options. Magnetic resonance imaging (MRI), magnetic resonance angiography (MRA), computed tomography angiography (CTA), etc. may also be useful in the clinical diagnosis of LHI.

The early diagnosis of MLHI, (i.e., before clinical deterioration), is very important because aggressive treatment such as decompressive craniectomy can be performed as soon as possible for patients who would benefit from the surgery. Some studies have revealed that the use of diffusion-weighted MR imaging (DWI), positron emission tomography (PET), microdialysis, electroencephalogram (EEG), CT parameters, evoked potential (EP), etc. may facilitate the early diagnosis of MLHI prior to clinical deterioration. For instance, an abnormal volume greater than 145 ml in DWI within the first 14 h indicates a high possibility of MLHI (Class IIa,

Level of Evidence B). However, further large-scale studies are needed to obtain a more definite and conclusive result with respect to early diagnosis of MLHI[5-9].

Intensive monitoring of neurological status and vital signs such as blood pressure, heart rate, respiration, blood oxygen concentration, body temperature, level of consciousness, muscle strength, and pupil size must be performed for every LHI patient. Tracking midline shifting of the cerebrum using CT or transcranial sonography is helpful for the early prediction of severe cerebral edema and transtentorial herniation[10,11] (Class IIa, Level of Evidence B). On the other hand, the clinical practicability of continuous intracranial pressure (ICP) monitoring for patients suspected with high intracranial pressure is controversial; Thus, it cannot substitute for close clinical and radiological follow-ups[12,13] (Class IIb, Level of Evidence B).

Treatment of large hemispheric infarction

A. General treatment principle

Blood pressure

In the acute stage, hypertension is present in most LHI patients. If the systolic blood pressure is below 220 mmHg and the diastolic blood pressure is below 120 mmHg, it is not necessary to lower the blood pressure immediately by administering antihypertensive drugs[14]. Instead, first priority should be given to the stress response that follows an ischemic stroke, and measures should be taken to prevent urinary bladder distension, control pain, and treat intracranial hypertension. A drastic drop in blood pressure in the absence of careful monitoring may lead to insufficient cerebral perfusion and could further exacerbate cerebral ischemia. Hence, we recommend lowering blood pressure only after the stress response has been dealt with and the systolic and diastolic blood pressures remain above 220 and 120 mmHg respectively. (Class I, Level of Evidence A).

Blood sugar

Since elevated blood sugar levels increase the risk of hemorrhagic infarction, electrolyte imbalance, and other complications in acute strokes, the prognosis is compromised[15]. Therefore, when blood glucose levels are higher than 200 mg/dl, low doses of insulin should be administered repeatedly to maintain blood glucose level below 110 mg/dl[16-18] (Class I, Level of Evidence A). In accordance with the 2007 and 2008 literature, the American Stroke Association recommends controlling blood glucose level within the normal range in cases wherein the glucose levels are higher than 140 mg/dl. The European Stroke Organization recommends insulin treatment if the blood glucose level is more than 180 mg/dl[14,19]. On the other hand, low blood glucose level can also exacerbate and complicate the clinical condition of stroke patients. In such cases, 10-20% glucose can be administered orally or intravenously[20].

Fluid

Intravenous infusion should first be set up at the emergency room. In order to prevent elevated blood glucose level and exacerbated cerebral edema, hypotonic 5% dextrose solution should not be administered [20-22]. (Class IIa, Level of Evidence B). In such cases, we recommend the use of isotonic fluids such as normal saline. In patients with conscious disturbances or dysphagia, administration of nutrition and fluids can be accomplished through a nasogastric tube. Furthermore, regular monitor of electrolytes is clinically imperative.

B. Treatment of mass effect and cerebral edema

The three objectives for the treatment of mass effect and cerebral edema are as follows: (a) reducing intracranial pressure, (b) maintaining adequate cerebral perfusion, and (c) preventing secondary injury from transtentorial herniation. When mass effect is apparent, mild dehydration is necessary in the acute stages. Nevertheless, undue water restriction on the contrary could compromise cerebral perfusion and should therefore be avoided.

Head position

A patient's head should be kept elevated by 30˚ in the neutral plane in order to facilitate cerebral venous outflow. Nevertheless, care must be taken to preclude hypovolemia because elevation of the head in such a situation could lead to a drop in cerebral perfusion pressure.

Analgesia, sedation, and neuromuscular blockade

Pain, restlessness, and anxiety may lead to unstable blood pressure and are not conducive to the control of ICP. Therefore, over-stimulation should be avoided, and the pain and discomfort should be relieved immediately. In patients where endotracheal intubation is mandatory, intravenous sedation may be essential. Sedation should be titrated in a way such that pain is minimized but still allows the evaluation of the patient's clinical status. This can be accomplished with intravenous propofol, etomidate, midazolam, etc.[23]. If patients remain unstable after the administration of analgesics and sedatives, further neuromuscular blockades may be necessary. Excessive muscular activity may increase ICP because it leads to increased intrathoracic pressure, and is not conducive to cerebral venous outflow

Osmotic agents

Usually, glycerol and mannitol are used to treat increased ICP after stroke. However, they should only be administered when there is evidence of brain edema or mass effect, and should not be put to use as a routine. To date, there is no strong evidence from clinical trials supporting the benefits of the regular use of osmotic agents in improving the prognosis of ischemic stroke [24] (Class IIb, Level of Evidence B). On the other hand, when used to treat severe stroke, glycerol seems to improve the clinical condition and decrease mortality[25-27] (Class IIa, Level of Evidence B). Clinically, when the use of osmotic agents is indicated, mannitol (0.25-0.5 g/kg body weight) is administered every 3-6 hours through rapid intravenous injections. The maximum daily dose of mannitol is 2 g/kg of body weight. Glycerol is usually administered intravenously over one hour in a dose of 250 ml 4-6 times a day. During osmotic agent therapy, blood osmolarity should be monitored and maintained at approximately 300-320 mOsm/l.

Barbiturate coma

Large doses of barbiturate can also facilitate ICP control through the reduction in cerebral metabolism. However, its use is frequently associated with a significant risk of complications and warrants close monitoring of the patient[28]. Furthermore, previous clinical trials did not provide strong evidence to support the significant effect of barbiturates in improving the prognosis[28,29] (Class IIb, Level of Evidence B).

Steroids

To date, clinical trials have revealed that the use of steroids in stroke patients cannot improve cerebral edema and facilitate ICP control; hence, it is not recommended in stroke patients[30,31] (Class III, Level of Evidence A).

Hyperventilation

Hyperventilation is an effective method to reduce ICP rapidly. Nevertheless, its effect is short-lived, and aggressive use of hyperventilation to substantially lower the partial pressure of carbon dioxide ($PaCO_2$) may compromise cerebral blood flow with secondary cerebral ischemia. Therefore, this treatment modality is used only in an emergency, and the target levels of $PaCO_2$ are 30-35 mmHg[23-32] (Class IIa, Level of Evidence B).

Hypothermia therapy

Cerebral temperature is a factor associated with cerebral ischemic damage. Hypothermia leads to the redistribution of oxygen, lowering of glucose consumption, inhibition of the blood-brain barrier breakdown, and suppression of accompanying inflammation. Consequently, therapeutic cooling may ameliorate brain damage. Moderate hypothermia (32-34˚C) can be effective in controlling intracranial hypertension. However, its long-term use (more than 24-48 h) is associated with a relatively high number of side effects including cardiopulmonary complications, thrombocytopenia, electrolyte imbalance, and rebound intracranial hypertension following hypothermia reversal[33-35] (Class IIb, Level of Evidence B). Therapeutic cooling should be performed with caution and patients should be monitored closely.

Decompressive craniectomy

In cases of LHI, large cerebral necrosis and subsequent edema may cause significant mass effect, which further compresses the surrounding cerebral tissue and

results in secondary ischemia and necrosis. Such a vicious cycle may eventually lead to transtentorial herniation. Therefore, early decompressive craniectomy may allow the infarcted brain to swell outwards; thus, effectively lower intracranial pressure and improve cerebral perfusion. In the past 1-2 decades, a number of literatures have revealed the benefits of decompressive craniectomy in improving survival, particularly when used along with intensive postoperative monitoring in the intensive care unit[36-46] (Class I, Level of Evidence A). Furthermore, timely decompressive craniectomy may also offer patients (especially those under 60 years) a better chance of survival and a better quality of life [38,40,45-47] (Class IIa, Level of Evidence B). Usually, surgery is indicated by the neuroimaging findings of significant mass effect and midline shifting coupled with clinical deterioration such as disturbed consciousness, dilated pupils, and absent light reflexes. Some researchers claim that early surgical intervention before clinical deterioration can further reduce mortality and lead to a better functional outcome[44-46,48] (Class IIa, Level of Evidence B). On the other hand, some believe that, without reliable indicators of MLHI, early surgical intervention may lead to inadequate surgeries in those patients whose LHI may be non-malignant; such surgeries would not necessarily benefit the prognosis of these patients[49,50]. Some investigations reveal that dominant hemispheric infarction is not a contraindication for surgery[40,43] (Class IIb, Level of Evidence B). In conclusion, decompressive craniectomy improves survival, and it may also improve the functional outcome[38,40,45-47,51]. To establish the extent of its benefits, further large-scale studies are required to identify the optimum time and right candidate for decompressive craniectomy[47,52].

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