

Treatment of space-occupying cerebral infarction*

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Objective: Patients with a hemispheric infarct accompanied by massive edema have a poor prognosis; the case fatality rate may be as high as 80%, and most survivors are left severely disabled. Various treatment strategies have been proposed to limit brain tissue shifts and to reduce intracranial pressure, but their use is controversial. We performed a systematic search of the literature to review the evidence of efficacy of these therapeutic modalities.

Data Sources: Literature searches were carried out on MEDLINE and PubMed.

Study Selection: Studies were included if they were published in English between 1966 and February 2002 and addressed the effect of osmotherapy, hyperventilation, barbiturates, steroids, hypothermia, or decompressive surgery in supratentorial infarction with edema in animals or humans.

Data Synthesis: Animal studies of medical treatment strategies in focal cerebral ischemia produced conflicting results. If any,

experimental support for these strategies is derived from studies with animal models of moderately severe focal ischemia instead of severe space-occupying infarction. None of the treatment options have improved outcome in randomized clinical trials. Two large nonrandomized studies of decompressive surgery yielded promising results in terms of reduction of mortality and improvement of functional outcome.

Conclusions: There is no treatment modality of proven efficacy for patients with space-occupying hemispheric infarction. Decompressive surgery might be the most promising therapeutic option. For decisive answers, randomized, controlled clinical trials are needed. (Crit Care Med 2003; 31:617–625)

KEY WORDS: brain infarction; middle cerebral artery infarction; edema; intracranial pressure; surgical decompression; therapeutics

Large cerebral infarcts are commonly associated with variable degrees of brain edema. In severe cases, this may lead to transtentorial or uncal herniation. Fatal space-occupying brain edema occurs in 1–5% of all patients with a supratentorial infarct (1). Transtentorial herniation accounts for up to 78% of deaths during the first week after supratentorial infarction and up to 27% of deaths during the first 30 days (1, 2). In younger patients with ischemic stroke, herniation is the cause of about half of the deaths in the first month (3). In recent prospective intensive care–based series, the case fatality rate of space-occupying cerebral infarcts was about 80%, despite maximal conservative therapy (4, 5).

Various treatment strategies have been proposed to limit brain tissue shifts and reduce intracranial pressure (ICP),

such as osmotic therapy, hyperventilation, and sedation with barbiturates (6–8). In the guidelines of the American Heart Association, osmotherapy and hyperventilation are recommended for patients whose condition is deteriorating secondary to increased ICP or brain herniation (6). These treatment options are considered standard care by experts in various stroke centers worldwide. However, no trials have addressed the efficacy of these therapies to improve clinical outcome (9), and several reports suggest that these are ineffective (4, 5, 10) or even detrimental (11, 12). In this article, we will review the evidence of efficacy of therapeutic modalities that have been proposed to improve outcome after space-occupying hemispheric infarction.

MATERIALS AND METHODS

Literature searches were carried out on MEDLINE and PubMed, using a combination of keywords covering brain infarction, brain edema, and the different interventional options. Keywords related to brain infarction were stroke, cerebral infarction, and cerebral ischemia, and the alternatives presented in the thesaurus of MEDLINE. Keywords related to edema were brain edema, brain swelling, and their alternatives. Furthermore, relevant papers were checked for references. Studies were

included if they were published in English between 1966 and February 2002 and addressed treatment of edema in supratentorial focal cerebral ischemia in animals (Table 1) or humans (Table 2). Treatment modalities that have only been used in animals but not in humans were excluded.

RESULTS

Osmotherapy

Mannitol. Osmotic agents, such as mannitol, a cell-impermeable nonmetabolizable sugar, are presumed to draw water from interstitial and intracellular spaces into the intravascular compartment by creating an osmotic pressure gradient over the semipermeable blood-brain barrier (13). In addition to its osmotic capacity, reported effects of mannitol include reduction of blood viscosity and improvement of microvascular cerebral blood flow (14–17), vasoconstriction with a reduction in cerebral blood volume and ICP lowering (18, 19), and scavenging of free radicals (20).

In various animal studies, mannitol, administered before or within 24 hrs after the onset of transient or permanent focal cerebral ischemia reduced edema formation or ischemic damage (21–31). In a recent study, a trend toward a dose-

*See also p. 659.

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DOI: 10.1097/01.CCM.0000050446.16158.80

emic brain tissue (37), resulting in a worsening of tissue shifts. In cats with cortical cold injury, accumulation of mannitol in damaged brain tissue has been reported after five doses of 0.33 g/kg. In the edematous white matter the mannitol concentration exceeded the plasma concentration by a ratio of 2.69:1. This caused a reversal of the osmotic gradient and aggravation of cerebral edema (12). In other animal studies, rebound phenomena have been observed (37). These have been attributed to the longer elimination half-life of mannitol from cerebrospinal fluid, with a consequent temporary reversal of the serum/cerebrospinal fluid concentration gradient during elimination (38, 39).

In a clinical study in nine patients with recent ischemic stroke, single doses of 40 g of mannitol were effective in temporarily reducing elevated ICP to >10% below the baseline value in 10 of 14 episodes. The maximum effect occurred at the end of infusion, and the effect was visible over 4 hrs (8). In a recent series of seven patients with edema and midline shift due to hemispheric infarction, successive magnetic resonance imaging before, during, and after the administration of a bolus of mannitol (1.5 g/kg) did not reveal any change in tissue midline shifts, nor did the neurologic status of the patients change. Although these findings dispel some of the concerns of increases in mass effect after administration of mannitol, the clinical implications concerning either beneficial or harmful effects are limited, because the study did not address the effects of multiple dosing (40). Furthermore, subsequent analyses of hemispheric volumes of these patients revealed that there was a slight reduction in brain volume after mannitol treatment that was restricted to the noninfarcted hemisphere (41).

No randomized clinical trial has addressed the effect of mannitol on outcome in patients with space-occupying hemispheric infarction. One early prospective (42) and one retrospective (43) clinical study failed to show a significant benefit on outcome in patients with acute stroke. However, these studies were not based on computed tomography, and cases of cerebral hemorrhage could therefore have been included inadvertently. In addition, clinically different infarct subtypes were included, and treatment was not primarily aimed at reducing edema formation in large infarcts. In a systematic (Cochrane) review,

outcome analyses could not be performed due to lack of appropriate trials (44).

Glycerol. The sugar glycerol has been reported to improve cerebral blood flow (45, 46) and to have edema-reducing and neuroprotective properties (47). Only few experimental studies have addressed the effect of glycerol in cerebral infarction. In rat models of focal cerebral ischemia, the compound reduced edema (48–51). Glycerol has been tested in several randomized and nonrandomized clinical trials of acute stroke, but none of these specifically addressed its effect on space-occupying hemispheric infarction. A systematic (Cochrane) review of these trials suggests a favorable effect of glycerol treatment on short-term survival, but no long-term efficacy. The lack of proven benefit on long-term survival does not support the routine use of glycerol in patients with acute ischemic stroke (52).

Hypertonic Saline. Sodium chloride is actively excluded from an intact blood-brain barrier, which makes it a more desirable osmotic agent than mannitol (53). In a recent study of transient focal cerebral ischemia in rats, edema in both the affected and the unaffected hemisphere decreased after continuous hypertonic (7.5%) saline infusion started 24 hrs after induction of ischemia (54). In a comparable study, hypertonic saline increased rather than decreased infarct volume. Water content in the contralateral (non-injured) hemisphere was significantly less in the hypertonic saline-treated group than in the control group at 22 hrs of reperfusion, whereas there was no difference in water content of the injured hemisphere between the two groups (35).

In patients with space-occupying hemispheric infarction or putaminal hemorrhage with perifocal edema, single doses of hypertonic saline temporarily reduced elevated ICP (8). A temporary reduction of elevated ICP, leading to an increased cerebral perfusion pressure, was also seen in eight patients treated with 75 mL of 10% saline after conventional therapy with mannitol had failed. However, the group of patients described in this study was heterogeneous; six had space-occupying hemispheric infarction and two had supra-tentorial hemorrhage with edema (55). In addition, patients received different combinations of other ICP-lowering therapies (two with decompressive hemicraniectomy, four with hypothermia, and two with cerebrospinal fluid drainage via an intraventricular catheter), which makes the results diffi-

cult to interpret. No clinical trials have addressed the effect of hypertonic saline on functional outcome.

Furosemide. Loop diuretics such as furosemide may decrease ICP by decreasing total body water and increasing blood osmolality and thereby removing water from the edematous brain (56, 57). In two studies of experimental brain edema induced by cortical freezing in rabbits, furosemide significantly decreased ICP (58, 59). In rats with transient focal cerebral ischemia, furosemide (0.5 mg/kg every 5 hrs) reduced body weight but had no significant effect on the water content of the affected hemisphere (31). There have been no controlled clinical studies testing the effect of loop diuretics on outcome after ischemic stroke.

Barbiturates

Barbiturates may have neuroprotective properties by reducing the cerebral metabolic rate (60–62) and by acting as free radical scavengers (63, 64). Reduction of the cerebral metabolic rate and the subsequent lowering of cerebral blood flow and volume could theoretically reduce edema formation and lower ICP.

Barbiturate treatment ameliorated the clinical course and reduced lesion size in some animal studies of focal cerebral ischemia (65–71) but had no effect on edema and ICP in experimental space-occupying cerebral infarction (71–73). In baboons with permanent MCA occlusion, fatal ICP elevation was even seen more often after barbiturate treatment than in controls. On the other hand, barbiturates reduced mortality if ischemia was transient and if treatment was initiated within 30 mins after the onset of ischemia, before edema formation had occurred (70, 74).

Case studies suggested that barbiturate treatment may be effective to reduce intracranial hypertension caused by traumatic brain injury (75), cerebral ischemia during aneurysm surgery (76), or severe preeclampsia (77). However, in most clinical reports, the effect of barbiturates on brain swelling secondary to infarction was disappointing (78, 79). In the only prospective—but uncontrolled—clinical study on this subject, the usefulness of barbiturate coma in reducing elevated ICP after MCA infarction was limited (10). Barbiturate coma was induced with thiopental infusion in 60 patients with critically increased ICP secondary to

large hemispheric infarction, after failure of osmotherapy and mild hyperventilation. Although doses were high enough to achieve a burst-suppression pattern on the electroencephalogram and ICP was significantly lowered in the early phases after initiation of therapy, long-term control of ICP could not be achieved. Moreover, cerebral perfusion pressure decreased during the course of treatment. Only five of the 60 patients treated with thiopental survived; all other patients died from transtentorial herniation. Randomized trials are lacking.

Steroids

In very high doses, steroids have been claimed to have neuroprotective properties in ischemic stroke (80). In addition, corticosteroids reduce vasogenic cerebral edema in patients with brain tumors (81). There is no evidence from experimental studies that steroids reduce edema in cerebral infarction (82–85). This may be explained by the fact that edema in ischemic stroke consists of both a vasogenic and a cytotoxic component (86).

Dexamethasone improved outcome after acute stroke in a single placebo-controlled clinical trial (87), whereas in other clinical studies, no favorable effects of dexamethasone (42, 88–93) or prednisolone (94) treatment on clinical outcome were found. A meta-analysis of randomized trials comparing corticosteroid treatment with placebo in patients with acute ischemic stroke did not show a positive treatment effect on functional outcome (95). There are no trials that addressed the efficacy of steroids to reduce edema formation in space-occupying cerebral infarction.

Hyperventilation

Hyperventilation lowers ICP by inducing serum and cerebrospinal fluid alkalosis and vasoconstriction, thereby reducing cerebral blood flow and cerebral blood volume (96). However, the effect of hyperventilation may diminish within hours (97). Moreover, rebound vasodilatation with increases of ICP may occur if normoventilation is resumed (56). This may even induce a steal phenomenon if vasodilatation is more profound in healthy than in ischemic brain tissue (98).

Several clinical studies suggested that prolonged hyperventilation induces cerebral ischemia (99, 100) and worsens clin-

ical outcome in patients with traumatic brain injury (11). In primate models of focal brain ischemia, hypocapnia initiated after induction of ischemia did not alter mortality, degree of neurologic deficit, or volume of the infarct (101, 102). Clinical studies in the early 1970s addressing the effect of normocapnic (40 mm Hg) and hypocapnic (20–25 mm Hg) hyperventilation in stroke found no beneficial treatment effect on patient outcome (103, 104). In these studies, hyperventilation was continued for 72–74 hrs. More recent clinical trials are lacking.

Hypothermia

Hypothermia is presumed to reduce cerebral ischemic damage by means of reducing brain metabolism (105, 106), preservation of the blood brain barrier (107), a reduction in the inflammatory response (108), and a reduced neurotransmitter release (109–111). In a variety of animal studies, hypothermia reduced infarct size after focal cerebral ischemia (108, 112–125). In experimental studies of hypothermia in transient focal (126) or global (127) cerebral ischemia, a reduction of edema development during reperfusion was found. In only one early study of acute ischemic stroke in primates, hypothermia (29°C) had a detrimental effect: all treated animals had infarction with massive edema and died (102).

Two nonrandomized studies in patients with severe space-occupying edema after MCA infarction suggested that moderate hypothermia (32–34°C) on an ICU could help to control critically elevated ICP values and improve clinical outcome. Hypothermia was associated with several side effects, of which thrombocytopenia, bradycardia, and pneumonia were most frequently encountered. Most deaths occurred during rewarming as a result of excessive ICP rise and fatal herniation (128, 129). A shorter rewarming period was associated with a more pronounced rise of ICP (129). Rebound ICP rise could possibly be prevented by slow and controlled, instead of passive, rewarming (130). In a recent nonrandomized open pilot study of hypothermia in severe MCA infarction, cooling to $32 \pm 1^\circ\text{C}$ seemed to be safe. No significant improvement of functional outcome in the hypothermia-treated group was seen, but sample sizes were small and outcome trends favored hypothermia (131). Randomized trials have not been performed.

Surgical Decompression

Because of the limitations of medical therapies, there have been proposals for decompressive surgery in patients with neurologic deterioration caused by space-occupying hemispheric infarction. This therapy is presumed to revert brain tissue shifts, to normalize ICP, and to preserve cerebral blood flow, thus preventing secondary brain damage. The technique of decompressive surgery is relatively simple and consists of a large hemicraniectomy and a duraplasty (132). Animal studies have shown that this intervention reduces mortality and improves functional and histologic outcome (133–136).

Case reports and small retrospective or noncontrolled studies suggested that hemicraniectomy lowers mortality without increasing the number of severely disabled survivors (137–142). This finding has been confirmed in two recent prospective series, in which patients younger than 70 yrs with clinical and computed tomographic evidence of acute severe MCA infarction were included. Computed tomographic signs consisted of an early parenchymal hypodensity of >50% of the MCA territory. In the first series, decompression was performed in 32 patients after clinical deterioration consisting of a further decrease in consciousness. Mortality was reduced from 79% in controls to 34% in surgically-treated patients, and poor functional outcome from 95% to 50%. The mean interval between the onset of symptoms and surgery was 39 hrs (143). In a subsequent study, in which hemicraniectomy was performed in 31 patients within 24 hrs after the onset of symptoms, mortality was reduced even further, to 16%, without an increase in the number of severely disabled survivors (144). Complications of the operative procedure were generally not serious and had no effect on patient outcome. Parenchymal bleeding occurred more often with smaller bone resections (145). In another small prospective series of patients ($n = 19$), hemicraniectomy reduced mortality and improved short-term clinical outcome (Glasgow Outcome Scale at 3 months) as compared with a nonrandomized control group ($n = 15$) (146). Other reports suggest that decompressive surgery is less effective in elderly patients (147) and that substantial recovery extends into the second half year and thereafter (Figs. 1 and 2) (148).

The results of the two larger prospective studies (143, 144) suggest a substantial benefit of decompressive surgery as compared with medical therapy alone. However, groups were not constituted by random selection. Control groups consisted of patients with a significantly higher age, more comorbidity, and more frequent lesions in the dominant hemisphere than those in the surgical groups. In addition, information on functional outcome was insufficient (143, 144). Randomized trials have not been performed.

DISCUSSION

None of the therapeutic strategies proposed to control cerebral edema formation and to reduce tissue shifts and raised ICP after space-occupying ischemic stroke is supported by adequate evidence of efficacy from experimental studies or clinical trials. If any, experimental support for these strategies is derived from studies with animal models of moderately severe focal cerebral ischemia, whereas in large space-occupying infarcts, their effects may be different. Several studies indeed suggest that the beneficial effects of treatment with mannitol (24, 149–151), hypothermia (152, 153), or barbiturates (70) demonstrated in transient or moderate focal cerebral ischemia may be absent in cases of permanent or more severe ischemia.

In rats, edema formation after cerebral infarction seems to occur earlier than in humans. Lin et al. (154) performed histopathologic examination of rat brains at 6, 24, and 72 hrs and at 7 days after the onset of transient focal cerebral ischemia and found that brain water content peaked at 24 hrs after the onset of ischemia. In patients, clinical deterioration from serious edema formation usually occurs between the second and the fifth day after stroke onset (4, 155–157). This difference in the timing of edema formation may have consequences for the extrapolation of the results of rat studies into the clinic.

Most treatments are based on the perception that a raised ICP is the dominant cause of neurologic deterioration. However, displacement of brain tissue rather than increased ICP is probably the most likely cause of the initial decrease in consciousness and further neurologic deterioration (155). One study, in which ICP was monitored in 48 patients with clinical signs of increased ICP caused by large hemispheric infarction, showed that ICP

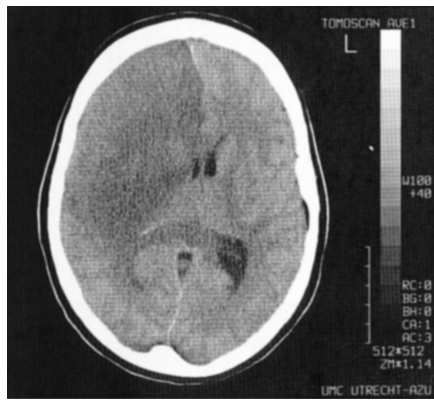


Figure 1. Computed tomographic scan of a 32-yr-old patient with a large infarct in the territory of the right anterior and middle cerebral arteries, accompanied by space-occupying edema and midline shift, 1 day after the onset of symptoms.

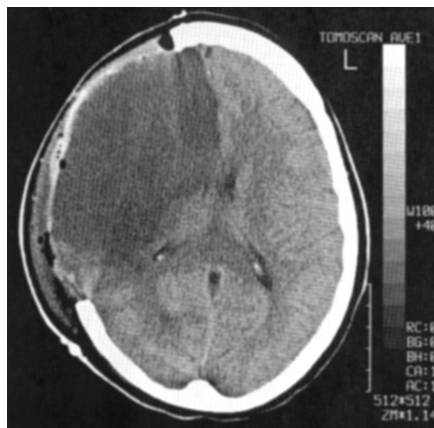


Figure 2. Computed tomographic scan of the same patient after decompressive surgery.

measurements were not helpful in guiding long-term treatment (158). Reducing ICP with osmotic agents or hyperventilation might even be harmful because the reduction in volume of the contralateral hemisphere, where the blood brain barrier and cerebral autoregulation are still intact, might be more pronounced than that of the infarcted hemisphere, thereby increasing brain tissue shifts (155). Moreover, osmotic agents like mannitol and glycerol may accumulate in the affected tissue, thereby reversing the osmotic gradient between tissue and plasma, leading to an exacerbation of edema (12). Therefore, the outcomes of osmotic treatment may be largely dependent on the timing and the duration of treatment (159).

According to the guidelines of the American Heart Association, patients with space-occupying cerebral infarction

There is no treatment modality of proven efficacy for patients with space-occupying hemispheric infarction.

whose condition is deteriorating secondary to edema formation should be treated with osmotic agents and hyperventilation (6). Other experts recommend decompressive surgery and hypothermia for the treatment of these patients. They suggest that early intervention generates better results in terms of mortality and functional recovery of survivors and that treatment should probably be started even before clinical deterioration in patients with massive infarction (160). There is no unequivocal evidence to support either opinion.

It remains unclear which patients should be candidates for intensive anti-edema treatment. Several variables have been studied as possible predictors of the development of fatal brain edema. An increased risk was found to be associated with clinical conditions such as a high National Institutes of Health Stroke Scale score at admission, early nausea and vomiting, hypertension, and heart failure, but the predictive value of the different conditions was weak (161, 162). Radiologic predictors of fatal brain edema include computed tomographic hypodensity of 50% or more of the MCA territory (161, 162) and lesion volume on diffusion-weighted MRI exceeding 145 cm³ (163). Although diffusion-weighted MRI has high sensitivity and specificity rates when performed within 14 hrs after stroke onset, the sensitivity of this variable may be considerably lower in earlier phases of the infarct (164). In these very early phases, other variables, such as a complete MCA territory perfusion deficit or MCA occlusion on magnetic resonance angiography may be more sensitive predictors of the development of malignant infarction (165, 166). An unambiguous decision based on one or on a combination of these variables cannot yet be made.

It also remains unclear whether patients with severe aphasia should be treated as aggressively as patients with-

out. Despite severe language disturbances, quality of life in these patients is not necessarily worse than in other patients (167). In our opinion, patients with aphasia should therefore not be excluded from trials testing treatment strategies in space-occupying infarction.

In animal studies, hypothermia reduced infarct size very consistently. Furthermore, nonrandomized studies in patients with severe space-occupying edema after MCA infarction suggested that moderate hypothermia (32–34°C) can help to control critically elevated ICP values and to improve clinical outcome (128–130). Thus, hypothermia deserves further research as a measure to prevent and treat massive edema formation. Surgical decompression might be a promising treatment option, given the suggested large reductions in mortality (143, 144). Before implementation of the different proposed strategies as standard treatment modalities, data from randomized controlled clinical trials are needed. Multicenter randomized trials of decompressive surgery for space-occupying hemispheric infarction are on their way (168, 169).

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