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Safety and Therapeutical Benefit of Hemicraniectomy Combined with Mild Hypothermia in Comparison with Hemicraniectomy Alone in Patients with Malignant Ischemic Stroke

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Key Words
Malignant cerebral ischemia · Hemicraniectomy · Hypothermia

Abstract
Introduction: Both for hemicraniectomy and for hypothermia, several reports describe a beneficial effect in patients with malignant supratentorial cerebral ischemia. We compared the safety and the clinical outcome in patients with a malignant supratentorial infarction who were treated with hemicraniectomy alone (HA) or received a combination therapy with hemicraniectomy and hypothermia of 35°C (HH), respectively. ***Methods:*** In a prospective and randomized study, 25 consecutive patients were treated after an ischemic infarction of more than two thirds of one hemisphere by HA (n = 13 patients) or the HH combination therapy (n = 12 patients). Safety parameters were compared between both treatment groups, the clinical outcome was assessed during treatment and after 6 months. ***Results:*** Age, cranial CT or MRI findings, initial National institutes of Health Stroke Scale Score (NIHSSS) and level of consciousness were not significantly different between both groups. Hemicraniectomy was performed within 15 ± 6 h after the ischemic event. Hypothermia was induced immediately after surgery. Overall mortality was 12% (2/13 vs. 1/12 in the two groups), but none of these 3 patients died due to treatment-related complications. There were no severe side effects of hypothermia. Duration of need for intensive care or for mechanical ventilation and infectious status did not differ significantly between both groups, but the need for catecholamine application was increased in the HH group. The clinical outcome showed a tendency for a better outcome in the HH compared with the HA group with respect to status after 6 months, as assessed by the NIHSSS (10 ± 1 vs. 11 ± 3, $p < 0.08$). ***Discussion:*** The present study suggests that a combined therapy of mild hypothermia and hemicraniectomy in malignant brain infarction does not imply additional risks by side effects and improves functional outcome as compared with hemicraniectomy alone.

Introduction

Stroke is still the second most frequent cause of death in western countries [1]. About 3–10% of patients with severe supratentorial stroke develop space-occupying

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peri-ischemic edema with subsequent transtentorial herniation and brainstem compression [2]. Hemicraniectomy has been shown to be a helpful procedure to reduce mortality to about 5–27% [3, 4] as compared with about 80% in conservative treatment [2, 5] so that hemicraniectomy seems to decrease the mortality rate and to improve the functional outcome of the patients although prospective randomized studies are still missing. A different therapeutic approach is induction of hypothermia. After several experimental studies [6–8], first human studies showed a beneficial effect of hypothermia in malignant brain infarction by reducing the mortality to about 45% [4, 9, 10]. The pathophysiological mechanism is unknown but may be due to a reduction of cerebral metabolism [11] combined with a reduction of cerebral oxygen demand [12] and cerebral blood flow [13], a decrease in the release of excitatory amino acids and stabilization of cell membrane and blood-brain barrier function [14]. However, human studies have shown that the benefit may be associated with an increased risk of side effects [4, 10]. The aim of this prospective study was therefore to investigate safety, feasibility and the beneficial effect of hemicraniectomy combined with immediate hypothermia (HH) in comparison to hemicraniectomy alone (HA) in order to analyze potential synergistic effects in stroke treatment to improve the patient outcome.

Methods

From June 2000 until June 2003, 25 consecutive patients with severe supratentorial ischemic stroke who fulfilled all inclusion criteria were enrolled in the study and were treated with hemicraniectomy alone (n = 13; HA group) or with a combination therapy of hemicraniectomy and hypothermia of 35°C (n = 12; HH group), respectively. The protocol was approved by the Ethical Committee of the Faculty of Medicine at the University of Freiburg. Patients were randomized to one of the treatment options. All patients were screened according to a standardized stroke protocol and were included in the study if fulfilling the following criteria: typical clinical signs for a large supratentorial infarction (National Institute of Health Stroke Scale Score, NIHSSS, >15 for right-hemispheric stroke and NIHSSS >20 for left-hemispheric stroke), signal changes in early diffusion-weighted and perfusion-weighted MRI involving >2/3 of the hemisphere without mismatch [15], age <65 years, no preexisting disability (Karnofsky Performance Status >70), no dementia and no tegmental syndrome. The extent of infarction was evaluated on the basis of the initial diffusion- and perfusion-weighted MRI. Clinical assessment was based on the NIHSSS, Barthel Index and modified Rankin Scale, which were applied immediately after admission and then 180 days after the event.

Additional medical treatment was similar in both groups with administration of crystalloid/colloid fluids or catecholamines to maintain a mean blood pressure of 90–110 mm Hg. Fluid homeostasis was maintained aiming at a central venous pressure between 8 and 12 cm H_2O. Blood glucose was kept between 120 and 150 mg% by intravenous insulin administration if necessary. All patients received a sedation according to a Ramsay score of 4–5 [16] with midazolam and fentanyl in combination with clonidine. Relaxation according to the train of four concept was achieved by repeated intravenous bolus administration of pancuronium. Patients were ventilated with a volume-controlled pressure-regulated mode, and pCO_2 was kept between 36 and 40 mm Hg (Evita IV, Dräger, Lübeck, Germany). The patients were positioned in bed with the upper part of the body raised by about 30°. No further drug treatment for brain edema was used.

In all patients of the HH group, mild hypothermia (35°C) was induced immediately after the operation and was achieved by an intravenous cooling device in 10 patients and by an external cooling device in 2 patients, respectively. The intravenous cooling device consisted of a 8.5-french intravenous catheter line (Icy, Cool Gard Perfusion Set, Alsius, Calif., USA), which was inserted into the inferior vena cava via the femoral vein and ended in three balloons which were perfused with cooled sterile saline solution. The cooling line was connected to a mobile temperature management device that could adjust the saline temperature depending on the patient's temperature. The remaining 2 patients received external cooling using a thermo wrap (Allon System, MTRE Advanced Technologies Ltd., Israel) in combination with cool ventilator air fanning of the body surface, administration of cooled saline infusions and cooled bladder lavage. All patients were cooled for 48 h. The target temperature of 35°C was reached within 2 ± 1 h (range 1.5–3.5 h) and controlled by repeated ear and continuous esophageal temperature probes. Active rewarming was attempted by a rate of 1°C/24 h. The patients of the HA group were kept normothermic (<37.5°C). Possible side effects of hypothermia as described by Schwab et al. [10], such as pneumonia, bradycardia (<40/min), cardiac arrhythmia or arterial hypotension (mean arterial blood pressure <80 mm Hg), were repeatedly controlled for. Platelet count, coagulation parameters and serum levels of urea and creatinine, liver and pancreas enzymes were determined twice a day. All patients underwent blood gas analysis including electrolytes every 2 h.

Decompressive craniectomy was performed as described by Schwab et al. [4] and Delashaw et al. [17]. In brief, the skull was opened at a diameter of about 14 cm in the frontotemporal line and about 10 cm in the temporoparietal line including the frontal, parietal, temporal and partially the occipital squama. The dura was then opened, and a lyophilized cadaver dura or homologous fascia was brought in underneath the open dura. Palacos reconstruction was performed 6 months after the procedure.

The following parameters were determined: duration of stay in the ICU, duration of need for mechanical ventilation and duration and maximal dose of catecholamine treatment. Mortality assessment was differentiated into death as a consequence of treatment-related problems (e.g. pneumonia, arrhythmia, cardiac failure, coagulopathy disorders including sepsis [18], pulmonary embolism) or peri- or intraoperative complications (e.g. intraoperative bleeding, postsurgical secondary intracerebral hemorrhage, subdural hematoma, infection of the wound).

Normally distributed data are expressed as means ± SD. Multivariable analysis was performed with logistic regression analysis. The Mantel-Haenszel χ^2 test was performed to compare variables. Data were considered significant at $p < 0.05$.

Table 1. Clinical data, NIHSSS, Barthel Index, modified Rankin Scale and treatment parameters in patients treated with HA or HH

	All	HH group	HA group	p value
Number	25	12	13	
Mortality, %		8% (1/12)	15% (2/13)	n.s.
Age, years	49 ± 10	49 ± 12	49 ± 6	n.s.
Time interval to start of hemicraniectomy, h	15 ± 6	15 ± 6	15 ± 6	n.s.
NIHSSS at admission	19 ± 2	18 ± 2	19 ± 2	n.s.
NIHSSS after 6 months	11 ± 2	10 ± 1	11 ± 3	0.08
Barthel Index after 6 months	75 ± 16	81 ± 14	70 ± 17	<0.1
Modified Rankin Scale after 6 months	2 ± 1	2 ± 1	3 ± 1	<0.18
Duration of ICU treatment, days		7 ± 2	7 ± 2	n.s.
Duration of mechanical ventilation, days				n.s.
Mean		112	119	
Range		73–156	84–163	
Maximal norepinephrine dosage, mg/h				0.051
Mean		0.9	1.3	
Range		0.5–1.4	0.7–2.7	

Results

Patients and Mortality

Of the 25 patients included in the study, 10 were female (6 vs. 4 in the HH and the HA groups, respectively). Sixteen patients (7/9) had suffered from a nondominant infarction of the middle cerebral artery (MCA) territory, 3 (1/2) of them showed additional involvement of the anterior cerebral artery or posterior cerebral artery territory. That is, there were more patients in the HA group who suffered from a right-sided infarct, which may result in a lower NIHSSS in this group, and there were more patients in the HA group with an additional infarct of the anterior or posterior cerebral artery which may result in a higher NIHSSS and a decreased Barthel Index in this group. Table 1 shows demographic data of the patients and the characteristics of infarction, figure 1 shows a typical imaging workup of a malignant cerebral ischemia in one of the patients. Twelve patients were included in the HH group and 13 in the HA group.

Three patients (1/2) died within the first week after the ischemic event due to myocardial infarctions (1/1) and pulmonary embolism (0/1). There were no statistical differences between the HH and HA groups in the NIHSSS at admission (18 ± 2 and 19 ± 2), age [49 ± 12 years (range 27–62) vs. 49 ± 6 years (range 41–59)] or time between the ischemic event and hemicraniectomy (15 ± 6 vs. 16 ± 6 h).

Clinical Outcome

No significant differences could be found in the number of deaths between both groups. Clinical outcome as measured by the NIHSSS (10 ± 1 vs. 11 ± 3 for HH vs. HA group, $p = 0.08$), and the Barthel Index (81 ± 14 vs. 70 ± 17, $p < 0.1$) showed a trend in favor of the combination treatment. Both groups differed at $p < 0.18$ with respect to the modified Rankin Scale (2 ± 1 vs. 3 ± 1).

None of the variables age, sex, side of infarction, time between ischemia and operation, and NIHSSS at admission showed any predictive value for the clinical outcome in the multivariable regression analysis.

As representative examples, two brief case histories are given in the following.

Case 1. A 27-year-old woman suffered an acute high-grade right-sided hemiparesis and aphasia (NIHSSS 21). Diffusion-weighted MRI revealed a malignant left-sided MCA infarction, due to cardiac embolism after cardiovalvulitis. Intra-arterial thrombolysis brought about no recanalization of the occluded MCA. Therefore, the patient was immediately cooled to 35°C and a large decompressive surgery was performed 16 h after the event. The patient could be extubated a few days after the operation and was transferred to a rehabilitation center 10 days later where she stayed for 4 months. The patient was able to perform all activities of daily living by herself afterwards and returned to work in an office with a residual NIHSSS of 7.

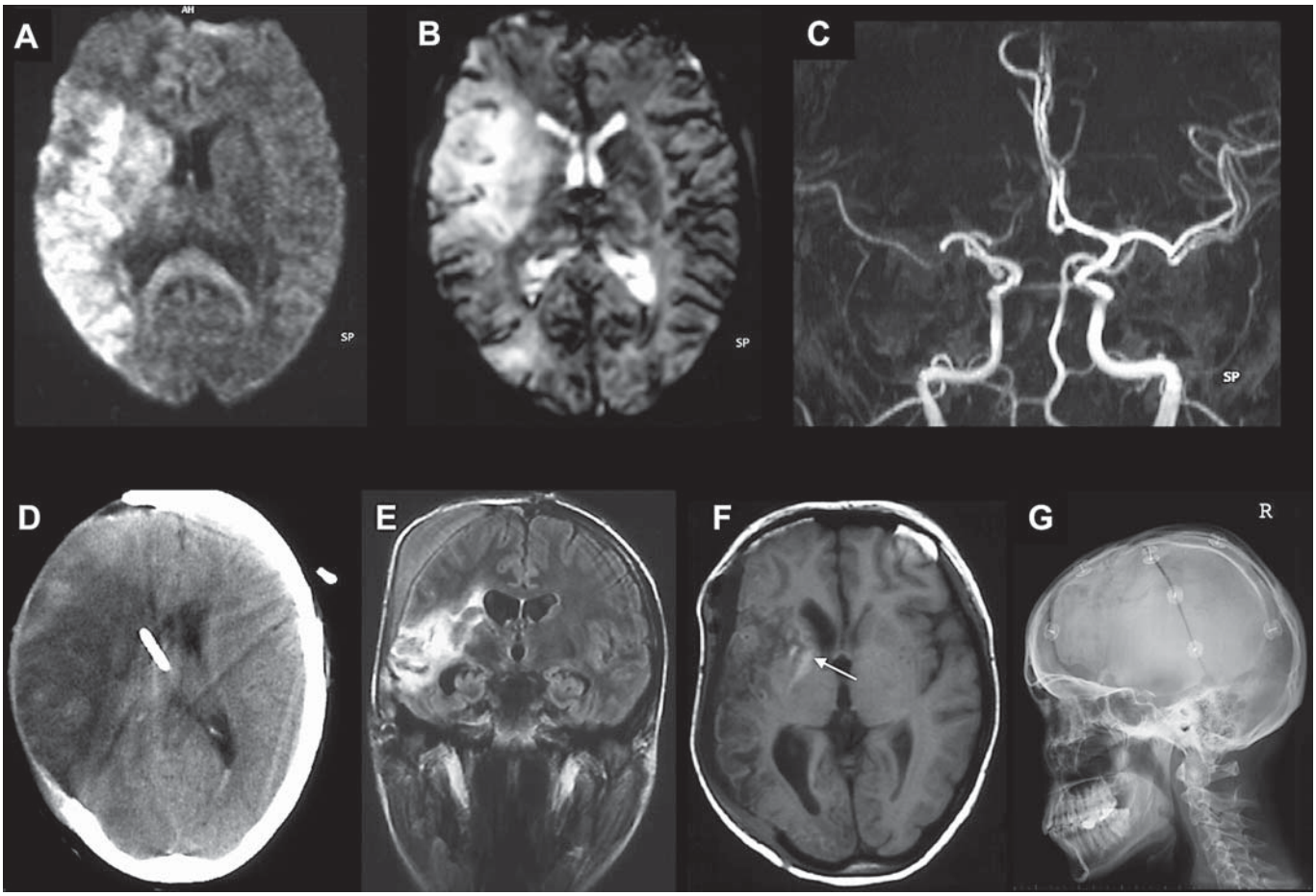

Fig. 1. A Typical diffusion-weighted MRI of a 27-year-old woman who was admitted to the hospital 4 h after the start of symptoms due to a cardiac embolism after cardiovalvulitis. **B** Corresponding image of perfusion deficit in perfusion-weighted MRI in comparison to the hyperintense area in diffusion-weighted imaging. **C** MR angiography of the occluded MCA on the right side. **D** Craniotomy after severe brain swelling caused by malignant right MCA infarction. Thirty days after hemicraniectomy, MRI shows a chronic epidural hematoma and a small hemorrhagic transformation at the cortex and medial pallidum (arrow, **E**, **F**). **G** Palacos reconstruction 6 months after the ischemic event. NIHSSS 21 at admission, 7 at follow-up 6 months later.

Case 2. Twelve hours after developing a malignant right-sided MCA infarction due to a coagulation disorder in the course of systemic lupus erythematosus, a 47-year-old man was admitted to our hospital (NIHSSS 19). MRI revealed a complete MCA infarction, and decompressive surgery was performed 19 h after the event. Hypothermia was induced via a femoral catheter immediately after the operation. The patient could be extubated a few days later and could be mobilized soon to walk with assistance. Eighteen days after the event he was transferred to a rehabilitation center. After 6 months he showed an NIHSSS of 10 and was able to live with his family in a handicapped-accessible home. After 1 year, he started working half-time in an office.

Intensive Care Treatment and Side Effects

No severe side effects of treatment could be observed during the cooling or the rewarming phase. There were no statistical differences between both groups with respect to complications such as pneumonia or cardiac arrhythmia between both groups. No septic syndrome could be diagnosed according to the criteria of the American College of Chest Physicians [18]. Severe sinus bradycardia (<40/min) was observed in 3 patients (1/12 vs. 2/13),

whereas no arterial hypotension could be observed. Platelet count and blood coagulation parameters were constant during the whole procedure, as well as serum levels of liver and pancreas enzymes, electrolytes, creatinine and urea. No differences were observed in the durations of ICU treatment (7 ± 2 days in both groups) or in the duration of mechanical ventilation [mean 112 (range 73–156) vs. 119 (range 84–163) days] between both groups. There was a tendency for a higher amount of catecholamine application in the combined treatment group [max. dose of norepinephrine 1.3 mg/h (range 0.7–2.7) vs. 0.9 (range 0.5–1.4), p = 0.051]. Mean results of blood pressure, heart frequency, blood gas analysis and laboratory parameters did not significantly differ between the HA and HH groups. There were no severe clinical complications in both groups during the follow-up.

Discussion

Up to 10% of all supratentorial infarctions are characterized by increasing tissue swelling and peri-ischemic edema, which may be followed by an increasing mass effect and tissue shift followed by transtentorial herniation. The prognosis of these patients is poor, and the mortality rate may be as high as 50–80% despite conservative intensive care treatment [2]. It has been demonstrated in several studies since the first reports dating from 1956 that hemicraniectomy and durotomy after malignant hemispheric infarctions is an efficient way to relieve the mass effect associated with increased intracerebral pressure [3, 4, 19–24]. Hemicraniectomy seems to decrease the mortality rate and improves the functional outcome of the patients [3, 4, 19, 23, 25]. As an alternative therapeutic approach, hypothermia has been shown to have a beneficial effect in extensive stroke both in animal experiments [7, 8] and in clinical human studies [9, 10]. In the comparison between both approaches, it has been demonstrated that hemicraniectomy is more powerful as compared with hypothermia [9, 10]. Georgiadis et al. [9] reported a mortality of 12% in the hemicraniectomy group and 47% for patients who received hypothermia alone. A similar mortality rate of 44% for hypothermia was reported by Schwab et al. [10] in a study with an interval of 14 h after onset of ischemic stroke and initiation of hypothermia. The present study is the first investigation of a combined therapy approach of hypothermia and hemicraniectomy in order to compare whether the combination adds any benefit to hemicraniectomy alone in patients with malignant supratentorial infarctions.

Both treatment groups did not differ in terms of age, sex, time between ischemia and surgery, extent of cerebral infarction and in the screening NIHSSS. In contrast to recent studies [9, 10], we did not find any severe side effects of hypothermia; in particular no uncontrollable blood pressure changes could be observed, probably due to the strict rewarming protocol. In addition the absence of any severe side effects might have been due to the use of a mild hypothermia of 35°C instead of a moderate hypothermia of 33°C, since severe complications were reported to occur more frequently using moderate hypothermia [9, 10]. The only difference in the HH group compared with the HA group was an increased demand of catecholamines to maintain blood pressure at the demanded level, perhaps due to a stronger vasodilatation after application of pancuronium for muscle relaxation in the HH group.

Clinical outcome showed a trend for a better outcome in the HH group as compared with the HA group according to the NIHSSS and the Barthel Index after 6 months which are measures of the functional outcome. This observation may be the result of the additional beneficial effect of the mild hypothermia therapy in combination with the hemicraniectomy. Compared with the literature, the mortality rate was relatively low overall and similar in both groups. However, in these studies patients received only hypothermia and not additional decompressive hemicraniectomy so that a comparison with respect to mortality between the present investigation and studies by Georgiadis et al. [9] or by Schwab et al. [10] is not possible. In previous studies, mortality for hypothermia alone was 47% [9] or 38% in a multicenter observational study, respectively [10]. However, fatal side effects in the rewarming phase accounted for 21% of the deaths. In contrast, we did not observe any fatal side effects in our mild hypothermia protocol. However, the rather small sample size of the present study does not allow definitive statements on this issue, all the more since the mean age in our group (48.9 years) was lower than the age in the studies reported by Georgiadis et al. (56 years) [9] or Schwab et al. (54 years) [10]. Another cause may be the less pronounced rebound effect in the rewarming period after hemicraniectomy. Animal experimental studies have shown an exacerbation of axonal injury after uncontrolled, rapid rewarming of cerebral tissue [26, 27], which is followed by disturbances of cerebral microcirculation, further vessel dilatation, an increase in the cerebral metabolic rate for oxygen, temporarily unmatched by cerebral blood flow [28], and impairment of the vascular smooth muscle as well as the endothelium [29], whereas

a slow rewarming showed no rebound effect [29]. Therefore, we applied a slow, feedback-controlled rewarming protocol.

The mortality rate in the HA group was similar to previous studies (Georgiadis et al. [9] published a rate of 12% and Mori et al. [3, 22] one of 16%). The lower mortality rate in recent studies as compared with early studies (5%/27%/21%/28%) [3, 4, 30, 31] may be due to improved surgical expertise. An additional cause for the low mortality rate in both groups in the present study may be the very short interval between the onset of ischemic symptoms and the start of the specific treatment (14.9 ± 5.6 h) as compared with previous studies (mean intervals, 30 h for hemicraniectomy, 24 h in the hypothermia group in the study of Georgiadis et al. [9]; delay in the early hemicraniectomy group of 21 h in the study by Schwab et al. [10]; interval of about 60 h in the study of Walz et al. [19]).

In conclusion, we could observe that hemicraniectomy in combination with mild hypothermia showed fewer side effects and can be considered therefore as an additional treatment option in patients with malignant supratentorial infarctions compared with the established technique of hemicraniectomy alone. Due to the rather mild hypothermia, severe side effects could be avoided. The rather small sample size did not allow to find a significant clinical benefit for the combined treatment; however, there seems to be a trend which makes multicenter studies with larger numbers of patients necessary to investigate if quality of life might be improved and a higher degree of independence in the activities of daily living might be achieved in patients after malignant ischemic stroke.

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