Review

Clinical review: Therapy for refractory intracranial hypertension in ischaemic stroke

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Abstract

The treatment of patients with large hemispheric ischaemic stroke accompanied by massive space-occupying oedema represents one of the major unsolved problems in neurocritical care medicine. Despite maximum intensive care, the prognosis of these patients is poor, with case fatality rates as high as 80%. Therefore, the term 'malignant brain infarction' was coined. Because conservative treatment strategies to limit brain tissue shift almost consistently fail, these massive infarctions often are regarded as an untreatable disease. The introduction of decompressive surgery (hemicraniectomy) has completely changed this point of view, suggesting that mortality rates may be reduced to approximately 20%. However, critics have always argued that the reduction in mortality may be outweighed by an accompanying increase in severe disability. Due to the lack of conclusive evidence of efficacy from randomised trials, controversy over the benefit of these treatment strategies remained, leading to large regional differences in the application of this procedure. Meanwhile, data from randomised trials confirm the results of former observational studies, demonstrating that hemicraniectomy not only significantly reduces mortality but also significantly improves clinical outcome without increasing the number of completely dependent patients. Hypothermia is another promising treatment option but still needs evidence of efficacy from randomised controlled trials before it may be recommended for clinical routine use. This review gives the reader an integrated view of the current status of treatment options in massive hemispheric brain infarction, based on the available data of clinical trials, including the most recent data from randomised trials published in 2007.

Introduction

Subtotal or complete middle cerebral artery (MCA) territory infarctions, including the basal ganglia, occasionally with additional infarction of the anterior cerebral artery (ACA) or the posterior cerebral artery (PCA) or both, are found in 1% to 10% of patients with supratentorial infarcts [1-3]. They are commonly associated with serious brain swelling, which usually manifests itself between the second and the fifth day after stroke onset [1-8]. Space-occupying cerebral infarction is a life-threatening event. Mass effect leads to the destruction of formerly healthy brain tissue and, in severe cases, to extensive brain tissue shifts resulting in transtentorial or uncal herniation and brain death [3,6,9]. These complications are responsible for the rapid neurologic deterioration seen in such patients [1]. In intensive care-based prospective series, the case fatality rate of these patients was approximately 78% despite maximum medical therapy [3,10,11]. For these catastrophic cerebral infarcts, the term 'malignant infarction' was coined by Hacke and colleagues [3] in 1996.

Clinically, these patients present with dense hemiplegia, head and eye deviation, and multimodal hemineglect; global aphasia coexists when the dominant hemisphere is involved [2,3]. The National Institutes of Health Stroke Scale score is typically greater than 20 when the dominant hemisphere is involved and greater than 15 when the nondominant hemisphere is involved [12,13]. They show a rapidly progressive deterioration of consciousness over the first 24 to 48 hours and frequently a reduced ventilatory drive [3]. Neuroimaging typically shows definite infarction of at least two thirds of the MCA territory, including the basal ganglia, with or without additional infarction of the ipsilateral ACA or the PCA territories, or an infarct volume of greater than 145 cm^3 using diffusion-weighted imaging [14-18]. Because of an increasing number of young patients suffering from brain infarction (a group of patients at particular danger of malignant infarction),

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ACA = anterior cerebral artery; ARR = absolute risk reduction; CPP = cerebral perfusion pressure; DECIMAL = DEcompressive Craniectomy In MALignant middle cerebral artery infarcts; DESTINY = DEcompressive Surgery for the Treatment of malignant INfarction of the middle cerebral arterY; GCS = Glasgow Coma Scale; HAMLET = Hemicraniectomy After Middle cerebral artery infarction with Life-threatening Edema Trial; ICP = intracranial pressure; MCA = middle cerebral artery; mRS = modified Rankin scale; PaCO$_2$ = arterial partial pressure of carbon dioxide; PCA = posterior cerebral artery; pCO$_2$ = partial pressure of carbon dioxide; pO$_2$ = partial pressure of oxygen; THAM = Tris-hydroxy-methyl-aminomethane.

finding an optimal treatment solution has made this a most urgent topic in neurointensive care medicine during the last decade.

Treatment options
1. Conservative treatment
1.1. General stroke treatment
As far as blood pressure, blood glucose level, body core temperature control, fluid and nutrition management, and prophylaxis of deep venous thrombosis are concerned, patients with malignant MCA infarctions are treated according to the current guidelines of general ischaemic stroke treatment [19-21]. There are some modifications:

Induced hypertension may be useful in case of haemo-dynamic relevant vessel stenoses or to maintain critical perfusion in the presence of radiologically confirmed penumbra [22]. However, there are no controlled trials to confirm this, and available data are contradictory [23,24]. In a prospective trial in patients with malignant MCA infarction, induced hypertension increased cerebral perfusion pressure (CPP) without a relevant increase of intracranial pressure (ICP) [25]. An exception is made in patients receiving decompressive surgery. In these cases, systolic blood pressure during the postoperative phase of the first 8 hours after surgery is kept at 140 to 160 mm Hg to avoid severe bleeding [26].

Previous recommendations of elevation of the head of 30° in patients with malignant MCA infarction should not generally be followed. The idea is that head elevation may improve venous drainage. Furthermore, an upright body positioning reduces the risk of nosocomial infections [27-29]. In fact, although elevation of the head may decrease ICP, the effect on CPP is less predictable. In several studies, head elevation increased CPP [30-32], decreased CPP [33,34], or left CPP unaltered [35-37]. Most of these studies investigated patients with traumatic brain injury or subarachnoid haemorrhage. However, in large ischaemic stroke, different pathophysio-logical aspects such as the possibility of salvaging tissue in the ischaemic penumbra must be taken into consideration. Only one study has investigated the effect of body positioning in patients with large hemispheric ischaemic stroke [34]. According to the results, a plane positioning of the head is recommended. Only in case of considerable increases in ICP or in patients at high risk of nosocomial infections, a moderate elevation of the head of 15° to 30° is recommended, always depending on the CPP [34]. Any form of compression of the jugular veins should be avoided.

As soon as ventilatory drive is depressed, airway protection becomes paramount, necessitating intubation, ventilation, and sedation. Patients should be intubated at a Glasgow Coma Scale (GCS) score of lower than 8, or if there are any signs of respiratory insufficiency (partial pressure of oxygen [pO_2] of less than 60 mm Hg or partial pressure of carbon dioxide [pCO_2] of greater than 48 mm Hg) or signs of ineffective

swallowing or cough reflexes, or if the airway is compromised [38]. Deep sedation is recommended to avoid uncontrolled increases of ICP [27,28]. The following parameters should be targeted: PaO_2 (arterial partial pressure of oxygen) above 75 mm Hg and arterial partial pressure of carbon dioxide ($PaCO_2$) of 36 to 44 mm Hg. In case of raised ICP, the ventilation mode should be changed: Minute ventilation should be adjusted to maintain PaCO2 levels between 35 and 40 mm Hg and pO_2 above 100 mm Hg. A minimum of 5 cm H2O of positive end-expiratory pressure and a minimum FiO2 (fraction of inspired oxygen) to maintain SaO2 (saturation of oxygen [arterial blood]) above 90% are advocated [26,27,39,40].

All patients with malignant MCA infarction should be treated at an experienced neurointensive care unit [26-28]. The treatment options listed below can be effective only with detailed haemodynamic, neuroimaging, and invasive multi-modal monitoring tools (at least ICP and CPP, measurement in the ipsilateral side), the possibility of rapid interventions, and an experienced neurosurgical department in house. CPP measurement and repeated neuroimaging are strongly recommended. ICP alone is not a good parameter for neurologic deterioration and does not monitor brain displacement [6].

1.2. Anti-oedema therapy
The use of osmotic agents is based on the idea of creating an osmotic pressure gradient over the semipermeable membrane of the blood-brain barrier and thereby drawing interstitial and intracellular water from the swollen brain into intravascular spaces. For the treatment of brain oedema after stroke, mannitol, glycerol, hydroxyethyl starch, and hypertonic saline are currently the most widely used [41]. According to the current guidelines, osmotherapy should be started in the case of increases of ICP [19-21]. The use of mannitol (100 ml of 20% solution or 0.5 to 1.0 g/kg every 4 to 6 hours; maximum daily dose, 2.5 g/kg), glycerol (250 ml of 10% solution, four times per day), or hydroxyethyl starch (6% hetastarch in 0.9% NaCl injection, 100 to 250 ml every 8 hours; maximum daily dose, 750 ml) is recommended. Onset of action of these substances is within minutes, and the duration is as long as 4 to 8 hours [27,28,41,42]. In repeated use, dosage depends on serum osmolality, which should be targeted at 315 to 320 mOsmol. Hyperosmolar saline solutions (10% NaCl, 75 ml, repeated doses) may be used as an alternative. The advantage of hyperosmolar saline is that it is actively excluded from an intact blood-brain barrier [43]. Another advantage is that it can be combined with mannitol because it counteracts mannitol-induced hyponatremia, which develops in almost every patient treated by repeated doses of mannitol [44,45].

Steroids are widely used to reduce oedema in brain tumours. However, they have not shown any benefit for brain oedema treatment in ischaemic stroke, although there are no trials investigating the use of steroids in space-occupying ischaemic

stroke [46-49]. In addition, the rate of infections and complications in patients with diabetes mellitus is significantly increased with steroids.

1.3. Intracranial pressure-lowering therapies
Barbiturates have been administered in a variety of clinical conditions to control elevated ICP, especially in head trauma. Barbiturates may be helpful in acute ICP crisis in those patients awaiting more definitive treatment. Their routine use, however, is discouraged [27,28,50].

Buffer solutions may be used as an option when other interventions have failed. Tris-hydroxy-methyl-aminomethane (THAM) (Tris buffer) is given by continuous intravenous infusion via a central venous catheter (1 mmol/kg as bolus infusion over 45 minutes followed by 0.25 mmol/kg-hour, aiming for a target arterial pH of 7.5 to 7.55) [28]. THAM can be used to raise blood pH independently from respiratory function. The mode of action is probably related to neutralization of an acidosis-related vasodilatation and thus a decrease of ICP [28,51]. ICP should fall by 10 to 15 mm Hg within 15 minutes after bolus infusion; otherwise, treatment is not effective [27,28].

Hyperventilation is not recommended unless intracranial hypertension cannot be controlled by any other therapy and the patient is considered a candidate for more definitive treatment such as decompressive surgery [27,28]. The patient's respiratory mode is adjusted for $PaCO_2$ (target 30 to 35 mm Hg) and venous oxygenation with jugular bulb oxymetry (>50%), which is best achieved by raising the ventilation rate at a constant tidal volume. After pCO_2 target is reached, it may take up to 30 minutes until ICP is reduced by 25% to 30%. Prolonged hyperventilation is discouraged because the effect wears off within 3 to 4 hours [27,28].

So far, none of these therapeutic strategies is supported by adequate evidence of efficacy from experimental studies or randomised clinical trials. To understand why medical treatment alone often fails to prevent clinical deterioration, the following points have to be remembered: (a) Clinical deterioration usually is not due to increases of global ICP but to massive local swelling and tissue shifts. Increase of ICP is a secondary late-stage result and represents a terminal and, most likely, an irreversible event that occurs when mass expansion exceeds intracranial compliance. (b) Many agents can work only at an intact blood-brain barrier, which is usually severely compromised in massive cerebral ischaemia. (c) CPP and midline shift are the major surrogate markers of treatment in massive infarction. ICP values are not associated with the extent of midline shift nor do they predict fatal outcomes, and reduction of ICP is not necessarily associated with an increase in CPP [52].

Therefore, from a pathophysiological point of view, all of the above-mentioned therapeutic strategies may be effective only

for a short period of time, if at all, but are doomed to fail in the long term [44,53]. Several reports suggest that they are not only ineffective but even detrimental [3,9,34,41,44,45,50, 54-61]:

Osmotic therapy with hyperosmolar agents aimed at lowering ICP and reducing brain oedema by drawing water from infarcted tissue may be detrimental by primarily dehydrating intact brain, contracting healthy brain tissue volume, thereby aggravating pressure differentials, and causing devastating shifts of brain tissue [6,42,44,58,62].

In malignant infarctions, there are large areas where the blood-brain barrier is significantly disrupted. Hyperosmolar agents have been demonstrated to accumulate in infarcted brain tissue, aggravating brain oedema and space occupation instead of reducing them and thereby (especially in the case of repeated use) worsening brain tissue shifts [55,59]. In addition, after discontinuing hyperosmolar therapy, rebound effects may occur [60,63-65].

Prolonged hyperventilation-induced hypocarbia and considerable decreases in cerebral blood flow by cerebral vasoconstriction both aggravate ischaemic brain injury [54,66-68]. Profound hyperventilation may also jeopardise oxygen delivery to the brain tissue at risk. The underlying physiological mechanism is the Bohr effect: In the presence of carbon dioxide, the dissociation of oxygen from haemoglobin increases. A decrease in blood carbon dioxide by hyperventilation increases the affinity of oxygen to haemoglobin. This leads to a reduction in brain tissue pO2 and, as a result, to increased ischaemic damage indicated by increases in extracellular glutamate, pyruvate, and lactate [69,70].

In some patients with poor cerebral compliance, strict hyperventilation may cause paradoxical ICP elevation by increasing thoracic venous and cerebrospinal fluid pressure. Other side effects include barotrauma and hypokalemia. As with osmotherapy, adverse rebound effects may occur if normoventilation is resumed too rapidly [26,28,54].

Barbiturates often do not lead to sustained control of ICP but may reduce CPP [50,71-75]. In addition, treatment may cause severe side effects such as hypotension, decreased cardiac performance, or severe infections. Cardiovascular side effects may be aggravated by concomitant dehydration advocated by osmotherapy and reduced cardiac filling pressures [28,50].

As a result, none of the conservative treatment options has shown a beneficial effect on outcome in clinical trials, except for glycerol, for which a few clinical trials demonstrate an effect on short-time survival. However, glycerol also failed to demonstrate a long-term benefit [46,61,76]. This failure of conservative treatment is reflected by our clinical experience: In larger case series of maximum conservative treatment in

Table 1

Studies on hypothermia in malignant hemispheric infarction

Authors	Number	Target temperature	Time to induction of hypothermia (hours)	Duration of hypothermia (hours)
Schwab *et al.*, 1998 [95]	25	33°C (external cooling)	4-24, mean 14 ± 7	48-72
Schwab *et al.*, 2001 [134]	50	32°C-33°C (external cooling)	4-75, mean 22 ± 9	24-72
Georgiadis *et al.*, 2001 [99]	6	33°C (endovascular cooling)	12-58, mean 28 ± 17	48-78
Georgiadis *et al.*, 2002 [124]	19	33°C (*n* = 8 endovascular cooling; *n* = 11 external cooling)	18-24, mean 24	24-116
Milhaud *et al.*, 2005 [94]	12	32°C-33°C (external cooling)	4-24, mean 11 ± 7	120-504

Table 2

Mortality data on patients with malignant middle cerebral artery infarction treated with hypothermia

Authors	Number	Mean age (years)	Mortality in hospital	Mortality up to 3 months	Mortality up to 6 months	Mortality up to 12 months
Schwab *et al.*, 1998 [95]	25	49	44%	48%	NA	NA
Schwab *et al.*, 2001 [134]	50	57	38%	38%	NA	NA
Georgiadis *et al.*, 2001 [99][a]	6	65	17%	NA	NA	NA
Milhaud *et al.*, 2005 [94][b]	10	52	50%	50%	50%	NA

[a]Target temperature in one patient 34.5°C. [b]Two patients were excluded in this analysis because they received hemicraniectomy in addition to hypothermia due to worsening of cerebral oedema on day 1 and day 7, respectively; both survived. NA, not available.

malignant MCA infarction, case fatality rates are 53% to 78% [3,11,77,78].

2. Mild to moderate hypothermia

Induced hypothermia is defined as physical or pharmacological lowering of the physiological body core temperature to 36.0°C to 36.5°C (minimal hypothermia), 33.0°C to 35.9°C (mild hypothermia), 28.0°C to 32.9°C (moderate hypothermia), or 10.0°C to 27.9°C (deep hypothermia) [79]. It is well known in ischaemic stroke that body temperature on admission and during the first 24 hours is associated with the extent of ischaemic damage and is an independent predictor of mortality and outcome [80-82].

Although the neuroprotective effect of hypothermia has been known since the 1950s, the earliest experimental findings in ischaemic stroke were reported in the late 1980s [83,84]. There are numerous animal experiments demonstrating promising results, but only a few of them on massive cerebral infarctions [85-88]. The beneficial effect was pronounced when hypothermia was started early and continued for more than 24 hours [89-91].

Only one randomised trial has investigated mild-moderate hypothermia in severe, but not necessarily malignant, stroke (cooling for acute ischaemic brain damage, or COOL-AID). Patients were randomly assigned to either hypothermia or standard medical treatment. Target temperature in the pilot trial was 32°C maintained for 12 to 72 hours. In the subsequent phase I trial, a target temperature of 33°C was maintained for 24 hours. Due to the small sample sizes, the studies did not show statistically significant differences in mortality or functional outcome [92,93]. There are no published controlled, randomised, or prospective comparative clinical studies of hypothermia in malignant MCA infarction. Available clinical studies in malignant cerebral infarction are listed in Table 1.

These report mortality rates of between 17% and 48% (Table 2). Data on functional outcome are summarized in Table 3. Only one study has evaluated functional outcome after 6 months in patients with malignant MCA infarction treated by hypothermia, and only 10 patients were involved [94]. Data on long-term outcome are completely lacking (Table 3).

Hypothermia in these studies was associated with a high rate of complications, the most frequent being pneumonia, severe bradycardia and heart failure with severe hypotension, and severe thrombocytopenia and coagulopathy. Especially in the rewarming phase, a high percentage of patients developed severe increases in ICP. Increased ICP and herniation were the most common reasons for early mortality [95]. Most studies on hypothermia in ischaemic stroke used body

Table 3

Functional outcome data on patients with malignant middle cerebral artery infarction treated with hypothermia

Authors	Number	Mean age (years)	Dominant/ nondominant hemisphere	+ ACA and/or PCA	Mean time to hypothermia (hours)	Mean time to follow-up (months)	Independent	Mild to moderate disability	Severe disability	Death
Schwab et al., 1998 [95]	25	49	68%/32%	20%	14	3	Median Barthel Index 70			48%
Schwab et al., 2001 [134]	50	57	NA	10%	22	3	NA	NA	NA	38%
Georgiadis et al., 2001 [99]	6	65	83%/17%	NA	28	NA	NA	NA	NA	17%
Milhaud et al., 2005 [94]	10	52	50%/50%	8%	11	6	10%	30%	10%	50%

Functional outcome was classified according to Gupta and colleagues [123] as (1) independent outcome (modified Rankin Scale [mRS] 0 to 1, Glasgow Outcome Scale [GOS] 5, Barthel Index [BI] greater than or equal to 90), (2) mild to moderate disability (mRS 2 to 3, GOS 4, BI 60 to 85), (3) severe disability (mRS 4 to 5, GOS 2 to 3, BI less than 60), and (4) death. In the case of patients in whom more than one outcome scale was given, we classified outcome according to the following priority: mRS − GOS − BI. NA indicates data not given or values of the BI, GOS, or mRS given as means [135,136]. ACA, anterior cerebral artery; PCA, posterior cerebral artery.

temperature for monitoring. It has to be kept in mind, however, that brain temperature is 0.5°C ± 0.3°C above rectal temperature, that temperature within the brain may vary up to 1°C, and that initial temperature in the ischaemic hemisphere is 0.8°C higher than in the healthy hemisphere [84,96-98].

As long as there is no sufficient evidence of benefit, hypothermia should be used only in the setting of clinical trials. Hypothermia is an invasive procedure that needs treatment in an experienced ICU, including ventilation, relaxation, and measurement of ICP. External cooling is complicated, especially in adipose patients because of the comparatively long time for cooling with increased use of muscle relaxants and anaesthetics. If available, endovascular cooling should be used because the target temperature can be obtained comparatively quickly (approximately 3.5 hours) [92,93,99]. Instead of passive rewarming, controlled rewarming and long rewarming periods (+0.1°C to 0.2°C per 2 to 4 hours) should be used to avoid increases in ICP or decreases in CPP [100]. Cooling of the head alone seems to be insufficient [96], although further clinical evaluation is required and devices are still being developed [101,102].

3. Decompressive surgery
Decompressive surgery in large ischaemic strokes dates back to as early as 1935 [103]. It is the only available treatment that primarily addresses mass effect, based on simple mechanical reasoning. The rationale is to remove a part of the neurocranium in order to create space to accommodate the swollen brain, to avoid ventricular compression, to reverse brain tissue shifts, and to prevent secondary mechanical tissue damage. Normalisation of ICP and tissue oxygenation is more a secondary effect [9,104-108].

Two different techniques are used: external decompression (removal of the cranial vault and duraplasty) or internal decompression (removal of nonviable, infarcted tissue [that is, in the case of malignant MCA infarction, temporal lobectomy]). The two can be combined [109,110]. In theory, resection of the temporal lobe may reduce the risk of uncal herniation. However, this has never been proven consistently by clinical studies, which show similar results as series using external decompression [111,112]. Resection of infarcted tissue is more complicated, and it is difficult to distinguish between already infarcted and potentially salvageable tissue. Therefore, in most institutions, external decompressive surgery (consisting of a large hemicraniectomy and duraplasty) is performed: In short, a large (reversed) question mark-shaped skin incision based at the ear is made. A bone flap with a diameter of at least 12 cm (including the frontal, parietal, temporal, and parts of the occipital squama) is removed. Additional temporal bone is removed so that the floor of the middle cerebral fossa can be explored. Then the dura is opened and an augmented dural patch, consisting of homologous periost and/or temporal fascia, is inserted

Figure 1
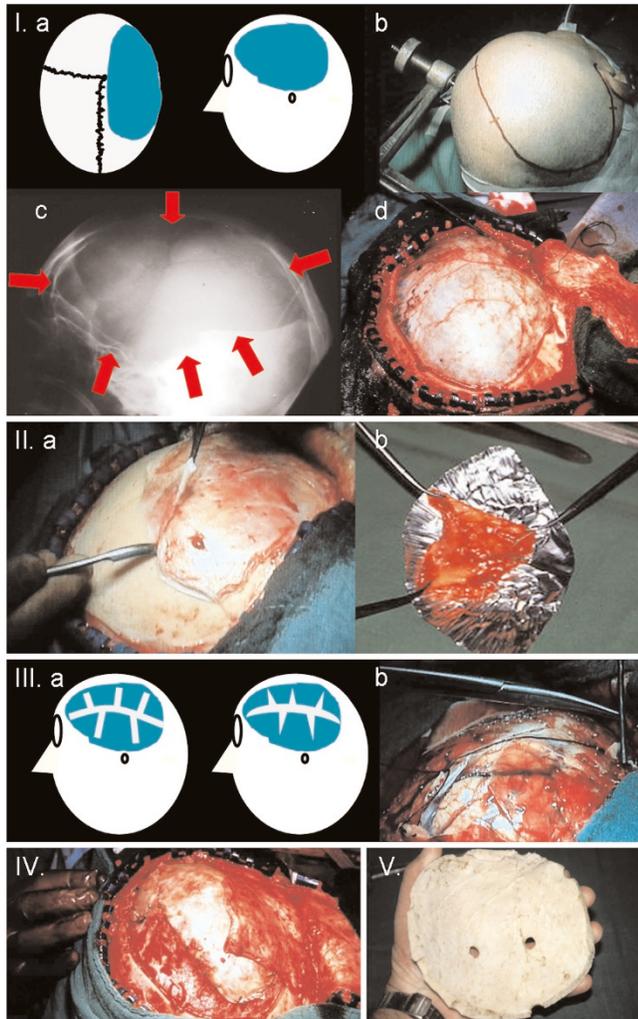
Hemicraniectomy: external decompressive surgery technique. I. Fronto-temporo-parietal hemicraniectomy: (a) schematic drawing of the hemicraniectomy defect, (b) incision, (c) craniectomy borders (to the skull base), (d) tense dura mater with swollen brain underneath. II. Dura mater is removed for duraplasty: (a) preparation, (b) dura stretched on aluminium foil. III. Dura incisions: (a) schematic drawing of incisions, (b) preparation. IV. Insertion of the dura (duraplasty). V. Bone flap is stored at −80°C. Cranioplasty is performed after 6 to 12 weeks.

Figure 2

Left hemispheric malignant middle cerebral artery infarction after hemicraniectomy (magnetic resonance imaging). The swollen brain is allowed to expand outside.

(usually, a patch of 15 to 20 cm in length and 2.5 to 3.5 cm in width is used). The dura is fixed at the margin of the craniotomy to prevent epidural bleeding. The temporal muscle and the skin flap are then reapproximated and secured. In surviving patients, cranioplasty usually is performed after 6 to 12 weeks, using the stored bone flap or an artificial bone flap (Figures 1 and 2). Complications occur rarely and include postoperative epidural and subdural haemorrhage and hygromas or wound and bone flap infections [77,109]. These can be recognized easily and usually do not contribute to perioperative mortality. A more common and far more serious problem is a hemicraniectomy

that is too small. Because the proportion of brain tissue to be allowed to shift outside the skull is closely related to the diameter of the bone flap (which is removed), small hemicraniectomies not only are insufficient but may lead to herniation through the craniectomy defect [113]. Ventriculostomy is not recommended; although it may help to decrease ICP by allowing drainage of cerebrospinal fluid, it promotes brain tissue shifts at the same time and therefore may be detrimental.

Between 1935 and 2007, more than 80 case reports and series of patients with malignant brain infarctions including more than 1,700 patients have been published. Larger case series were not published until 1995 [77]. Only a few prospective trials have compared decompressive surgery with conservative treatment. Some of them used historical control groups, and most control groups consisted of patients with a higher age, more comorbidity, and (more frequently) lesions of the dominant hemisphere [3,77,104,109,111,114-122]. These studies report mortality rates of 0% to 33% in surgically treated patients compared with 60% to 100% in conservatively treated patients. In a review by Gupta and colleagues [123] analysing all available individual patient data from 138 patients, the overall mortality rate after hemicraniectomy after a period of 7 to 21 months was 24%. Only one study compared decompressive surgery with hypothermia [124], and one study compared mild

Table 4

Mortality data in patients with malignant middle cerebral artery infarction: studies with comparative data on conservative treatment versus decompressive surgery

Authors	Patients treated with conservative treatment	Patients treated with decompressive surgery	Mean age (years)	Mortality in hospital	Mortality up to 3 months	Mortality up to 6 months	Mortality up to 12 months
Delashaw et al., 1990 [118][a]	4	9	NA vs. 57	100% vs. 0%	100% vs. 11%	100% vs. NA	100% vs. NA
Steiger 1991 [119][b]	7	8	NA	100% vs. 25%	100% vs. 25%	100% vs. 25%	NA
Rieke et al., 1995 [77], Hacke et al., 1996 [3], Wirtz et al., 1997 [104], Schwab et al., 1998 [109][c]	55	63	56 vs. 50	78% vs. 25%	NA vs. 25%	NA	NA
Holtkamp et al., 2001 [114][d]	12	12	73 vs. 65	83% vs. 17%	83% vs. 25%	83% vs. 25%	83% vs. 33%
Mori et al., 2001 [120]	15	19	72 vs. 63	60% vs. 11%	67% vs. 16%	NA	NA
Mori et al., 2004 [111][e]	15	19	72 vs. 65	62% vs. 12%	NA	71% vs. 24%	NA
Kuroki et al., 2001 [121][f]	7	8	80 vs. 72	86% vs. 13%	NA	NA	NA
Cho et al., 2003 [115][g]	10	42	64 vs. 63	80% vs. 29%	NA	NA	NA
Maramattom et al., 2004 [116][h]	10	14	63 vs. 55	60% vs. 0%	NA	NA	NA
Yang et al., 2005 [122][i]	14	10	66 vs. 59	64% vs. 10%	64% vs. 10%	NA	NA
Wang et al., 2006 [117][j]	41	21	67 vs. 62	NA	NA	22% vs. 29%	NA

Authors	Patients treated with hypothermia	Patients treated with decompressive surgery	Mean age (years)	Mortality in hospital	Mortality up to 3 months	Mortality up to 6 months	Mortality up to 12 months
Georgiadis et al., 2002 [124]	19	17	56 vs. 52	47% vs. 12%	NA	NA	NA

Authors	Patients treated with decompressive surgery + hypothermia	Patients treated with decompressive surgery	Mean age (years)	Mortality in hospital	Mortality up to 3 months	Mortality up to 6 months	Mortality up to 12 months
Els et al., 2006 [125][k]	12	13	49 vs. 49	8% vs. 15%	8% vs. 15%	8% vs. 15%	NA

[a]Not randomised. All four patients in the nonintervention group had a dominant MCA infarction, and all nine patients in the intervention group had a nondominant MCA infarction.
[b]Not randomised. All patients were younger than 60 years. There is a selection bias because conservatively treated patients were not regarded as being suitable for surgery.
[c]Not randomised. These studies represent the largest case series in the literature using the case series of Hacke and colleagues (1996) [3] as historical control group. Mortality rates of early versus delayed surgery were 16% versus 34%.
[d]Not randomised. There is a selection bias by advanced age and more comorbidity in conservatively treated patients. All patients were older than 55 and younger than 75 years.
[e]Not randomised. There is a selection bias because treatment decision was based primarily on the consent by the patient´s relatives. Some patients received internal decompression.
Mortality rates of early versus late surgery were 19% versus 28%. The case series of 2004 included the patients of the case series of 2001.
[f]Not randomised. The study used historical controls.
[g]Not randomised. Mortality rates of ultra-early (<6 hours) versus delayed surgery were 8% versus 37%.
[h]Not randomised. Hemicraniectomy was performed only in patients, who deteriorated clinically.
[i]Not randomised.
[j]Not randomised. There was no difference between late and early hemicraniectomies.
[k]Randomised. Twelve patients received mild hypothermia (35°C) in addition to hemicraniectomy. In the group treated by hemicraniectomy alone more patients had a right-sided infarction and additional infarction of the ACA or PCA.
ACA, anterior cerebral artery; NA, not available; PCA, posterior cerebral artery.

hypothermia plus hemicraniectomy with hemicraniectomy alone [125] (Tables 4 and 5).

Various trials suggest that decompressive surgery not only reduces mortality but also increases the number of patients

Table 5

Mortality data in patients with malignant middle cerebral artery infarction: studies with reviews on conservative treatment versus decompressive surgery

Authors	Patients treated with conservative treatment	Patients treated with decompressive surgery	Mean age (years)	Mortality
Gupta *et al.*, 2004 [123]	-	138	50	Overall mortality 24% (follow-up 7-21 months)
Morley *et al.*, 2002 [137]		Gives an overview on available data. No trial fulfills the criteria of a randomised controlled study design to be included in a meta-analysis.		

with independent functional outcome without increasing the number of severely disabled patients [109,111,115,118, 126]. Other studies doubt these results, especially in patients with increased age and with additional infarction of the ACA or PCA [116,117,122,127,128]. Among other predictors that have been proposed to predict unfavourable outcome are preoperative midline shift, low preoperative GCS, presence of anisocoria, early clinical deterioration, and internal carotid artery occlusion [129,130]. In the review by Gupta and colleagues [123], age was the only prognostic factor for poor outcome, whereas time to surgery, the presence of brainstem signs prior to surgery, and additional infarction of the ACA or PCA territory were not associated with outcome. Data from comparative studies and reviews are summarized in Tables 6 and 7.

These controversial results lead to constant discussion among experts about the benefit of decompressive surgery in malignant MCA infarction and to large regional differences in the application of the procedure. This dilemma could be resolved only by randomised trials. Since 2000, five randomised trials have been conducted: the American HeADDFIRST (Hemicraniecomy And Durotomy Upon Deterioration From Infarction Related Swelling Trial), the French DECIMAL (DEcompressive Craniectomy In MALignant middle cerebral artery infarcts) trial, the Dutch HAMLET (Hemicraniectomy After Middle cerebral artery infarction with Life-threatening Edema Trial), the Philippine HeMMI (Hemicraniectomy For Malignant Middle Cerebral Artery Infarcts) trial, and the German DESTINY (DEcompressive Surgery for the Treatment of malignant INfarction of the middle cerebral arterY) trial [16-18,131,132].

DESTINY and DECIMAL were stopped early in 2006, and the results were published recently [16,17]. In both trials, decompressive surgery significantly reduced mortality, but the primary endpoint in both trials, dichotomization of the modified Rankin scale (mRS) score of less than or equal to 3, failed to show statistically significant results. Nevertheless, both trials were stopped not only because of ethical considerations to continue randomisation, but also because of expectations of a prospectively planned pooled analysis of the three European trials (DECIMAL, DESTINY, and

HAMLET). This pooled analysis is the first in the field of stroke in which individual patient data from three different randomised trials were pooled while these trials were still ongoing. Of the 93 patients who were included, 51 were randomly assigned to decompressive surgery and 42 to conservative treatment. Results demonstrate that decompressive surgery (a) significantly reduces mortality (71% versus 22%, $p < 0.0001$, absolute risk reduction [ARR] 50%), (b) significantly increases the chance to survive with an mRS score of less than or equal to 4 (that is, not being bedridden and completely dependent) (24% versus 75%, $p < 0.0001$, ARR 51%), and (c) also significantly increases the chance to survive with an mRS score of less than or equal to 3 (that is, being able to walk and being independent in at least some activities of daily living) (21% versus 43%, $p < 0.014$, ARR 23%) (Figures 3 and 4) [133]. There is no statistically significant heterogeneity between the three trials, and the treatment effects remain essentially the same for all analyses if baseline differences between the treatment groups are taken into account. The resulting numbers needed to treat are 2 for survival, 2 for the prevention of an mRS score of 5 or death, and 4 for the prevention of an mRS score of 4 or 5 or death. Decompressive surgery was beneficial in all predefined subgroups, including age (dichotomized at 50 years), presence of aphasia, and time to randomisation (dichotomized at 21.5 hours), as measured by an mRS score of less than or equal to 4 at 12 months.

Summary
For many years, there has been no agreement among experts concerning the question of which treatment is beneficial in patients with malignant MCA infarctions. In comparison with the usually unsuccessful conservative treatment strategies, hypothermia and decompressive surgery seem to be much more promising therapies [9,53,95]. Although hypothermia has been demonstrated to be feasible in patients with large hemispheric infarctions, data on safety and efficacy are currently insufficient to recommend hypothermia in patients with malignant infarctions outside clinical trials [99,134].

Because of promising results from numerous case reports, retrospective case series, and a small number of prospective studies, decompressive surgery has already been increasingly

Table 6

Functional outcome data in patients with malignant middle cerebral artery infarction: studies with comparative data on conservative treatment versus decompressive surgery

Authors	Patients treated with conservative treatment	Patients treated with decompression	Mean age (years)	Dominant/ nondominant hemisphere	+ ACA and/or PCA	Mean time to surgery (hours)	Mean time to follow-up (months)	Independent outcome	Mild to moderate disability	Severe disability	Death
Delashaw et al., 1990 [118]	4	9	NA / 57	100%/0% / 0%/100%	NA / 56%	NA / NA	NA / 15	0% / 22%	0% / 22%	0% / 44%	100% / 11%
Steiger 1991 [119]	7	8	NA / NA	NA / NA	NA / NA	NA / NA	6 / 6	0% / 75%	0% / 75%	0% / 75%	100% / 25%
Rieke et al., 1995 [77] Hacke et al., 1996 [3] Wirtz et al., 1997 [104] Schwab et al., 1998 [109]	55	63	56 / 50	62%/38% / 17%/83%	22% / 35%	NA / 30	1 / 3	22% / 2%	22% / 40%	22% / 33%	78% / 25%
Mori et al., 2001 [120] Mori et al., 2004 [111]	21	50	72 / 65	52%/48% / 26%/74%	33% / 36%	NA / 63	6 / 6	5% / 10%	0% / 10%	24% / 56%	71% / 24%
Kuroki et al., 2001 [121]	7	8	80 / 72	NA / NA	NA / NA	NA / NA	NA / NA	14% / 87%	14% / 87%	14% / 87%	86% / 13%
Holtkamp et al., 2001 [114]	12	12	73 / 65	83%/17% / 25%/75%	67% / 42%	NA / 42	9 / 5	0% / 0%	0% / 0%	17% / 67%	83% / 33%
Cho et al., 2003 [115]	10	42	64 / 63	60%/40% / 52%/48%	50% / 38%	NA / 50	6 / 6	20% / 71%	20% / 71%	20% / 71%	80% / 29%
Maramattom et al., 2004 [116]	10	14	63 / 55	40%/60% / 22%/78%	0% / 71%	NA / 36	1 / 1	0% / 0%	10% / 38%	30% / 63%	60% / 0%
Yang et al., 2005 [122]	14	10	66 / 59	43%/57% / 30%/70%	57% / 60%	NA / 62	3 / 3	0% / 10%	0% / 30%	36% / 50%	64% / 10%
Wang et al., 2006 [117]	41	21	67 / 62	56%/44% / 38%/62%	NA / NA	NA / 48	6 / 6	0% / 0%	25% / 14%	54% / 57%	22% / 29%

Authors	Patients treated with hypothermia	Patients treated with decompression	Mean age (years)	Dominant/ nondominant hemisphere	+ ACA and/or PCA	Mean time to surgery (hours)	Mean time to follow-up (months)	Independent outcome	Mild to moderate disability	Severe disability	Death
Georgiadis et al., 2002 [124]	19	17	56 / 52	100%/0% / 0%/100%	26% / 24%	NA / 30	NA / NA	NA / NA	NA / NA	NA / NA	47% / 12%

Authors	Patients treated with decompression + hypothermia	Patients treated with decompression	Mean age (years)	Dominant/ nondominant hemisphere	+ ACA and/or PCA	Mean time to surgery (hours)	Mean time to follow-up (months)	Independent outcome	Mild to moderate disability	Severe disability	Death
Els et al., 2006 [125]	12	13	49 / 49	NA / NA	NA / NA	15 / 15	6 / 6	92% (median mRS 2) / 88% (median mRS 3)			8% / 12%

Functional outcome was classified as described in Table 2. ACA, anterior cerebral artery; NA, not available; PCA, posterior cerebral artery.

Table 7

Functional outcome data in patients with malignant middle cerebral artery infarction: studies with reviews on conservative treatment versus decompressive surgery

Authors	Patients treated with conservative treatment	Patients treated with decompression	Mean age (years)	Dominant/ nondominant hemisphere	+ ACA and/or PCA	Mean time to surgery (hours)	Mean time to follow-up (months)	Independent outcome	Mild to moderate disability	Severe disability	Death
Gupta *et al.*, 2004 [123]	-	138	50	20%/80%	32%	59.3	7-21	7%	35%	34%	24%
Morley *et al.*, 2002 [137]	Gives an overview on available data.										

No trial fulfills the criteria of a randomised controlled study design to be included in a meta-analysis.

Functional outcome was classified as described in Table 2. ACA, anterior cerebral artery; PCA, posterior cerebral artery.

Figure 3

Functional outcome after 12 months - conservative treatment (mRS)
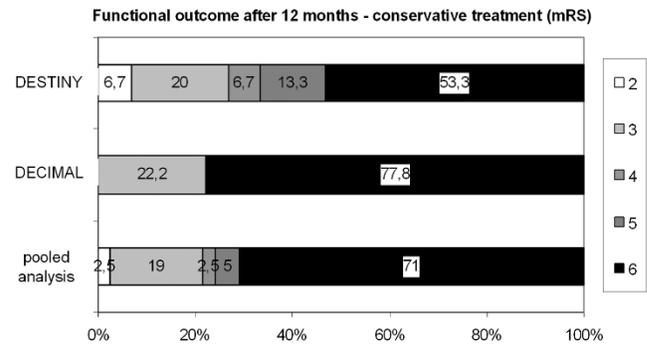
Mortality and functional outcome after conservative treatment in patients with malignant middle cerebral artery infarction. Results from randomised controlled trials. The pooled analysis includes 93 patients (all patients from DECIMAL and DESTINY and 23 patients from HAMLET). DECIMAL, DEcompressive Craniectomy In MALignant middle cerebral artery infarcts; DESTINY, DEcompressive Surgery for the Treatment of malignant INfarction of the middle cerebral arterY; HAMLET, Hemicraniectomy After Middle cerebral artery infarction with Life-threatening Edema Trial; mRS, modified Rankin scale.

Figure 4

Functional outcome after 12 months - hemicraniectomy (mRS)
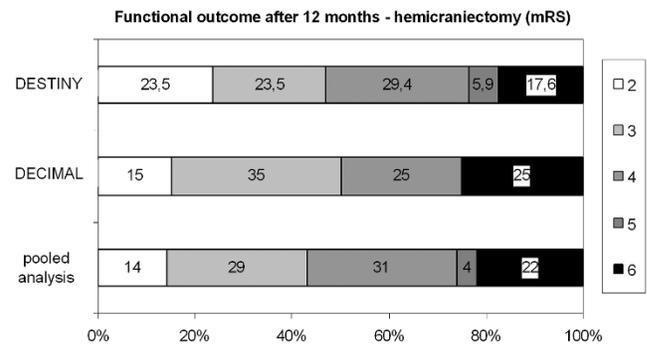
Mortality and functional outcome after hemicraniectomy in patients with malignant middle cerebral artery infarction. Results from randomised controlled trials. The pooled analysis includes 93 patients (all patients from DECIMAL and DESTINY and 23 patients from HAMLET). DECIMAL, DEcompressive Craniectomy In MALignant middle cerebral artery infarcts; DESTINY, DEcompressive Surgery for the Treatment of malignant INfarction of the middle cerebral arterY; HAMLET, Hemicraniectomy After Middle cerebral artery infarction with Life-threatening Edema Trial; mRS, modified Rankin scale.

incorporated into routine intensive care protocols [77,109, 123]. In 2007, the results from nonrandomised studies were confirmed by a pooled analysis of three randomised controlled trials, supporting the widespread opinion among experts that hemicraniectomy in malignant MCA infarction not only reduces mortality but also leads to an improved outcome of the survivors without increasing the number of completely dependent patients [133]. So far, early hemicraniectomy is the only effective treatment in malignant ischaemic stroke.

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Competing interests

The authors declare that they have no competing interests.

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