Hypothermia Reduces Perihemorrhagic Edema After Intracerebral Hemorrhage

Rainer Kollmar, MD*; Dimitre Staykov, MD*; Arnd Dörfler, MD; Peter D. Schellinger, MD; Stefan Schwab, MD; Jürgen Bardutzky, MD

Background and Purpose—The prognosis of spontaneous intracerebral hemorrhage (sICH) is poor because of the mass effect arising from the hematoma and the associated peri-hemorrhagic edema, leading to increased intracranial pressure. Because the efficacy of surgical and anti-edematous treatment strategies is limited, we investigated the effects of mild induced hypothermia in patients with large sICH.

Methods—Twelve patients with supratentorial sICH >25 mL were treated by hypothermia of 35°C for 10 days. Evolution of hematoma volume and perifocal edema was measured by cranial CT. Functional outcome was assessed after 90 days. These patients were compared to patients (n=25; inclusion criteria: sICH volume >25 mL, no acute restriction of medical therapy on admission) from the local hemorrhage data bank (n=312). Side effects of hypothermia were analyzed.

Results—All patients from both groups needed mechanical ventilation and were treated in a neurocritical care unit. All hypothermic patients (mean age, 60±10 years) survived until day 90, whereas 7 patients died in the control group (mean age, 67±7 years). Absolute hematoma size on admission was 58±29 mL (hypothermia) compared to 57±31 mL (control). In the hypothermia group, edema volume remained stable during 14 days (day 1, 53±43 mL; day 14, 57±45 mL), whereas edema significantly increased in the control group from 40±28 mL (day 1) to 88±47 mL (day 14). ICH continuously dissolved in both groups. Pneumonia rate was 100% in the hypothermia group and 76% in controls (P=0.08). No significant side effects of hypothermia were observed.

Conclusions—Hypothermia prevented the increase of peri-hemorrhagic edema in patients with large sICH. (Stroke. 2010; 41:1684-1689.)

Key Words: edema ■ hypothermia ■ intracerebral hemorrhage ■ intracranial pressure

Intracerebral hemorrhage (ICH) causes 10% to 15% of first-ever strokes and is usually associated with a poor outcome. The 30-day mortality rate accounts up to 52%. Major factors contributing to the unfavorable prognosis during the acute phase of spontaneous intracerebral hemorrhage (sICH) are the size of hematoma, rebleeding or hematoma expansion, and intraventricular hemorrhage. After the acute phase, high morbidity and mortality are essentially caused by the evolution of a peri-hemorrhagic, space-occupying edema associated with gradually increasing intracranial pressure (ICP). Although the natural course of edema formation is still not fully understood, edema commonly increases strongly during the first week and reaches its maximum during the second week after bleeding onset.

To date, there is no effective therapy for spontaneous ICH. Large randomized trials targeting the intracerebral blood clot failed to demonstrate benefits, including hematoma evacuation or factor VIIa treatment. Similarly, there is no proven therapy of peri-hemorrhagic edema. However, experimental and clinical data indicate that induced hypothermia is useful for neuroprotection and the treatment of cerebral edema after acute brain injury, such as ischemic stroke, brain trauma, and global cerebral ischemia after cardiac arrest.

Recent experimental studies suggest that hypothermia also has neuroprotective effects after ICH and can considerably reduce edema formation by various mechanisms. However, substantial clinical data on the use of therapeutic hypothermia for ICH are lacking.

Therefore, we investigated the effects of mild hypothermia (35°C) over a period of 10 days in patients who require intensive care treatment because of large (>25 mL) supratentorial sICH.

Subjects and Methods

Patient Selection

The cooling management protocol of this prospective pilot study was approved by the local ethics committee. Because a hematoma size of
~30 mL is considered as the crucial value for high morbidity and mortality, all patients with a supratentorial intracerebral hematoma $>25$ mL who required intensive care were included. Exclusion criteria were international normalized ratio $>1.4$, known coagulopathy; ICH caused by trauma, intracerebral tumor, or vascular malformation; infratentorial ICH; enrollment $>12$ hours after symptom onset; and age younger than 18 years. A total of 12 consecutive patients were treated by mild hypothermia.

Patients with sICH in the control group were identified from our prospectively organized ICH database (since 2007; n = 312). To minimize matching bias, inclusion criteria were supratentorial ICH with a hematoma size on the cranial CT at admission of $>25$ mL and no acute decision on admission to stop further medical treatment. Of a total of 312 patients, 255 were excluded because of a hematoma size of $<25$ mL. From the remaining 57 patients, 3 patients were ruled out because of infratentorial ICH, and 7 patients were ruled out because of early (<36 hours) surgical hematoma evacuation. In the last step, 22 of the remaining 47 patients with early orders for limitation of care were excluded. Hence, 25 patients remained in the control group.

### Basic Management

All patients included in the historical control group received standard medical treatment according to the European Stroke Initiative guidelines for monitoring and treatment of ICH. All patients were mechanically ventilated because of poor level of consciousness or need for airway protection; midazolam was used for sedation and sufentanil was used for analgesia. Pethidine was used for treatment of shivering and Cisatracurium was used for neuromuscular blockade when necessary. According to our institutional standards of neurocritical care, ICP was recorded hourly using an external ventricular catheter. ICP increase ($>20$ mm Hg for $>15$ minutes) was treated with 125 to 250 mL of 20% Mannitol or 100 mL of 10% saline. Core body temperature was measured continuously with a Foley temperature bladder catheter.

### Endovascular Hypothermia

A 9.3-Fr, 38-cm catheter central line (ICY, IC-3893; Alsius) and a temperature management device (CoolGard 3000; Alsius) were used in this study, as described previously. Mild hypothermia was induced within 12 hours after symptom onset and continued for 10 days. However, patients were not treated by hypothermia within the first 3 hours after symptom onset. At a minimum time of 3 hours from symptom onset, target temperature was 35°C (bladder temperature). The standard rewarming rate was 0.5°C per 24 hours. No antipyretics were used during hypothermia.

### Management of Temperature in Controls

In the control group, tympanic temperature was measured every 6 hours and temperatures $>37.5$°C were treated with acetaminophen and metamizol.

### Imaging and Data Collection

According to our institutional protocol, all sICH patients requiring intensive care received cranial CT controls on days 1 to 3, day 6, day 11, day 14, and before discharge.

CT scans were performed on a fourth-generation CT scanner (Somatom; Siemens). Each CT scan consisted of 10 to 12 slices of 4.8-mm thickness for the scull base and 10 to 12 slices of 7.2-mm thickness for the cerebrum. Measurements of blood and edema volumes were performed using the Siemens Leonardo V semiautomatic software for volumetry. For this purpose, a region of interest was set by generously tracing the hemorrhage, including the perifocal hypodense area on each slice. The software then reconstructed a 3-dimensional dataset and added up all voxels within a threshold range set between 5 and 33 Hounsfield units for perifocal edema and

### Statistical Analysis

Statistical tests were performed with the SPSS 16.0 software package. Data are given as mean±standard deviation, if not indicated differently. Normality of distribution was tested using the Shapiro–Wilk and Kolmogorov–Smirnov tests. Absolute edema volumes were not distributed normally. Accordingly, single comparisons of absolute edema between the 2 groups at different time points were performed using the nonparametric Mann–Whitney U test. All other data, including relative edema values at all time points, were distributed normally. The unpaired t test was used for single comparisons of relative edema and ICH volumes between the 2 groups. A multifactorial analysis of variance (general linear model for variance analysis) was performed for between-group and within-group comparisons of the time course of relative edema in the hypothermia and match group. Frequency distributions were analyzed using the Fisher exact and $\chi^2$ tests. $P<0.05$ was considered significant.

### Results

#### Patient Characteristics

Twelve patients (7 male, 5 female) with a mean age of 60±10 years were treated with mild hypothermia. On admission, median Glasgow coma scale score was 5 (range, 3–10) and mean parenchymal hematoma volume was 58±29 mL. A total of 25 patients (15 male, 10 female) meeting the inclusion criteria of the control group were identified from the data bank. As shown in the Table, baseline characteristics on admission did not differ significantly between the hypothermia group and the historical control group.

Additional intraventricular hemorrhage was present in 8 patients of the hypothermia group and 14 patients of the control group (Table). Intraventricular hemorrhage was complicated by hydrocephalus in 1 patient of the hypothermia group and 4 patients of the control group ($P=1.0$, Fisher exact test). Hydrocephalus was treated with external ventricular drainage and intraventricular fibrinolysis consisting of administration of single doses of 4 mg recombinant tissue plasminogen activator up to a maximum of 20 mg, or until clearance of the third and fourth ventricles on CT was achieved.
Course of Temperature and ICP
The course of body temperature for both groups is illustrated in Figure 1. The temperature in the hypothermia group was 35.3°C ±0.2°C compared to 37.3°C ±1°C 12 hours after symptom onset. A target temperature of 35°C could be maintained for the entire time period of 10 days without significant changes.

An ICP increase (>20 mm Hg for >15 minutes) was not observed in any of the hypothermia patients during the 14-days period. In contrast, 11 (44%) of 25 control patients had ICP crises.

In-Hospital Mortality
In the control group, 6 patients (24%) died because of space-occupying edema and subsequent cerebral herniation during hospital treatment in the intensive care unit. One patient died in the rehabilitation hospital. None of the hypothermia-treated patients died during the hospital stay (Fisher exact test, 2-sided P=0.07).

Volume of the Hemorrhage
The mean volume of ICH on admission was 58±29 mL (range, 27–103 mL) in the hypothermia group and 57±31 mL (range, 26–129 mL) in the control group (P=0.98). A plot of the initial ICH volumes in both groups is shown in the Supplemental Figure available online at http://stroke.ahajournals.org. ICH volume gradually decreased over the next 14 days in both groups and showed no significant difference at the investigated days (Figure 2).

Volume of Peri-Hemorrhagic Edema
The course of edema evolution is shown in Figures 2, 3, and to 4. The peri-hemorrhagic edema volume on admission was comparable between the 2 groups (hypothermia group 53±43 mL vs control group 40±28 mL; P=0.26). In hypothermia patients, the peri-hemorrhagic edema remained essentially identical during the entire 14-days observation period (within-group comparison, analysis of variance, P=0.9). In contrast, in the control group, edema increased markedly already within the first 48 hours after sICH onset, and the within-group comparison (analysis of variance) showed a significant difference between relative edema at admission and all following time points (days 2–14: F=83.8, P<0.001). The between-group comparison of the time course of relative edema in the hypothermia and control groups revealed a statistically significant difference (analysis of variance, F=4.93, P=0.035).

Single comparisons at corresponding time points revealed a significantly larger absolute and relative edema volume in the control group as compared to the hypothermia group starting at day 3 and persisting on days 6, 11, and 14 (Figures 2 and 4).

Complications During Hypothermia
Respirator-associated pneumonia developed in all patients during hypothermia; severe pneumonia with the need for a fraction of inspired oxygen >0.5 occurred in 2 hypothermia patients. All patients could be sufficiently treated with antibiotics. In the control group, pneumonia was observed in 19 patients (76%; Fisher exact test, 2-sided P=0.08). Other complications during hypothermia were asymptomatic thrombocytopenia <100 000/uL in 4 patients, hypokaliemia in 2 patients, and shivering in 6 patients. No coagulopathy was observed as measured by international normalized ratio and partial thromboplastin time. Self-limited bradycardia episodes of <40 beats per minute occurred in 3 patients without the need for intervention. No local complications were observed during the use of catheters for endovascular cooling, and no catheter exchange attributable to catheter malfunction or infection was necessary.

Mortality and Outcome at Day 90
Although no patient in the hypothermia group died until day 90, 7 patients in the control group died (modified Rankin Scale [mRS] score, 6).

Out of the surviving patients (n=12) in the hypothermia group, 2 patients (16%) had mRS score of 3, 6 patients (50%) had mRS score of 4, and 4 patients (33%) had mRS score of 5.

Out of the surviving patients (n=18) in the control group, 2 patients (11%) had mRS score of 2, 2 patients (11%) had
mRS score of 3, 3 patients (17%) had mRS score of 4, and 11 patients (61%) had mRS score of 5.

Discussion

We report on the effects of mild therapeutic hypothermia in patients with large supratentorial sICH. The cooling regimen we used, namely endovascular cooling for 10 days with a target temperature of 35°C, was chosen for several reasons. With the mild level of hypothermia (35°C), we intended to minimize side effects of lowering body temperature. The period of 10 days was chosen to span the duration of treatment over the known critical phase of development of peri-hemorrhagic edema. Finally, endovascular cooling was superior to other approaches regarding maintenance of a constant body temperature over this relatively long period of time. Two major aspects emerge from our pilot study.

First, prolonged hypothermia for 10 days initiated within 12 hours after ICH onset was feasible and relatively safe, as compared to that in a historical control group. The type of complications observed in the present study were comparable to those described in previous studies on induced hypothermia in ischemic stroke patients, with pneumonia representing the most common side effect. However, pneumonia also was a frequent complication in the control group (76%). The high incidence most likely contributes to severe disease, including previously described central immunodeficiency syndrome and ventilator-associated pneumonia. However, pneumonia could be sufficiently treated in all patients. Importantly, prolonged hypothermia had no effect on coagulation parameters, such as international normalized ratio, partial thromboplastin time, or thrombocyte counts, and did not lead to hematoma expansion in any patient.

Second, hypothermia essentially stopped the progression of peri-hemorrhagic brain edema. This finding is of high significance. Although the mass effect of the initial hematoma is the major determent for high morbidity in the acute phase of sICH, the progressive evolution of peri-hemorrhagic edema represents the main factor for clinical deterioration in the subacute phase, and the growth of edema is strongly related to the size of underlying hematoma in sICH. Thus, in the present study, only patients with large hematoma (>$25 mL) were included because these patients were expected to likely have critical extent of peri-hemorrhagic edema in the course of the disease.

Because the natural evolution of edema is usually characterized by a marked increase during the first week, with the maximum occurring during the second week, hypothermia was induced early, within 12 hours, after bleeding onset and maintained for 10 days in all patients. Importantly, the effects of hypothermia on the peri-hemorrhagic brain edema

Figure 3. Representative CT scans for a patient in the control group (A) and in the hypothermia group (B) at days 1, 3, and 11. The yellow line surrounds the region of interest for volume calculation. Blue areas represent peri-hemorrhagic edema on a threshold base algorithm.

Figure 4. Relative edema is indicated by a ratio of absolute edema volume and initial hematoma volume. *P<0.05; **P<0.01.
were permanent and not transient. This finding is remarkable because rewarming of the patients could have led to a delayed increase of edema and associated increase of ICP, as seen in large cerebral infarcts.\textsuperscript{25,26}

Using this regimen, hypothermia was a highly effective anti-edematous therapy. Because the edema essentially stopped growing, no patient had episodes of critical ICP increase during the 14-day observation period. These effects were associated with excellent survival rate during the first 90 days after ICH. Notably, at this time, 8 of 12 patients (66\%) reached a mRS score of 3 or 4.

In contrast, 44\% in the control group with essentially identical baseline hematoma size had at least 1 episode of critical ICP increase and 6 patients died during intensive care unit stay because of the space-occupying edema progression, despite maximal medical treatment.

The presented clinical data are in accordance with experimental studies in which hypothermia decreased edema during the first 72 hours after experimental ICH.\textsuperscript{14–16} Because of the small study group and short observational time of 90 days, there is no clear evidence whether prolonged mild hypothermia also has neuroprotective effects, as have been observed after cardiac arrest and perinatal asphyxia.\textsuperscript{12}

Certainly, this study has limitations, mainly because of its pilot character. Only a small number of patients were treated by hypothermia, and outcome parameters were assessed after a relatively short interval of 90 days after ICH. In addition, we compared these patients to a historical control group from an ICH database.

However, the study was a pilot study to evaluate a novel treatment approach. Thus, it was designed as a feasibility and safety trial and not as a controlled randomized study to investigate efficacy on outcome. The comparison to a historical control group has clear limitations and does not allow definite interpretation and generalization of the observed data. However, to minimize bias by the matching procedure, we used simple inclusion criteria including hematoma volume and decision to treat the patient. In addition, 2 other major predictors for outcome in sICH patients, age and initial Glasgow coma scale score, were comparable between the groups. It can be argued that hypothermia would have been even more effective on outcome when started as soon as possible after symptom onset. Because even mild hypothermia might impair coagulation and therefore increase the hematoma size, we avoided treating patients by therapeutic hypothermia within the first 3 hours after symptom onset.

Still, the most important clinical finding was that all treated patients survived. In contrast, 28\% of historical controls had died after 90 days. These findings are promising because the overall prognosis of patients with this size of hematoma is poor.\textsuperscript{3,5}

**Conclusion**

In conclusion, mild hypothermia was feasible and safe in patients with severe supratentorial sICH, and it stopped edema growth without a rebound phenomenon during rewarming. Further clinical studies are needed to answer the question of whether mild hypothermia has anti-edematous effects after sICH and if it leads to improved functional outcome.

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**Disclosure**

None.

**References**


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