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REVIEW ARTICLE

Evidence-Based Guidelines for the Management of Large Hemispheric Infarction

A Statement for Health Care Professionals from the Neurocritical Care Society and the German Society for Neuro-Intensive Care and Emergency Medicine

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Abstract Large hemispheric infarction (LHI), also known as malignant middle cerebral infarction, is a devastating disease associated with significant disability and mortality. Clinicians and family members are often faced with a paucity of high quality clinical data as they attempt to determine the most appropriate course of treatment for patients with LHI, and current stroke guidelines do not provide a detailed approach regarding the day-to-day management of these complicated patients. To address this need, the Neurocritical Care Society organized an international multidisciplinary consensus conference on the critical care management of LHI. Experts from

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neurocritical care, neurosurgery, neurology, interventional neuroradiology, and neuroanesthesiology from Europe and North America were recruited based on their publications and expertise. The panel devised a series of clinical questions related to LHI, and assessed the quality of data related to these questions using the Grading of Recommendation Assessment, Development and Evaluation guideline system. They then developed recommendations (denoted as strong or weak) based on the quality of the evidence, as well as the balance of benefits and harms of the studied interventions, the values and preferences of patients, and resource considerations.

Keywords Large malignant stroke · Large hemispheric infarction · Cerebral edema · Hemicraniectomy · Critical care management

Introduction

The term 'malignant MCA infarction' was first introduced in 1996 to describe a severe middle cerebral artery (MCA) syndrome with typical clinical symptoms, following a uniform clinical course and ending in transtentorial herniation [1]. Prediction of this "malignant course" using clinical and radiological variables is, therefore, important and has been the matter of intense investigation for the last two decades. This syndrome has also become known as large hemispheric infarction (LHI).

Clinicians and family members are often faced with a paucity of high quality clinical data as they attempt to determine the most appropriate course of treatment for patients with LHI. Current guidelines for stroke in general emphasize risk factors, prevention, natural history, and acute management, but offer limited discussion of the critical care issues involved in the care of LHI patients specifically [2, 3]. Although the recently published American Heart Association guidelines on management of cerebral and cerebellar infraction with swelling addressed some of the critical care management issues, this statement is addressing specific questions that intensivists deal with on a day-to-day basis on rounds [4]. In order to comprehensively review these issues, the Neurocritical Care Society (NCS) in collaboration with the German Society for Neuro-Intensive Care and Emergency Medicine organized a multidisciplinary conference on the critical care management of LHI.

The definition of LHI with regard to this consensus statement is an ischemic stroke affecting the total or subtotal territory of the MCA, involving the basal ganglia at least partially, with or without involvement of the adjacent (i.e., ACA or PCA) territories.

Statement of Purpose

The purpose of this guideline is to provide evidence-based recommendations for the critical care management of patients following LHI. It is intended to be used by critical care physicians, nurses, and allied health professionals in the management of adult patients with LHI.

Methods

A committee identified topics of interest based on clinical decision points in the critical care management of LHI

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patients. The committee recruited European and North American experts from the fields of neurosurgery, neurocritical care, neurology, interventional neuroradiology, and neuroanesthesiology, and divided them into different subtopic-related panels based on expertise. Each panel performed a critical literature review and summarized the findings in tables; draft recommendations were prepared based on this data. Before the conference, this draft information was distributed to the larger group of conference participants.

For each clinical question, the panel assessed the quality of the data and developed recommendations using the Grading of Recommendation Assessment, Development and Evaluation GRADE system [5]. The panel graded the quality of the evidence as very low, low, moderate, or high. The panel considered quality of evidence in terms of the likelihood that the further research would change their level of confidence in the estimate of effect for an intervention [6].

The GRADE system classifies recommendations as strong or weak, according to the quality of evidence, the balance between risks and benefits, patient preferences, and cost considerations. Evaluating each of these components individually and explicitly is a defining feature of this guideline system. One advantage of GRADE is that it allows for strong recommendations in the setting of lower quality evidence, as long as there are other mitigating factors.

At the NCS annual meeting in October 2012, each panel member presented a summary of the data and recommendations to the group. The committee met again in Mannheim Germany on January 23–26, 2013 during the German Society for Neuro-Intensive Care and Emergency Medicine annual meeting. The committee reviewed key studies and the recommendations made by individual panel members. The final questions were reviewed at the conference and feedback was obtained from a larger auditorium of interdisciplinary neurocritical care practitioners.

Results

Airway Management

- What are the indications for intubation and extubation in LHI?
- What is the best timing for tracheostomy in LHI?

Impaired level of consciousness (LOC), decreased respiratory drive, loss of protective reflexes, and the development of dysphagia may lead to respiratory failure in LHI patients. Numerous studies have examined stroke patients requiring mechanical ventilation [7–13]. However, the panel found only one prospective observational study that addressed mechanical ventilation (MV) and intubation in LHI specifically. This study suggested a Glasgow coma scale (GCS) score of <10 or respiratory failure as indications for intubation [14]. Additional predictors of MV were history of hypertension and infarct size $>2/3$ of the MCA territory [8].

Given a lack of LHI-specific data, the decision to intubate should be triggered by general clinical features such as a GCS <10, hypoxic or hypercarbic respiratory failure, loss of protective reflexes, signs of increased intracranial pressure, infarct size $>2/3$ of MCA territory, and midline shift on imaging [8], co-existence of pulmonary edema or pneumonia [8, 11], or imminent surgical procedure.

The panel considered the relative value of intubating LHI patients, considering the high use of ICU resources and the poor prognosis despite ICU care [10, 12]. However, these studies may have been influenced by nihilistic or self-fulfilling prophecies in the absence of a proven effective treatment option. The growing body of evidence supporting advanced options for severe LHI therapy, including hemicraniectomy, means that life-saving intubation and initiation of mechanical ventilation should be considered for LHI patients. Despite the very low quality of evidence directly related to LHI, the panel determined that the benefits of intubation likely far exceed the risks in a patient with the above clinical features, and issued strong recommendations related to the decision to intubate.

The prediction of successful extubation is equally crucial, as impaired LOC and a high prevalence of dysphagia may lead to a high rate of extubation failure. Re-intubation is associated with increased morbidity and mortality in ICU patients [15]. Unfortunately, classic predictors of successful extubation in general critical care are unreliable in the brain-injured ICU patient and prospective studies in the LHI population do not exist [16, 17]. In a small retrospective study of MCA stroke patients, a composite GCS score ≥ 8 with an eye subscore of 4 was associated with successful extubation [18].

Tracheostomy is frequently necessary if timely extubation is not feasible. Although early tracheostomy has not been studied in LHI patients, exclusively, in a retrospective study on mixed ICU stroke patients, it was associated with better outcome as well as reductions in ventilation duration, ICU stay, and costs [19]. A more recent randomized trial on early tracheostomy in mixed cerebrovascular ICU patients (including those with LHI) demonstrated safety, feasibility, and reduction of sedation needs [20]. Predictors for tracheostomy have been suggested by retrospective studies for intracerebral hemorrhage but not for LHI [21, 22]. There is currently insufficient evidence on the potential outcome benefits of tracheostomy in general or early tracheostomy in LHI specifically. Thus, general customs for tracheostomy in ICU patients should be applied. The panel deemed that it is reasonable to tracheostomize LHI patients between days 7 and 14 if previous weaning attempts were not successful before then.

Recommendations

- LHI patients with signs of respiratory insufficiency or neurological deterioration should be intubated immediately (*strong recommendation, very low quality of evidence*).
- Extubation should be attempted in LHI patients who meet the following criteria, even if communication and cooperation cannot be established (*strong recommendation, very low quality of evidence*):
  - Successful spontaneous breathing trials
  - Absence of oropharyngeal saliva collections
  - Absence of demand for frequent suctioning
  - Presence of cough reflex and tube intolerance,
  - Free of analgesia and sedation
- Tracheostomy should be considered in LHI patients failing extubation or in whom extubation is not feasible by 7–14 days from intubation (*weak recommendation, low quality of evidence*).

Hyperventilation

- Does hyperventilation effectively treat increased ICP in LHI?

Hyperventilation is often employed in increased ICP to induce hypocarbia and cerebral vasoconstriction. The effect on ICP is usually seen within minutes, but it is short-lived. In LHI patients, specifically, there are concerns regarding the use of this therapeutic intervention related to worsening ischemic injury from vasoconstriction [23–25] and rebound vasodilation with increases in ICP with restoration of normocapnea [26, 27]. Very early studies of hyperventilation in patients with stroke found no benefit on patient outcome with the use of this intervention [28, 29]. Overall, there is limited data to support the use of hyperventilation as standard therapy for brain edema.

Recommendations

- We recommend against prophylactic hyperventilation in LHI patients (*strong recommendation, very low quality of evidence*).
- We suggest using hyperventilation for short period of time as a rescue maneuver in LHI patients showing clinical signs of brain herniation (*weak recommendation, very low quality of evidence*).

Analgesia and Sedation

- Should analgesia and/or sedation be administered in LHI patients? If so, which pharmacologic agents should be used?
- Are daily wake-up trials recommended?

Analgesia and sedation have been studied extensively in non-neurological ICU patients, but much more rarely in the brain-injured patients. There is currently no data to indicate superiority of any analgesic or sedative agent in neurocritical care [30]. Likewise, the application of sedation scores, pain scores, sedation protocols, analgesia protocols [31, 32], and devices such as bispectral index (BIS) have only been addressed in small studies on brain-injured ICU patients [33, 34], but not in LHI patients specifically.

In the acute phase of their disease, LHI patients often require analgesia and sedation to decrease pain, anxiety, and agitation. Additionally, sedation and analgesia may facilitate medical goals such as lowering ICP, enabling procedures and operations, or terminating seizures. There is limited evidence to guide specific choices of agents or monitoring protocols. The panel agreed that clinicians should avoid unnecessary or excessive analgesia and sedation, as this might lead to hypotension, immunosuppression, thromboembolic events, prolonged coma and ventilation, and other agent-specific side effects.

Wake-up trials were initially reported to be beneficial regarding reduction of ventilation duration [35] and outcome [36, 37] for some ICU populations. However, patients with exhausted ICP compliance may pose a high risk for critical ICP increase during wake-up trials. Recent studies have failed to confirm a benefit associated with daily wake-up protocols [38]. Furthermore, these protocols have not been studied in LHI-specific populations. Sedation interruption in other neurocritical care populations (TBI and SAH) was associated with potentially negative effects such as transient rises in ICP and stress hormone levels [39, 40].

Recommendations

- We recommend analgesia and sedation if signs of pain, anxiety, or agitation arise in LHI patients (*strong recommendation, very low quality of evidence*).
- We recommend the lowest possible sedation intensity and earliest possible sedation cessation, while avoiding physiologic instability and discomfort in LHI patients (*strong recommendation, very low quality of evidence*).
- We recommend against the routine use of daily wake-up trials in LHI patients. Caution is particularly warranted in patients prone to ICP crises. Neuromonitoring of at least ICP and CPP is recommended to guide sedation, and daily wake-up trials should be abandoned or postponed at signs of physiological compromise or discomfort (*strong recommendation, very low quality of evidence*).

Gastrointestinal Tract

- How should dysphagia be assessed in LHI patients?
- When should LHI patients receive a nasogastric tube?
- When should LHI patients receive a percutaneous enterogastric tube?

Dysphagia affects 30–50 % of acute stroke patients. Screening for dysphagia has been reported to decrease pneumonia in the general stroke population [41]. Dysphagia screening tests such as the gugging swallowing screen have been found useful in acute stroke patients, but patients with large or multiple strokes or rapid decline in LOC were not included. Thus, it is difficult to estimate the validity of these tests in LHI patients [42]. The swallowing provocation test, which assesses the involuntary part of swallowing by means of a thin oropharyngeal catheter, might overcome problems with patient vigilance or cooperation [43]. After initial screening, dysphagia can be confirmed and differentiated by endoscopic swallowing tests that do not necessarily require a patient's cooperation. Fiberoptic endoscopic evaluation of swallowing in particular can be done in severely affected and uncooperative patients, and it has been found to be reliable and predictive in studies on acute stroke patients [44, 45].

Studies on best timing of nasogastric feeding tube placement are lacking for LHI [46]. Likewise, predictors of the need for percutaneous endoscopic gastrostomy (PEG) tube placement have only been studied in mixed ischemic stroke populations. A prospective cohort study of patients with dysphagia following stroke suggests that early enteral feeding in undernourished patients is of benefit, although no time scale was given [47]. A similar study indicated that the decision to place a PEG should be based on impaired swallow and the need for enteral feeding for more than two weeks, or the inability to tolerate NG feeding on at least two occasions [48].Two retrospective analyses have found that a high National Institute of Health Stroke Scale (NIHSS) score is most predictive of PEG need [49, 50].

Although there is a lack of studies directly focusing on food intake, delivery, and gastrointestinal function in LHI patients, the evidence from typical ICU care is transferrable to the LHI population.

Recommendations

- We suggest dysphagia screening in the early phase of LHI. Dysphagia can be assessed once the patient is weaned from sedation and ventilation (*weak recommendation, very low quality of evidence*).
- LHI patients with dysphagia should receive a nasogastric tube as soon as possible (*weak recommendation, very low quality of evidence*).
- We suggest that high NIHSS scores and persisting dysphagia on endoscopic swallowing should prompt discussion with the family on placement of a PEG tube between weeks 1 and 3 of the ICU stay (*weak recommendation, very low quality of evidence*).

Glucose Control

- How should glucose be controlled in LHI patients?

Both hyperglycemia and hypoglycemia have been associated with increased morbidity and mortality in acute ischemic stroke. A recent retrospective analysis in mixed Neurological Intensive Care Unit (NICU) patients showed no benefits of tight glucose control. Rather, patients had higher rates of hypoglycemia and mortality [51]. Likewise, a recent systematic review and meta-analysis in mixed NICU patients found no mortality benefits of intensive insulin therapy, but rather an association with hypoglycemia [52]. Hypoglycemia is particularly troublesome in the ischemic brain. On the other hand, very loose glycemic control was associated with worse neurologic recovery [51].

The panel concluded that intermediate glucose control (140–180 mg/dl) is most appropriate for this patient population [52]. Clinical data on the effects of glucose control in LHI patients specifically have not been published.

Recommendations

- We recommend that hypoglycemia and hyperglycemia should be avoided in LHI. Intermediate glycemic control (serum glucose level 140–180 mg/dl) should be the target of insulin therapy in LHI patients (*strong recommendation, very low quality of evidence*).
- We recommend that intravenous sugar solutions should be avoided in *LHI* (*strong recommendation, very low quality of evidence*)

Hemoglobin Control

- What is the optimal hemoglobin level in LHI patients?

Anemia is associated with worse outcome in ischemic stroke, both in the acute and subacute phases [53, 54]. Currently, no evidence exists on the effect of anemia on LHI patients in particular, although theoretically optimizing oxygen carrying capacity should play a decisive role in treating the ischemic and oligemic brain tissue of LHI patients. Hence, the physiological benefits of RBC transfusion suggested in neuromonitoring studies in TBI and SAH patients [55, 56] may be assumed for LHI patients as well.

A recent systemic review and meta-analysis found insufficient evidence to recommend either a restrictive or liberal transfusion strategy in NICU patients [57]. However, it is important to emphasize that LHI patients were not included in those trials to a noteworthy extent. More research is clearly necessary to establish optimal hemoglobin levels and transfusion strategies in LHI. Until then, we consider it reasonable to use RBC transfusion below a hemoglobin level of 7 g/dl (the generally accepted ICU threshold) or if systemic or cerebral monitoring suggests a compromised arteriovenous oxygen extraction.

Recommendations

- We recommend maintaining a hemoglobin of 7 g/dl or higher in LHI patients (*strong recommendation, very low quality of evidence*).
- Clinicians should also consider specific situations such as planned surgery, hemodynamic status, cardiac ischemia, active significant bleeding, and arteriovenous oxygen extraction compromise when determining the ideal hemoglobin for a patient (*weak recommendation, very low quality of evidence*).
- Consider reducing blood sampling wherever possible in order to decrease the risk of anemia in LHI (*Weak recommendation, very low quality of evidence*).

Deep Venous Thrombosis Prophylaxis

- How should deep venous thrombosis (DVT) prophylaxis be administered to LHI patients?

Even though DVT prophylaxis is standard of care, compliance is imperfect and the incidence of DVT in the stroke patient is approximately 3 % [58]. In the CLOTS1 trial, incidence of DVT was 11.4 % during days 7–10 post-stroke, as compared to 3.1 % during days 25–30 post-stroke [59]. As such, the CLOTS1 investigators recommended that DVT prophylaxis should be started early and continued for at least 4 weeks. These investigators also showed that thigh-length graduated compression stockings (TLGCS) are not beneficial in prevention of DVT or PE [60]. More skin ulcers, necrosis, and leg ischemia were found in the TLGCS group. The use of below-knee stockings resulted in more DVTs than in TLGS [61]. The effectiveness of intermittent pneumatic compression (IPC) in reducing risk of DVT was recently assessed in CLOTS3 trial [62]. The use of IPC was associated with an absolute risk reduction of 3.6 %. The rate of DVT in the IPC group was 8.5 % compared to 12.1 % in the placebo group.

Subcutaneous heparin effectively prevents DVT in patients with acute stroke and its bleeding risk is outweighed by the benefits of thromboembolic prevention [63]. Low molecular weight heparin (LMWH) appears to be superior to unfractionated heparin in several studies, although LHI patients were not specifically assessed [64–66]. A small study in intracerebral hemorrhage patients found that heparin is safe when started within two days [67]. While not directly related to LHI patients, this evidence might support safety of heparin in this group.

Given what is known about the general stroke population, DVT prophylaxis in LHI should be started early and continued at least as long as the patient is immobilized. Although LHI patients certainly have a higher bleeding risk than the general ischemic stroke patient, the panel determined that this risk does not outweigh the benefits of DVT prophylaxis.

Recommendations

- We recommend early mobilization to prevent DVT in hemodynamically stable LHI patients with no evidence of increased ICP (*strong recommendation, very low quality of evidence*).
- We recommend DVT prophylaxis for all LHI patients upon admission to the ICU and for the duration of immobilization (*strong recommendation, very low quality of evidence*).
- We recommend using IPC for DVT prophylaxis (*strong recommendation, moderate quality of evidence*)
- We recommend using LMWH for DVT prophylaxis (*strong recommendation, low quality of evidence*).
- We recommend against the use of compression stockings for DVT prophylaxis (*strong recommendation, moderate quality of evidence*).

Anticoagulation

- If LHI is due to a cardioembolic mechanism or if the patient has high thromboembolic risk, when should anticoagulation be initiated after LHI?

After LHI, anticoagulation should be reinitiated in patients with increased thromboembolic risk, such as those with atrial fibrillation (AF) or prosthetic valves. The best point in time for this re-initiation is highly controversial. Since studies on anticoagulation in LHI do not exist, conclusions must be extrapolated from the general ischemic stroke and intracranial hemorrhage populations.

The HAEST study of patients with ischemic stroke and AF demonstrated a stroke recurrence rate of 8.5 % within 14 days even in spite of LMWH prophylaxis, thereby illustrating the importance of anticoagulation in this population [68]. In anticoagulated patients with ICH, guidelines for the re-initiation of anticoagulation range from 2 days to 4 weeks [69, 70]. In patients with prosthetic valves where anticoagulation was withheld after ICH, thromboembolism occurred in 3 % during the first 30 days

[71] and in none during the first 15 days [72]. Because they were not studied specifically, it is questionable whether these observations can be generalized to LHI patients.

Given their complicated course, it is reasonable to reinitiate oral anticoagulation after 2–4 weeks in most LHI patients. In selected patients with an extraordinarily high thromboembolic risk (e.g., prosthetic valve with TEE evidence of intracardiac thrombus), an earlier initiation of individualized therapy (e.g., with a modest aPTT heparin strategy) might be reasonable. If bleeding risk prohibits the use of warfarin, aspirin is an appropriate alternative. Compared with warfarin, aspirin is slightly less effective in preventing stroke in patients with AF, but it is safer in patients at high risk for bleeding [73].

Recommendations

- We suggest that oral anticoagulation be reinitiated 2–4 weeks after LHI in patients at high thromboembolic risk (*weak recommendation, very low quality of evidence*).
- We suggest that earlier re-initiation of oral anticoagulation should be based on clinical risk assessment and additional diagnostic tests (e.g., prosthetic valve, acute DVT, acute PE, or TEE showing intracardiac thrombus) (*weak recommendation, very low quality of evidence*).
- We suggest using aspirin during the period of no anticoagulation in LHI with AF or increased thromboembolic risk, provided surgery is not imminent (*weak recommendation, very low quality of evidence*).

Blood Pressure Management

- What is the optimal blood pressure in LHI patients?

While optimal blood pressure (BP) targets are theoretically important in the management of acute ischemic stroke, specific goals have not been established for LHI patients. There is no specific evidence to support a different BP management paradigms in LHI than in standard ischemic stroke. A MAP >85 mmHg appears reasonable in ischemic stroke without hemorrhagic transformation. SBP should be lowered to <220 mmHg [3]. Since fatal neurologic deterioration is frequently associated with delayed ischemia and infarction of the anterior or posterior cerebral artery territories, it makes sense to avoid excessive hypotension after LHI [3].

Data from the general stroke population suggest that BP variability early after admission is associated with infarct expansion, clinical deterioration, worse outcomes, and mortality. Absolute baseline blood pressure values have no significant impact on these outcomes, especially in patients who did not recanalize [74, 75]. This evidence, although indirect and of low quality, should prompt clinicians to pay particular attention to blood pressure stabilization in the acute phase of LHI, for instance during sedation, intubation, or surgery.

Recommendations

- We recommend that clinicians follow current blood pressure management guidelines for ischemic stroke in general when caring for LHI patients. Maintain a MAP >85 mmHg in ischemic stroke without hemorrhagic transformation. Lower SBP to <220 mmHg (*strong recommendation, low quality of evidence*).
- We suggest avoiding blood pressure variability, especially in the early phase of LHI treatment (*weak recommendation, low quality of evidence*).

Steroid Therapy

- Do steroids effectively reduce brain edema in LHI?

The use of corticosteroids for acute stroke was reviewed by Cochrane group [76]. The only data that could be pooled in their review pertained to the outcome of death at 1 year; there was no difference with steroid treatment (OR 0.97; 95 % CI 0.57–1.34). Only one of the seven included trials reported non-fatal adverse effects, which were limited to gastrointestinal bleeding, hyperglycemia, and infection in about 10 % of the patients enrolled [77]. The review concluded that treatment with corticosteroids does not provide any morbidity or mortality benefit following acute stroke.

The panel only identified one randomized controlled trial including examining steroid use in patients with LHI; this study was also included in the Cochrane systematic review [77]. This study randomized a total of 112 patients to receive either placebo or high-dose dexamethasone within 48 h of symptom onset. There was no difference in the primary endpoints of death at day 21 or neurological outcome between the two treatment groups.

The overall paucity of evidence does not allow for adequate assessment of the impact of steroid therapy on cerebral edema in LHI patients.

Recommendation

- We recommend against using steroids for brain edema in patients with LHI (*strong recommendation, low quality of evidence*).

Barbiturate Therapy

- Do barbiturates effectively treat brain edema in LHI?

Barbiturates are often thought to be a therapeutic option for treating cerebral edema refractory to other interventions. There are currently no randomized controlled trials assessing the use of barbiturates in LHI. In a prospective observational case series, Schwab et al. investigated the impact of a high-dose thiopental coma on ICP and outcome in patients with severe cerebral edema after LHI [78].

Overall, this study suggested that barbiturate coma has no benefit in the management of increased ICP in LHI and was associated with significant hypotension.

Recommendation

- Barbiturate therapy is not recommended in patients with LHI because the risks outweigh the benefits (*strong recommendation, low quality of evidence*).

Temperature Control

- Does hypothermia or normothermia have any role in the management of brain edema after LHI?

The panel did not find any RCTs addressing the role of hypothermia or normothermia in the management of LHI. A number of studies have demonstrated the safety and feasibility of hypothermia in ischemic stroke patients even when combined with systemic thrombolysis [79–82]. Although some studies found hypothermia to be generally safe [81–83], hypotension, hematologic effects, and infections were common side effects [84]. Hypothermia was found to significantly reduce ICP in patients with LHI [85–87], but is not as effective as hemicraniectomy [88]. A combined approach of hemicraniectomy with hypothermia may be of further clinical benefit [83]. The rewarming phase is critical since rebound increase in ICP can be observed [86].

This practice appears to be safe and feasible, although the quality of supporting evidence is low. Hypothermia seems to reduce ICP crises; however, these potential benefits have not been fully evaluated. It is also important to keep in mind the potential side effects of hypothermia such as pneumonia and coagulopathy. Further studies are required to identify the optimal target temperature and cooling duration.

Recommendations

- We suggest considering hypothermia as a treatment option in patients who are not eligible for surgical intervention *(weak recommendation, low quality of evidence).*
- If hypothermia is considered, we suggest a target temperature of 33–36 °C for duration of 24–72 h (*weak recommendation, low quality of evidence*).
- We suggest maintaining normal core body temperature (*weak recommendation, very low quality of evidence*).

Head Position

- What is the optimal head position in patients with LHI?

To assist in venous drainage and subsequently prevent ICP elevation, it is a standard practice to elevate the head of bed in patients with neurological injury. There are no well-controlled clinical trials that have shown any benefit from this intervention. The degree of head elevation is important since elevation $>45°$ may compromise CPP [89, 90]. In one observational study, investigators assessed backrest elevation of 15° and 30°, and then a return to 0° while continuously recording ICP, MAP, CPP, and MCA peak mean flow velocity [91]. Intracranial pressure was significantly decreased with the 30° backrest elevation, however, MAP and CPP were significantly decreased as well. Cerebral perfusion pressure was maximal in the horizontal position but ICP was also at it highest value. It is important to keep in mind that this could result in a higher risk of aspiration and vigilance should be exercised.

Recommendation

- We suggest a horizontal body position in most patients with LHI. However in patients with increased ICP, we suggest a 30° backrest elevation (*weak recommendation, very low quality of evidence*).

Osmotic Therapy

- Does osmotic therapy effectively treat brain edema and improve outcome in LHI?
- What are the potential complications associated with the use of these agents?

There is no large comparative effectiveness or prospective randomized studies comparing osmotic therapy regimens in the setting of LHI. Most prospective studies have been observational in design and have focused on the treatment of existing edema rather than its prevention. Glycerol has been examined previously in small series, where improved control of ICP was observed safely, however no information regarding mortality or functional outcome was available [92, 93]. Both mannitol and hypertonic saline appear to be safe therapeutic options, without causing exacerbation of tissue shifts as assessed by imaging endpoints [94–96].

Recommendations

- We recommend using mannitol and hypertonic saline for reducing brain edema and tissue shifts in LHI only when there is clinical evidence of cerebral edema (*strong recommendation, moderate quality of evidence*).
- We suggest using osmolar gap instead of serum osmolality to guide mannitol dosing and treatment duration (*weak recommendation, low quality of evidence*).
- Hypertonic saline dosing should be guided by serum osmolality and serum sodium (*strong recommendation, moderate quality of evidence*).

- We recommend using mannitol cautiously in patients with acute renal impairment (*strong recommendation, moderate quality of evidence*).
- We recommend using hypertonic saline cautiously in patients with volume overload states (i.e., heart failure, cirrhosis, etc.,) since this agent will expand intravascular volume (*strong recommendation, high quality of evidence*).

Neuroimaging by CT and MRI

- Can neuroimaging by CT or MRI predict neurological deterioration and "malignant" course after LHI?

The panel identified nine observational and four case-control studies that reviewed the role of CT in LHI prognostication. Several predictor variables were identified. A hypodensity covering >50 % of the MCA territory had an 85 % positive predictive value for fatal clinical outcome, with a sensitivity and specificity of 61 and 94 %, respectively [97–101]. Poor outcome was also associated with poor collateral blood flow, lack of recanalization, and distal ICA or proximal MCA occlusion [1]. Presence of carotid T occlusion on angiography predicted fatal outcome with a positive predictive value of 47 %, a negative predictive value of 85 %. The sensitivity of this sign to predict mortality was 53 % and the specificity was 83 % [102]. Involvement of additional vascular territories was also associated with fatal brain edema [99, 103, 104]. Infarct volume >220 ml was found to be very predictive of brain edema and herniation [105, 106]. Midline shift >3.9 mm was also predictive of malignant infarction [105–107].

Regarding MRI-based prognostication, the panel identified seven observational studies; six were retrospective and one was prospective. An apparent diffusion coefficient (ADC) of <80 % (denoting 80 % threshold ADC values compared to the contralateral unaffected hemisphere) and volume of >82 ml within 6 h of symptoms onset was found to be predictive of LHI with a sensitivity and specificity of 87 and 91 %, respectively [108]. The stroke volume on diffusion weighted imaging (DWI) was also found to be predictive of LHI although the accuracy of this measure did vary among the different studies depending on the cutoff volume used. DWI volumes assessed were >82 ml [109], 145 ml [106, 110], and >177 ml [111]. Patients with DWI infarct volumes greater than 145 ml were more likely to develop malignant edema requiring hemicraniectomy [112].

In its totality, the evidence regarding the use of neuroimaging in LHI prognostication is derived mainly from observational studies using different neuroimaging techniques at different time points after onset of symptoms.

Recommendation

- We recommend using early changes on CT and MRI to predict malignant edema after LHI (*strong recommendation, low quality of evidence*).

Ultrasound

- What is the value of transcranial Doppler (TCD) and transcranial color-coded duplex (TCCS) sonography for the prediction of malignant course after LHI?

Although the overall evidence on ultrasound monitoring in LHI is limited, the reliable assessment of midline shift (MLS) by TCCS has been reproducible in several small prospective studies [113–116]. Some reported that all patients with a shift of less than 4 mm survived, while all patients with values exceeding 4 mm died of cerebral herniation [114]. MCA occlusion on sonography within the first 12 h after MCA infarction and lack of recanalization within 24 h was associated with a mortality of 61 %.

The main advantages of ultrasound-based monitoring are its bedside availability and favorable safety profile. Therefore, especially in less stable patients, TCCS may represent an attractive alternative to serial CT-scans, which require transportation and expose the patient to radiation. Insufficient bone window may represent a limitation of ultrasound-based monitoring in some patients. Another difficulty is that a reliable ultrasound examination usually requires a skilled and experienced examiner.

Recommendation

- We suggest using TCCS as a complimentary test to predict malignant course and possibly as a primary test if the patient is too unstable to be transferred outside the ICU for neuroimaging (*weak recommendation, low quality of evidence*).

Evoked Potentials

- Can Evoked Potentials be used to predict malignant course after large hemispheric stroke?

One retrospective study demonstrated that pathologic Brainstem auditory evoked potentials (BAEPs) within 24 h of symptom onset with side-to-side difference of amplitudes of more than 50 % could predict malignant course, whereas somatosensory evoked potential (SEP) findings were inconclusive [117]. This study suggests that evoked potentials could be used to predict malignant clinical course after large MCA infarction.

Recommendation

- We suggest considering BAEP as a complimentary method to predict malignant course within the first 24 h after MCA infarction, particularly in patients too unstable to be transported to neuroimaging (*weak recommendation, very low quality of evidence*).

EEG

- Can EEG predict a malignant course after LHI?
- Is there a utility for continuous EEG monitoring in patients with LHI?

There is limited data supporting continuous EEG in either prognostication or management of patients with LHI. One study investigated the value of early standard EEG for the prediction of malignant course in LHI [118]. The absence of delta and presence of theta, and fast beta frequencies within the lesion localization were significantly associated with benign course, whereas diffuse slowing and delta activity within the focus were rather predictive for malignant course. However, the predictive values for malignant course were too low to form the basis for irrevocable treatment decisions.

Another study investigated the correlation between quantitative continuous EEG and cerebral perfusion pressure (CPP) [119]. The authors reported an association between loss of fast EEG activity and low CPP. In patients who underwent decompressive hemicraniectomy, a better outcome was reported when patients showed a presence of a 5–10 Hz frequency peak [120]. Another study demonstrated a good correlation between brain symmetry index and NIHSS [121]. These two studies constitute limited evidence indicating that continuous EEG, especially its quantitative analysis, may be a promising monitoring tool.

Recommendations

- We suggest considering EEG in the first 24 h after stroke to assist with predicting clinical course in LHI (*weak recommendation, very low quality of evidence*).
- We suggest that continuous and quantitative EEG represent a promising non-invasive monitoring technique and a tool for estimation of prognosis after LHI that might be useful in the future pending further study (*weak recommendation, very low quality of evidence*).

Invasive Multimodal Monitoring

- Can invasive multimodal monitoring (ICP, microdialysis, ptiO$_2$) predict malignant course after LHI?
- What is the value of invasive multimodal monitoring in preventing secondary complications after LHI?

There exists limited evidence on the use of invasive multimodal monitoring in patients with LHI. Microdialysis has been investigated in small prospective studies, mainly focusing on its feasibility as a part of multimodal monitoring [92, 122–125]. Some of these studies have demonstrated that the use of microdialysis is feasible for monitoring of treatment effects of hypothermia [124, 125] or osmotic agents [92].

The feasibility of parenchymal [86, 91, 92, 122–132] or epidural [133] ICP monitoring in patients with LHI has also been assessed mainly in small prospective studies. Some studies have reported an association between high ICP values and mortality or poor outcome [126, 133]. However, one recent study reported that midline shift and herniation might occur with normal ICP values (< 20 mmHg) [127]. Overall though, the value of ICP measurement in LHI remains unclear.

Few studies have assessed the feasibility of tissue oxygen pressure (ptiO2) monitoring in LHI [122, 123, 130, 131]. Continuous multimodal neuromonitoring in patients with large stroke found that a CPP of 50–60 mmHg and a pbtiO2 of 10 mmHg are critical thresholds for secondary ischemia of the peri-infarct tissue and infarct growth [123].

These small retrospective studies show that when performed in the ipsilateral peri-infarct tissue, invasive multimodal neuromonitoring is better used to detect complications (such as secondary infarction of peri-infarct tissue) once they occur, rather than to prevent their development.

Recommendation

- Invasive multimodal monitoring has not been sufficiently studied, and therefore cannot be recommended in the routine management of LHI (*weak recommendation, low quality of evidence*).

Surgical Management

- Should decompressive hemicraniectomy (DHC) be offered to patients with LHI?
- What are the selection criteria for DHC in LHI?
- What is the optimal timing and size for DHC?
- Should age and hemispheric dominance play a role in the decision to offer DHC to LHI patients?
- Should temporal lobectomy or duraplasty be offered as an adjunct therapy to DHC?

LHI is associated with cerebral edema, increased ICP, and a high rate of herniation [1]. Even with optimal medical management, outcomes are often poor. Surgery in the form

of DHC has been advocated as a life-saving intervention since Scarcella first described the operative approach nearly 60 years ago [134]. Over the last 30 years, enthusiasm for this procedure has fluctuated.

Several observational studies [111, 135–143], systematic reviews [144, 145], and clinical trials [146–149] have addressed the question of best surgical treatment options for LHI. As of 2007, five prospective randomized trials investigating the efficacy of DHC were reported. The Hemicraniectomy And Durotomy Upon Deterioration From Infarction-Related Swelling Trial (HeADDFIRST) was a phase 2 feasibility study [150]. The investigators reported a non-significant reduction in mortality from 46 % with medical therapy to 27 % in the surgically treated group [150]. However, functional outcomes were not reported, leaving open to question the issue of quality of life in these survivors. Later, three European clinical trials [The French Decompressive Craniectomy in Malignant Middle Cerebral Artery Infarct (DECIMAL), the German Decompressive Surgery for the Treatment of Malignant Infarction of the Middle Cerebral Artery (DESTINY) trial, and the Dutch Hemicraniectomy after Middle Cerebral Artery Infarction with Life-threatening Edema (HAMLET) trial] demonstrated the benefits of DHC in LHI [146–148]. A pooled analysis of these three trials demonstrated the robust effect of DHC on mortality [151]. All patients in the clinical trials were younger than 60 years of age, had severe strokes with NIHSS >16, and were randomized within 48 h regardless of symptoms suggesting transtentorial herniation [151]. The pooled analysis provided much more definitive evidence indicating that DHC can be a life-saving procedure. DHC more than doubled the chances of survival, from 29 to 78 %. This staggering absolute risk reduction of 49 % translates into a number needed to treat of 2 to avoid one fatal outcome [152]. However, there was no significant improvement in functional outcome of survivors when dichotomized to mRS 0–3 versus 4–6 [151]. In some cases, the reduction in mortality was offset by increased disability, leading some to conclude that DHC prolongs poor quality life.

The optimal timing and selection criteria for DHC remain uncertain. Since not all patients with LHI develop severe mass effect and herniation, various clinical predictors (e.g., NIH Stroke Scale score), radiographic criteria (e.g., location of thrombus, appearance of CT, or MRI scans) and/or laboratory tests (e.g., serum S100B levels) have been used to predict which patients would benefit from DHC [151].

There is an ongoing debate over whether to wait for signs of neurological deterioration, brain stem herniation, and/or major midline shift, or whether to operate as soon as the diagnosis of MCA infarction is made. A common practice of "prophylactic" DHC leads to overutilization and unnecessary procedures, whereas a reactive policy of waiting for signs of deterioration may compromise any potential recovery. Several studies have examined the effect of early decompression (<24 h) vs. late decompression (>24 h) [153, 154]. Although some have shown decreased mortality rate, reduced rate of herniation, and decreased time in the ICU, others have shown increased disability [154]. In both DECIMAL [148] and DESTINY [147] trials, DHC was performed within 24 h after onset of symptoms and mortality was significantly reduced. In addition, neurological outcome was significantly improved 6 and 12 months after stroke. Another variable in the DHC timing decision is the appearance of clinical herniation signs. Several studies have shown worse clinical outcome and increased mortality rate in patients with clinical signs of herniation prior to DHC [103, 140, 155].

The size of the DHC is also a very important variable that needs to be addressed. Suboptimal DHC with a size smaller than 12 cm has been linked to increased cerebral complications and decreased survival rate [156]. Most studies recommend a diameter of DHC of at least 12 cm [138, 140, 146–148, 153]. Some studies describe a size larger than 13–14 cm in diameter [136, 142, 154] or even including the superior sagittal sinus [111]. Some emphasized the effect of an additional resection of the temporal muscle to maximize the decompressive effect of DHC [157]. Other surgical decisions, such as the timing of cranioplasty, storage of the bone flap, and replacement with autologous versus synthetic flap, have not been systemically studied in large randomized trials.

The preponderance of evidence argues strongly in favor of offering DHC to young (<60 years) patients with LHI [147, 151, 158]. Clinical trials that included patients up to 75 years of age demonstrated that DHC was associated with improved survival but not with improved functional outcome, particularly in those 60 years or older [138]. Until the recent publication of DESTINY II trial [149], the benefits of DHC in patients older than 60 years were uncertain. DESTINY II study was a randomized controlled trial in patients 61 years and older with LHI [159]. The results showed a decrease in mortality rate from 70 to 33 % in the DHC group, but 32 and 28 % of patients that survived remained in a very poor neurological status quantified as mRS of 4 and 5, respectively. Only 7 % of patients showed a mRS of 3 as the best outcome that could be achieved. Although the authors concluded that DHC significantly increase the probability of survival without most severe disability, data clearly show that the increased survival rate was achieved by a significant increase of patients with poor and very poor outcome (mRS5).

Patients with LHI of the dominant hemisphere are often not offered DHC because severe residual aphasia is often regarded an unacceptable outcome. One small study

reported that LHI of a dominant hemisphere was not associated with worse functional outcomes or quality of life (QoL) measurements of QoL [160]. A systematic review by Gupta et al. also provided stronger evidence that DHC in the dominant hemisphere was not associated with worse outcomes [144]. Interestingly, the results of the pooled analysis of all DHC also indicated that stroke laterality did *not* influence functional outcome among survivors [151].

Very few trials reported on temporal lobectomy as a potential therapeutic option for LHI [136, 142, 161]. In all three studies, the effect of this procedure on outcome and survival rate has not been assessed. In the majority of clinical trials, temporal lobectomy was not performed with DHC. Similarly, the panel found little evidence to support duraplasty. Although it is mandatory to open the dura in order to achieve a maximal decompressive effect of DHC, whether to close it with or without a duraplasty remains a controversial decision. In the majority of DHC cases, closure of the dura was performed with the help of a duraplasty. The material used for the duraplasty did not affect the outcomes or complications rates. [162]

In summary, there appears to be a strong association between DHC and improved survival after LHI. The majority of the evidence supports the role of DHC in patients <60 years of age. Although the recent DESTINY II results have shown decreased mortality in DHC patients older than 60 years, most survivors had a substantial disability [149].

The decision about whether or not to perform DHC must also address its known complications, such as anesthetic risks, surgical risks (pain, infection, bleeding, and extra-axial fluid collections), the "syndrome of the trephined" (headache, seizures, and worsening of neurological deficit), higher rates of hydrocephalus, and the risks of cranioplasty (bleeding, infection). Since LHI patients often have many medical co-morbidities, these risks can be substantial. Furthermore, the costs of DHC must be acknowledged, including the direct costs of the procedures and the prolonged hospitalization, as well as the costs of chronic care associated with functional dependency in a patient who might have otherwise died soon after their infarction.

Recommendations

- We recommend DHC as a potential therapy to improve survival after LHI regardless of patient age (*strong recommendation, high quality of evidence*).
- In patients older than 60 years, we recommend taking in consideration patients and family wishes, since in this age group, DHC can reduce mortality rate but with a higher likelihood of being severely disabled (*strong recommendation, moderate quality of evidence*).
- There is currently insufficient data to recommend against DHC in LHI patients based on hemispheric dominance (*strong recommendation, low quality of evidence*).
- To achieve the best neurological outcome, we recommend performing DHC within 24–48 h hours of symptom onset and prior to any herniation symptoms (*strong recommendation, moderate quality of evidence*).
- We recommend a size of 12 cm as an absolute minimum for DHC. Larger sizes of 14–16 cm seem to be associated with better outcomes (*strong recommendation, moderate quality of evidence*).
- We suggest that that lobectomy or duraplasty should only be considered as an individualized treatment option (*weak recommendation, low quality of evidence*).
- We suggest that the resection of the temporal muscle should only be considered as an individualized treatment option (*weak recommendation, low quality of evidence*).

Ethical Considerations

- Is the reduction of mortality after DHC achieved at the expense of functional dependency?
- Is modified rankin scale (mRS) score of 4 considered a desirable outcome after LHI?

The concern of many clinicians has been that a reduction in mortality might be outweighed by a major disability in most survivors, leaving them severely disabled and facing a life of dependency, pain, and hopelessness. Therefore, the choice of performing DHC should hinge on the patient's willingness to accept survival with some degree of disability. Most studies use the mRS to describe the degree of disability.

How much disability can be expected after DHC? The pooled analysis by Vahedi [151] indicates that the mortality reduction from DHC in patients younger than 60 years does *not* come at the cost of an increased risk of survival with severe disability (mRS 5). The reduction in the proportion of patients rated as dead or severely disabled (mRS 5 or 6) was similar, and the proportion of patients with an mRS of 5 was similar in the two groups [151]. However, the proportion of patients with slight-to-moderate disability (mRS 2 or 3), was increased from 21 % to 43 % [151].

Key issues regarding the true benefit of DHC are related to the definition of poor outcome in the available clinical trials. The three available studies on DHC after LHI used definitions of poor outcome based on a mRS of 4–6 [146, 148, 159]. In the pooled analysis by Vahedi et al. [151],

two definitions of poor outcome at 12 months were tested (primary definition mRS 5–6 and secondary definition mRS 4–6) [151]. Significantly fewer patients had mRS 5–6 or 4–6 at 12 months in the DHC arm.

But is mRS score of 4 considered a desirable outcome after DHC [163, 164]? Only patients or their closest caregivers could answer this important question. Foerch et al. found that patients who had received DHC and their caregivers were split as to whether they would make the same treatment decision again [111]. Benejam et al. found that most DHC patients and caregivers agreed that the decision to undergo DHC was correct, and their responses were not related to their functional outcomes [165]. Kiphuth et al. asked individual patients and caregivers if they would retrospectively consent for DHC in light of their functional outcome at 12 months [163]. Out of 28 patients, 82 % retrospectively consented for DHC, however these patients had an mRS <5. Those with an mRS of 5 would have not consented for DHC and low QoL was most often declared in this sub-group. There was one patient with an mRS of 4 that would have not consented for DHC. An important point is that the mRS represents a rather rough categorization of outcome. It does not sufficiently account for cognitive deficits or impaired communication.

Whether DHC survivors have a better functional outcome as compared to survivors of medical treatment is not really clear, particularly because it is not determined whether an mRS of 4 can be considered a favorable outcome. Resolving this ethical issue with the help of patients and family members should be the main goal of future studies. The results of these studies also suggest that functional outcome and QoL may depend on the patients' and relatives' views of survival and dependency. There may also be socio-demographic differences in understanding the concept of functional outcome and QoL, although this has not been thoroughly studied. It is also imperative that future studies develop tools to aid in the identification of patients who would survive LHI due to DHC but with a severely reduced functional status.

Recommendation

- We suggest that the decision to perform DHC should depend on values and preferences of patients and relatives regarding survival and dependency (*weak recommendation, low quality of evidence*).

Quality of Life (QoL)

- Is survival after LHI associated with good QoL?

Most LHI studies have primarily concentrated on impairment and disability, whereas health-related QoL remains understudied. Only two of the three major RCTs on DHC after LHI reported endpoints related to QoL. In the HAMLET study, QoL was a secondary endpoint, measured by the Medical Outcomes Study (SF-36) and a visual analog scale (VAS) [146, 166, 167]. There were no overall significant differences in QoL except for the physical summary score which was better in the medical arm compared to surgical arm [146]. In the DECIMAL study, QoL was assessed by the French version of the stroke impact scale (SIS) v2.0 which is an 8-domain scale with 4 physical domains and 4 psychosocial domains [148, 168]. There were no overall significant differences in QoL, however the authors described that all survivors were able to acknowledge that, "life is worth living" [148].

Several published observational studies have also addressed this issue [111, 136, 142, 155, 160, 165, 169, 170]. These studies have used the SF-36, SIS v2.0 and 3.0, and other scales such as the sickness impact profile (SIP) [171], the Aachener life quality inventory (ALQI), or the EuroQoL [172]. Results from these studies are contradictory but raise several important issues. Primarily, psychological domains appear to be less affected than motor domains, although depression remains very prevalent in this population. As well, the perception of QoL depends on other factors such as family support and premorbid life style. Finally, it is important to acknowledge that the two RCTs that studied QoL were underpowered to detect significant differences for secondary endpoints, highlighting the need of more research in this area.

Overall, the few studies published that have dealt with QoL have reported somewhat divergent results. QoL appears to be similar in survivors of LHI treated conservatively or with DHC.

Recommendation

- We suggest that future research use QoL as an outcome measure in LHI patients (*weak recommendation, low quality of evidence*).

Conclusions

The International Consensus Conference on Critical Care Management of Patients Following Large Hemispheric Infarct was designed to help develop recommendations for treating LHI patients. One significant challenge the reviewers faced was the paucity of large clinical trials addressing important clinical management questions. The GRADE system allowed the panels to make recommendations not based only on the quality of the evidence but to also incorporate the factors such as risk benefit ratio, patient values and preferences, and resource consideration.

It was clear that additional research is needed across the continuum of LHI patient care. Unfortunately, this type of clinical research could be difficult to execute given the

complexity and variability of these patients. In the meantime, these guidelines can be used as a road map in treating patients with LHI. It should be noted that all guidelines need to be considered in the context of regional needs and resources, particularly when it comes to weak recommendations. The panel encourages guideline users to consider the nuances of the evidence presented as they implement these recommendations in their own practice. As the evidence grows, these recommendations will need to be reviewed accordingly.

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