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ORIGINAL ARTICLE

Mild Prolonged Hypothermia for Large Intracerebral Hemorrhage

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Abstract
Background Perihemorrhagic edema (PHE) develops after intracerebral hemorrhage (ICH). It can worsen the clinical situation by its additional mass effect. Therapeutic hypothermia (TH) might be an effective method to control PHE, but has not been sufficiently studied in ICH patients.
Methods We report data on $n = 25$ consecutive patients with large supratentorial ICH (volume $>$ 25 ml) who were treated by mild TH of 35 °C for 8–10 days. Body temperature was controlled by endovascular cooling catheters. We followed the clinical course during hospital stay and measured volumes of ICH and PHE in regularly performed serial cranial computed tomography. Outcome was assessed after 3 and 12 months. These data were compared to a historical group of $n = 25$ patients with large ICH.
Results While PHE continuously increased in the historical control group up to day 10, PHE volumes in the hypothermia group remained stable. There was a significant difference from day 3 after symptom onset. Shivering (36 %) and pneumonia (96 %) were the most frequent complications during TH. Mortality rate was 8.3 % in TH versus 16.7 % in the control group after 3 months and 28 versus 44 % after 1 year.
Conclusions These data support the promising results of our first case series on TH in large ICH. TH prevents the development of PHE and its complications. Side effects of TH appeared often, but could be treated sufficiently. Therefore, TH might represent a new therapy for PHE after large ICH, but has to be further tested in randomized trials.

Keywords Intracerebral hemorrhage · Perihemorrhagic edema · Hypothermia

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Introduction

Spontaneous intracerebral hemorrhage (ICH) is the most devastating subform of stroke, causing high morbidity, mortality, and disability [1]. Several important factors including initial hematoma volume [2], hematoma enlargement [3], or the presence of intraventricular hemorrhage (IVH) [4] have been identified as predictors of poor outcome and high mortality after ICH. After the immediate damage caused by tissue disruption and compression by the hematoma, blood and blood breakdown products initiate a secondary cascade of blood–brain barrier damage and inflammatory processes in the tissue surrounding the hematoma, thereby leading to the development of perihemorrhagic edema (PHE) [5]. The question if PHE exerts a significant clinical impact after ICH is still not sufficiently studied and remains controversial [6, 7]. However, especially in larger ICH the additional mass effect caused by PHE seems to contribute to neurological deterioration [8], and PHE volume and growth seem to play a role as predictors of short-term mortality [9].

In a pilot study on 12 consecutive patients with large ICH, we could demonstrate that prolonged mild hypothermia reduces PHE growth after ICH and could possibly affect short-term mortality [10]. We now report our experience from 25 patients with large ICH who were treated with prolonged mild hypothermia and in whom

short- (3 months) and long-term outcome (1 year after the bleeding) was assessed.

Patients and Methods

Patient Selection

The cooling management protocol of this prospective study was approved by our institutional ethics committee, as previously described [10, 11]. Patients with a supratentorial ICH >25 ml who required intensive care were included. Exclusion criteria were international normalized ratio >1.4; known coagulopathy; ICH due to trauma, intracerebral tumor, or vascular malformation; infratentorial ICH; enrolment >24 h after symptom onset; and age < 18 years. Spontaneous ICH patients of the control group were identified from our prospectively organized ICH database. Patients with an ICH volume >25 ml who were not subjected to early do-not-treat or do-not-resuscitate orders and had received multiple (>3) follow-up CT in the course of treatment were included in the analysis.

Basic Management

All patients including the historical control group received standard medical treatment according to the European Stroke Initiative guidelines for monitoring and treatment of ICH [12]. All patients were mechanically ventilated, because of poor level of consciousness or need of airway protection; midazolam was used for sedation, and sufentanil for analgesia. Pethidine was used for treatment of shivering, and cisatracurium for neuromuscular blockade, when necessary. According to our institutional standards of neurocritical care, intracranial pressure (ICP) was recorded hourly using an external ventricular catheter or a parenchymal ICP probe. ICP increase (>20 mmHg for >15 min) was treated with 125–250 ml of 20 % mannitol or 100 ml of 10 % saline. Body core temperature was measured continuously with a Foley temperature bladder catheter. Brain temperature was not measured.

Endovascular Hypothermia

A 9.3 F 38-cm catheter central line (ICY®, IC-3893, Zoll Medical) and a temperature management device (Thermogard®, Zoll Medical), were used in this study as described previously [10]. Mild hypothermia was induced within 24 h after symptom onset and continued for 8–10 days. Target temperature was 35 °C bladder temperature. The standard rewarming rate was 0.5 °C per 24 h. No antipyretics were used during hypothermia.

Management of Temperature in Controls

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

Imaging and Data Collection

According to our institutional protocol, all ICH patients requiring intensive care received cranial CT controls on days 1, 2, and 3, between days 4 and 6, between days 7 and 10, and between days 11 and 14. CT scans were performed on a fourth generation CT-scanner Siemens Somatom. Semi-automatic analysis of blood and edema volumes were performed using a Siemens Leonardo workstation as previously described in detail [13]. Relative edema was calculated as a unitless ratio by dividing absolute edema volume by initial hematoma volume.

Assessment of Complications

Complications of endovascular hypothermia were closely monitored in the hypothermia group. Shivering, coagulation disorders, infections, and local complications at the catheter insertion site were recorded.

Assessment of Outcome

For the hypothermia group, a structured telephone follow-up questionnaire was completed with all patients or their relatives at 3 months and 1 year after symptom onset. For the control group, a single telephone interview was completed, because at the time point of follow-up more than 1 year from symptom onset had passed for all patients. Within this interview, early outcome was also discussed in detail, as far as possible.

Statistical Analysis

Statistical tests were performed with the SPSS 16.0 software package (www.spss.com). Data are given in mean ± standard deviation, if not indicated differently. Normality of distribution was tested using the Shapiro–Wilk and Kolmogorov–Smirnov tests. Normally distributed data were compared using Student's two tailed t test. Other data were compared using non-parametric tests. An analysis of variance (ANOVA) was performed for between group comparisons of the time course of absolute and relative edema between the hypothermia and control groups. The Bonferroni correction was used for multiple comparisons. Frequency distributions were analyzed using the Fisher's exact and Chi-square tests. A $p < 0.05$ was considered statistically significant.

Results

Twenty-five patients with large ICH, including 12 patients previously reported [10], were treated with prolonged mild hypothermia. Demographic, clinical, and radiological characteristics of the treated cohort and the historical control group are shown in (Table 1).

The course of PHE and ICH volumes in both groups is shown in (Fig. 1). PHE volume increased continuously during the course of follow-up in the control group and reached a plateau after 7–10 days. In the hypothermia group, PHE volumes remained stable. Starting from day 3 after symptom onset, PHE values were significantly larger in the control group, as compared to the hypothermia group. No significant rebound of PHE was observed in the hypothermia group during and after rewarming. However, one patient with a very large ICH volume (92 ml), experienced late edema rebound 4 days after being rewarmed and consecutively died of herniation.

The course of hematoma resolution was similar in both groups. Any hematoma enlargement in the first follow-up CT scan after initiation of hypothermia was observed in nine patients (36 %). The mean hematoma growth in those patients comprised 4.2 ± 3 ml (7.2 ± 2.9 % of initial ICH volume). One patient experienced more extensive hematoma growth (from 14.6 to 44.2 ml) before he was subjected to hypothermia, actually qualifying for participation in the study after early rebleeding and clinical deterioration.

Shivering was observed in nine patients (36 %) treated with hypothermia. Six of those patients had to be treated with neuromuscular blockade (Table 2). Twenty-four patients (96 %) suffered respirator-associated pneumonia. A complicated course with consecutive sepsis occurred in two patients. All infections could be treated sufficiently. Thrombocytopenia (thrombocyte count <100.000) occurred in four patients (16 %) during hypothermia and remained clinically asymptomatic. No severe thrombocytopenia (<50.000) was observed. Prothrombin time (PTT) increased to 38–45 s in five patients (20 %) during hypothermia and remained clinically unapparent. One patient (4 %) suffered local deep vein thrombosis at the site of catheter insertion. Another patient suffered pulmonary embolism, however, in this patient no deep vein thrombosis could be detected by means of ultrasound examination. The patient remained stable and could be discharged from the intensive care unit after 25 days. Two patients experienced short self limited episodes of bradycardia (<40 beats/min). In one patient atropine was administered after bradycardia and a single episode of asystole (<4 s) (Table 3).

One patient from the hypothermia group was lost to follow-up. For the remaining 24 patients from the

Table 1 Demographic, clinical, and radiological characteristics

	Hypothermia $n = 25$	Control $n = 25$
Age (years)	63 ± 9.3	67 ± 7.5
Male (*n*/%)	14/56	15/60
GCS (median, IQR)	3 (3–8)	4 (3–8)
ICH volume (ml)	54.4 ± 25	57.4 ± 31.1
PHE volume d1 (ml)	45.7 ± 33.5	40.0 ± 28.0
IVH present	18/25	14/25

GCS glasgow coma scale; *IQR* interquartile range; *ICH* intracerebral hemorrhage; *PHE* perihemorrhagic edema; *IVH* intraventricular hemorrhage

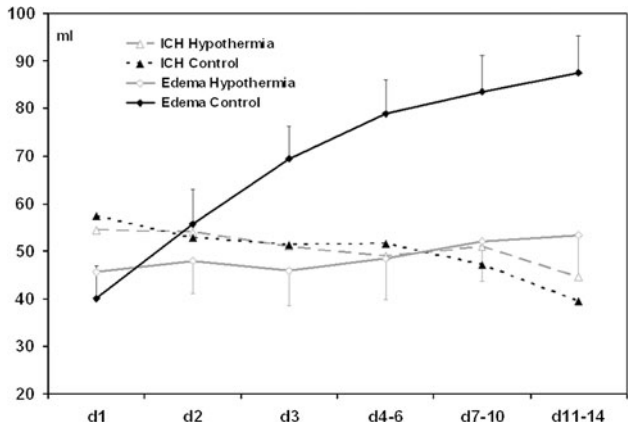

Fig. 1 Course of intracerebral hemorrhage and perihemorrhagic edema volumes in patients treated with prolonged mild hypothermia, as compared to controls. Significantly larger edema volumes in the control group were observed on day 3 (ANOVA, $F = 5.393$, $p = 0.025$), days 4–6 ($F = 6.873$, $p = 0.012$), days 7–10 ($F = 6.502$, $p = 0.015$), days 11–14 ($F = 6.314$, $p = 0.016$). *ICH* intracerebral hemorrhage

Table 2 Treatment characteristics

	Hypothermia $n = 25$	Control $n = 25$	*p*
Tracheostomy (*n*/%)	24/96	11/44	0.0001*
EVD (*n*/%)	17/68	13/52	0.39*
ICP probe (*n*/%)	5/20	0/0	–
Lumbar drainage (*n*/%)	5/20	6/24	1.0*
Pethidine (*n*/%)	9/36	–	–
Neuromuscular blockade (*n*/%)	6/24	–	–
LOS (days; mean ± SD)	27 ± 11	19 ± 11	0.02+

EVD external ventricular drainage; *ICP* intracranial pressure; *LOS* length of stay; *SD* standard deviation

* Fisher's exact test; "+" student's *T* test

Table 3 Complications

	Hypothermia $n = 25$	Control $n = 25$	p
Pneumonia (*n*/%)	24/96	19/76	0.1*
Sepsis (*n*/%)	2/8	0/0	–
Myocardial infarction (*n*/%)	0/0	1/4	–
Deep vein thrombosis (*n*/%)	1/4	0/0	–
Pulmonary embolism (*n*/%)	1/4	0/0	–
Bradycardia (*n*/%)	3/12	0/0	–
Thrombocytopenia (*n*/%)	4/16	0/0	–

* Fisher's exact test

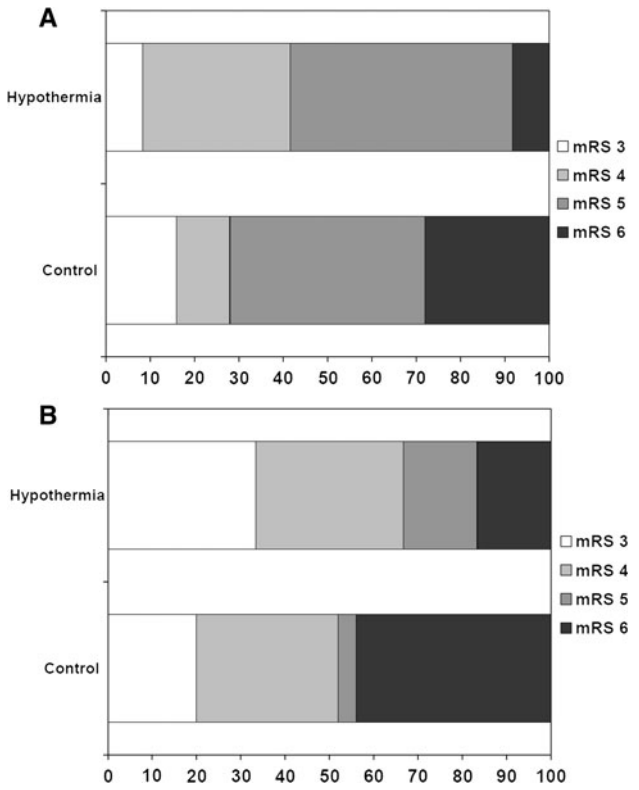

Fig. 2 Functional outcome in patients treated with hypothermia ($n = 24$) compared to patients who received standard treatment ($n = 25$) 3 months (**a**) and 1 year (**b**) after symptom onset, represented with the modified Rankin scale. *mRS 3* moderate disability, able to walk unassisted; *mRS 4* moderate severe disability, unable to attend own bodily needs without assistance, unable to walk unassisted; *mRS 5* severe disability, requires constant nursing care and attention, bedridden, incontinent; *mRS 6* dead. *mRS* modified Rankin scale

hypothermia group, outcome could be assessed at 3 months and 1 year after symptom onset. The modified Rankin scale scores assessed at the two time points are shown in (Fig. 2). At 3 months after the bleeding, two patients from the hypothermia group had a mRS of 3, eight patients had a mRS of 4, and 12 patients had a mRS of 5. Mortality comprised 8.3 % (two patients). At 1 year, eight patients had a mRS of 3, eight patients had a mRS of 4, and four patients a mRS of 5. Mortality comprised 16.7 % (four patients) at this time point. In the control group, four patients had a mRS of 3 at 3 months, three patients had a mRS of 4, and 11 patients had a mRS of 5. Mortality comprised 28 % (seven patients) at this time point. One year after the event, five patients from the control group had a mRS of 3, eight patients had a mRS of 4, and one patient a mRS of 5. Eleven patients (44 %) had died.

Discussion

We found that patients with large ICH (>25 ml) treated with prolonged mild endovascular hypothermia for 8–10 days develop less PHE over a follow-up period of 2 weeks, as compared to controls who received standard guideline based treatment. Thereby we could confirm the preliminary results of our pilot study, published previously [10], in the present larger cohort. Although we observed no PHE rebound during or immediately after rewarming, one patient suffered late edema rebound, deteriorated clinically 4 days after discontinuation of endovascular cooling and died of herniation several days later. This patient had a very large hematoma volume (>90 ml). However, three other patients had hematomas of comparable sizes and did not experience PHE rebound. Therefore, ICH size is certainly not the only parameter which could explain this phenomenon, however, there might be an upper limit of ICH volume, from which edema rebound after rewarming becomes more probable. Considering the long duration of hypothermia and the late occurrence of rebound in our patient, this issue certainly deserves further investigation, as it may represent an important problem in a setting similar to our study design. The duration of 8–10 days of cooling in the protocol of this study was chosen empirically; however, newer data on the natural course of PHE after ICH have shown that edema growth continues up to 7–11 days after symptom onset [9]. Although hypothermia, when applied early in the course of treatment, may change the dynamics of PHE, we cannot exclude that longer cooling may be more efficient, especially with respect to the rebound phenomenon after rewarming.

The course of ICH resolution did not differ between the hypothermia group and the historical control group (Fig. 1). Although hematoma enlargement was observed in approximately one-third of the patients treated with hypothermia, this proportion was even smaller than reported in the literature [3, 14]. The occurrence of rebleeding could not be attributed directly to the treatment, because the mild coagulation disorders (thrombocytopenia, increase in PTT) which occurred during hypothermia did not affect any of the patients who suffered hematoma enlargement.

The larger patient cohort treated with prolonged hypothermia in this study allowed us to gain more experience with complications of this treatment regimen. Infections were common during hypothermia and some patients suffered a more severe course with sepsis. Despite of that, all infections could be treated sufficiently with intravenous antibiotics. Ventilator associated pneumonia affected 24 patients (96 %) of the hypothermia group, however, pneumonia was also very common in controls (78 %) and generally occurs more frequently in patients who require prolonged mechanical ventilation [15]. Although other studies investigating the utilization of hypothermia in ventilated patients with ischemic or hemorrhagic stroke usually report lower infection rates, as compared to this study, the occurrence of severe infections in the setting of hypothermia [16, 17], especially with prolonged treatment [10, 18], seems to be a common finding. As severe pneumonia or sepsis may significantly affect outcome, future research of strategies aiming at prevention of those complications, e.g., prophylactic antibiotics, or selective decontamination of the digestive tract, is warranted [19]. Heart rhythm disturbances, i.e., only bradycardia in this study, had a mild character and were of minor clinical importance. The same applied to coagulation disorders, as they remained clinically unapparent. Impairment of thrombocyte function and clotting factors caused by hypothermia, potentially able to cause bleeding complications, represents a major concern in the setting of this study [19]. However, previous research has indicated that those effects do not play an important role in very mild hypothermia at 35 °C [19–22]. Moreover, no increased bleeding rates have been reported from larger recent studies on hypothermia in traumatic brain injury, ischemic stroke or subarachnoid hemorrhage [18, 23, 24]. Although the size of our study is relatively small, it confirms the safety of prolonged mild hypothermia (35 °C) in patients with ICH, with regard to bleeding complications. Local thrombosis at the catheter insertion site occurred in only one patient and another patient suffered minor pulmonary embolism. In both patients, those complications could be managed without a significant impact on the further course of treatment; however, they certainly deserve more attention in the setting of prolonged endovascular hypothermia—an increased alertness and more intensified screening for deep vein thrombosis on the one hand and possibly, further technical improvement of the antithrombotic properties of the catheters on the other.

Mortality was relatively low in the hypothermia group, comprising only 8.3 % after 3 months and 16.7 % 1 year after symptom onset. Considering the mean ICH volume of 54 ml those results are encouraging and may indicate, in accordance with our previous findings [9], that edema evolution may play an important role as a determinant of short-term mortality in patients with large ICH. Therefore, prolonged hypothermia may represent a promising treatment approach for reduction of edema growth in such patients. Generally, life-saving treatment in the acute phase of large ICH may result in survival with severe disability; however, this apprehension was not confirmed in our study. The functional outcome in survivors of the hypothermia group 1 year after the bleeding event was fairly good with approximately one-third of the patients being able to walk without assistance. There was also an improvement in outcome in a large proportion of patients (50 %) between the first and the second assessment. Six patients who had a mRS of 4 at 3 months improved to a mRS of 3 at 1 year. Other six patients improved from a 5 to a 4 on the mRS in the same time span. The proportion of patients with moderate severe or severe disability (mRS 4 or 5) after 1 year did not differ between the hypothermia ($n = 10$, 40 %) and the control group ($n = 9$, 36 %).

Our study has limitations, mainly derived from its small sample size and the comparison with a historical control group. Those limitations include the differences in treatment as shown in Table 2, as well as the different methods for assessment of body temperature used in the hypothermia and control groups. Therefore, no firm conclusions related to mortality and functional outcome can be made based on our preliminary data. Hopefully, those questions can be answered after completion of the ongoing German–Austrian randomized controlled trial cooling in intracerebral hemorrhage (CINCH) [11].

Conclusion

We could confirm in a prospective cohort of 25 patients that prolonged mild hypothermia at 35 °C reduces PHE after large ICH. The treatment caused complications in our patients; however, those complications could be recognized and treated successfully in the setting of a neurocritical care unit. In comparison to historical controls with similar hematoma size, patients treated with hypothermia had a lower mortality rate 3 months and 1 year after the bleeding. Furthermore, one-third of the treated patients were able to walk without assistance 1 year after symptom onset. Therefore, even patients with large ICH who survive the critical phase of edema growth may have the chance of satisfactory long-term recovery; however, this issue should be investigated further.

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