Original Paper

Cerebrovascular Diseases

Cerebrovasc Dis 2015;40:228–235
DOI: 10.1159/000439178

Received: December 22, 2014
Accepted: July 30, 2015
Published online: October 21, 2015

Is Hypothermia Helpful in Severe Subarachnoid Hemorrhage? An Exploratory Study on Macro Vascular Spasm, Delayed Cerebral Infarction and Functional Outcome after Prolonged Hypothermia

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Key Words
Subarachnoid hemorrhage · Vasospasm · Delayed cerebral infarction · Hypothermia

Abstract
Background: Therapeutic hypothermia (TH) is an established treatment after cardiac arrest and growing evidence supports its use as neuroprotective treatment in stroke. Only few and heterogeneous studies exist on the effect of hypothermia in subarachnoid hemorrhage (SAH). A novel approach of early and prolonged TH and its influence on key complications in poor-grade SAH, vasospasm and delayed cerebral ischemia (DCI) was evaluated. ***Methods:*** This observational matched controlled study included 36 poor-grade (Hunt and Hess Scale >3 and World Federation of Neurosurgical Societies Scale >3) SAH patients. Twelve patients received early TH (<48 h after ictus), mild (35°C), prolonged (7 ± 1 days) and were matched to 24 patients from the prospective SAH database. Vasospasm was diagnosed by angiography, macrovascular spasm serially evaluated by Doppler sonography and DCI was defined as new infarction on follow-up CT. Functional outcome was assessed at 6 months by modified Rankin Scale (mRS) and categorized as favorable (mRS score 0–2) versus unfavorable (mRS score 3–6) outcome. ***Results:*** Angiographic vasospasm was present in 71.0% of patients. TH neither influenced occurrence nor duration, but the degree of macrovascular spasm as well as peak spastic velocities were significantly reduced ($p < 0.05$). Frequency of DCI was 87.5% in non-TH vs. 50% in TH-treated patients, translating into a relative risk reduction of 43% and preventive risk ratio of 0.33 (95% CI 0.14–0.77, $p = 0.036$). Favorable functional outcome was twice as frequent in TH-treated patients 66.7 vs. 33.3% of non-TH ($p = 0.06$). ***Conclusion:*** Early and prolonged TH was associated with a reduced degree of macrovascular spasm and significantly decreased occurrence of DCI, possibly ameliorating functional outcome. TH may represent a promising neuroprotective therapy possibly targeting multiple pathways of DCI development, notably macrovascular spasm, which strongly warrants further evaluation of its clinical impact.

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1015–9770/15/0406–0228$39.50/0

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Introduction

Occurrence of delayed cerebral ischemia (DCI) in subarachnoid hemorrhage (SAH) is a major contributor to morbidity and mortality [1, 2]. Recent research increased understanding of mechanisms underlying DCI reflecting a multifactorial process, that is, inflammation, microthrombosis, disturbed autoregulation, spreading depolarization and cerebral vasospasm [2–5]. Yet, within the last few decades, randomized controlled trials (RCTs) investigating treatment strategies for DCI have failed to improve clinical end points [1]. Thus, development of a more comprehensive treatment approach targeting multiple pathways seems necessary [2, 5].

Therapeutic hypothermia (TH) has been shown to modulate various pathways including molecular, metabolic and inflammatory processes [6]. TH has been questioned recently but still remains an accepted neuroprotective treatment after cardiac arrest [7, 8]. An currently ongoing RCT evaluates TH as adjunctive therapy to systemic thrombolysis in ischemic stroke (http://www.eurohyp1.org) [11] based on neuroprotective effects described in both ischemic and hemorrhagic stroke patients [6, 9, 10]. Only few experimental and clinical reports exist for patients with SAH treated with TH, mainly describing a reduction of intracranial pressure (ICP) [12–14]. However, interpretation remains limited as varying treatment modalities, heterogeneous protocols and patient populations were investigated.

Detailed analyses of TH-induced effects after SAH are lacking. The present study was designed to investigate a novel approach of early and prolonged TH on the key complications – vasospasm and DCI – in poor-grade SAH.

Methods

Patient Selection and Study Design

All patients admitted to the neurocritical care unit during the years 2010–2012 were screened for eligibility. Inclusion criteria for this exploratory pilot study consisted of: aneurysmal SAH with complete aneurysm closure within 24 h, poor-grade SAH defined as Hunt and Hess-Scale 4–5, World Federation of Neurosurgical Societies Scale 4–5 and modified Fisher Scale 3–4, necessity for external ventricular drainage because of hydrocephalus, obligatory sedation and mechanical ventilation, absence of brainstem symptoms, initiation of TH with achievement of target temperature within 48 h after symptom onset. Exclusion criteria consisted of: clinical instability (i.e. new-onset brainstem symptoms, referring to disturbed brainstem reflexes, that is, pupillary light reflex, corneal reflex, pharyngeal reflex) within the first 24 h upon neurocritical care unit admission, exceeding the pre-defined time window for initiation of TH (e.g. longer transfer from peripheral hospitals, etc.) and incompletely obliterated aneurysm or evidence of additional, non-ruptured, non-treated aneurysms. The local ethics committee of the University Hospital Erlangen-Nuremberg, Germany, approved the study. Informed consent was obtained from relatives or legal representatives to receive TH as individual 'rescue therapy' for the participating critically ill SAH patients.

A matched controlled design was used to compare (i) characteristics of cerebral macrovascular spasm, (ii) occurrence of DCI during hospital stay, (iii) mortality and (iv) functional outcome. Matching procedure applied 1:2 ratio matching according to following prioritization process: amount of SAH and intraventricular hemorrhage (modified Fisher Scale and Hijdra score), clinical status on admission (GCS, Hunt and Hess, World Federation of Neurosurgical Societies) and patient age. Hence, 12 patients received TH and were matched to 24 patients from a prospective institutional SAH database (patients admitted during 2010–2012 fulfilling above-mentioned inclusion and exclusion criteria). We obtained all clinical parameters through our prospective institutional database. Functional outcome was assessed by the modified Rankin Scale (mRS) 6 months after disease onset. For outcome evaluation, we conducted a semi-quantitative telephonic interview directly with the patients, their legal representatives or their closest relatives. A favorable outcome was defined as mRS score of 0–2 and unfavorable outcome as mRS score of 3–6.

TH Protocol

The pre-specified TH protocol employed: TH induction within 48 h after symptom onset, to a target body core temperature of 35° (measured by bladder catheter), for a prolonged period of 7 ± 1 days. This protocol targeted the multiple pathophysiological mechanisms of DCI [2], very early in development-phase, for a prolonged period based upon reasonable safety profile of mild TH [10] and to cover the known time period of peak vasospasm generation. Endovascular cooling was carried out by central line catheter (ICY®, IC-3893, Zoll-Medical) that was placed in the femoral vein according established protocols [10]. Shivering during TH was treated at Bedside Shivering Assessment Scale score >1 initially with deeper sedation or consecutively with pethidine infusions and muscle relaxants in refractory cases [15]. We carried out a step-wise re-warming process with a maximal temperature increase of 0.5°C over 24 h. Screening for TH-associated complications, coagulopathy and thrombosis, infections (pneumonia, sepsis), enzyme elevation (α-amylase, AST, ALT), electrolyte disorders and cardiac arrhythmias was performed on a daily basis [16].

General Neurocritical Care Unit Treatment

Patients received standard medical therapy according to guidelines [1, 17]. Aneurysms were occluded by endovascular approach or neurosurgical clipping within the first 24 h of admission. We treated ICP levels greater 20 mm Hg with hypertonic saline or mannitol infusions monitored by external ventricular drainage or parenchymal probes [18]. All patients were sedated using midazolam or propofol in combination with sufentanil for analgesia. General temperature management for the control group as well as for the TH group after re-warming consisted of paracetamol (1 g) infusions if body core temperature raised over 38.3°C. Intravenous nimodipine was continuously administered

at a dose of 2 mg/h immediately after admission and was switched to oral application as soon as possible. A cerebral perfusion pressure of 70 mm Hg was targeted maintaining euvolemia and controlling blood pressure using catecholamine support, if necessary. Hemodilution was not applied and packed RBC transfusions were given at restrictive thresholds (Hb <8 g/dl). Lung protective mechanical ventilation targeted $PaCO_2$ levels between 35–40 mm Hg as measured according to the pH-Stat methodology [19].

Imaging

Initial diagnosis of SAH was based on CT (SOMATOM Definition AS+, Siemens, Erlangen, Germany) and aneurysms identified using diagnostic subtraction angiography. Two neuroradiologists blinded to clinical data, with access to information such as date, time and methodology of endovascular procedures and surgical treatment, evaluated the scans independently and scored neuroradiological parameters [20, 21]. In cases of discrepant scoring, a second consensus analysis was carried out. Initial follow-up imaging was performed within 24 h and consecutive scans were carried out at 48–72 h intervals.

Doppler Investigations, Macrovascular Spasm and DCI

Three certified physicians performed routine extracranial and transcranial Doppler examinations using 2-MHz (pulsed-wave) and 4-MHz (continuous-wave) probes (Sonara/tek, MediLab, Würzburg, Germany) starting on the day of admission and routinely every 24–48 h thereafter up to a maximum of 21 days (a total of n = 337 Doppler examinations). All cerebral vessels were insonated at specific depths for the assessment of flow velocities (e.g. peak flow velocities) and were converted by validated conversion formula, as previously described [22]. We used middle cerebral artery (MCA) velocities to compare possible treatment effects between patients receiving TH and those not receiving TH [23]. Definition of Doppler-based vasospasm, referred to as macrovascular spasm throughout the manuscript consisted of present mean flow velocities greater than 120 cm/s and/or a Lindegaard ratio higher than 3, which was chosen for early detection [1, 17, 22, 24]. Macrovascular spasm was confirmed as angiographic vasospasm by diagnostic subtraction angiography (n = 15), CT angiography and perfusion scanning (n = 25) as well as by MRI (n = 6). The definition of DCI was exclusively based on native follow-up CT imaging and required a newly demarcated cerebral infarction. Attentive care was taken to differentiate DCI from peri-procedural lesions associated to interventional procedures or microsurgical repair. A new onset of clinically relevant focal neurological deficit was not assessable, since all patients' required mechanical ventilation during stay. For DCI detection, a median number of 8 (95% CI 3–12) CT scans was available.

Statistical Analysis

Statistical Analysis was performed with SPSS 20.0 (www.spss.com). The significance level was set at $\alpha = 0.05$. Corrections for multiple comparisons were not applied in relation to the exploratory nature of this investigation. Statistical tests were 2-sided. The Kolmogorov–Smirnov test was applied to determine distribution of the data. Latter are presented as mean ± SD (compared using the Student t test) or as median and interquartile range (compared using the Mann–Whitney U test), as appropriate. The Pearson χ^2 and the Fisher's exact tests were used to compare frequency distributions of categorized variables between patients treated with TH as opposed to those without TH. Corresponding ORs with 95% CIs are given for the analysis of investigated end points, that is, DCI and functional outcome.

Results

Table 1 compares matching parameters, baseline characteristics and risk factors for DCI development [25]. No significant differences were noted between both groups. Especially, in TH-treated patients, the rate of thromboembolic complications was not different. In TH patients, statistical trends were documented for a shorter duration of hospital stay (TH: 21.8 (±9.2) vs. Ø-TH: 32.4 (±23.5); p = 0.090) and lower rate of ventriculoperitoneal shunt surgery (TH: 1 (8.3%) vs. Ø-TH: 8 (40.0%); p = 0.059). Sub-analyses showed that ventriculoperitoneal shunt dependency was most strongly associated with length of hospital stay (receiver operating characteristic analysis: AUC = 0.924, 95% CI 0.840–1.00, p < 0.001) likely mediating the observed difference of longer hospital stay in untreated patients. In treated patients, target temperature was reached within 48 h and remained stable during the treatment phase (fig. 1). Body temperature remained significantly reduced beyond the period of intravascular cooling with differences up to day 18 in treated patients (p < 0.05).

Characteristics of Cerebral Macrovascular Spasm

For the investigated cohort of 36 patients, a total of 337 Doppler examinations were performed.

Frequency of Macrovascular Spasm. Doppler-based macrovascular spasm was present in 83.3% of TH patients vs. 87.5% in non-TH patients. Verification by other diagnostic modalities resulted in a vasospasm rate for TH-treated patients of 60.0% vs. untreated patients 76.2% (p = 0.302; table 2).

Onset and Duration of Macrovascular Spasm. Figure 2 displays the comparison of MCA velocities providing an overview of time course and degree of Doppler-based macrovascular spasm. Macrovascular spasm occurred at 3–4 days in all patients, and the duration of macrovascular spasm in TH was 13.3 ± 5.4 days vs. 16.1 ± 3.5 in non-TH patients (p = 0.108).

Degree of Macrovascular Spasm. A significant reduction of mean MCA velocities was noted on both insonated hemispheres in TH-treated patients (p < 0.05). This difference was apparent between days 7–12 (fig. 2).

Table 1. Matching characteristics, DCI risk factors and in-hospital measures for all analyzed TH vs. non-TH SAH patients

SAH (n = 36)	TH (n = 12)	Ø-TH (n = 24)	p value
Matching characteristics			
Age, years†	48.9±9.6	51.3±11.9	0.289
Glasgow coma scale‡	8 (3–14)	8 (4–13)	0.779
Hunt and hess-scale‡	4 (4–5)	4 (4–5)	0.856
World federation of neurosurgical societies-scale‡	4 (4–5)	4 (4–5)	0.679
Modified-fisher-scale‡	4 (3–4)	4 (3–4)	0.212
Hijdra-sum-score‡	24 (17–30)	26 (18–31)	0.645
Neuroradiological data			
Anterior communicating artery aneurysm*	6 (50.0)	11 (45.8)	0.806
MCA aneurysm*	3 (25.0)	5 (20.8)	0.544
Posterior circulation aneurysm*	3 (25.0)	8 (33.3)	0.456
Coiling of aneurysm*	10 (83.3)	21 (87.5)	0.549
Risk factors for DCI			
History of smoking*	3 (25.0)	7 (29.2)	0.559
History of diabetes*	1 (8.3)	2 (8.3)	1
Sepsis*	2 (16.7)	6 (25.0)	0.455
Hyperglycemia*	7 (58.3)	13 (54.2)	0.806
Acute hydrocephalus*	10 (83.3)	18 (75.0)	0.691
History of hypertension*	8 (66.7)	13 (54.2)	0.475
Hemoglobin, mmol/l†	8.4±0.8	7.8±1.4	0.246
In-hospital measures and complications			
Gender*, ♀	9 (75.0)	15 (62.5)	0.359
Duration of ventilation†, days	20.1±10.3	18.8±15.3	0.760
Tracheostomy*	8 (66.7)	8 (33.3)	0.058
Pneumonia*	10 (83.3)	15 (62.5)	0.268
Ventriculitis*	2 (16.7)	3 (20.8)	1
Duration of EVD†, days	15.5±7.4	19.5±10.7	0.312
Lumbar drainage*	8 (66.7)	18 (75.0)	0.440
Ventriculoperitoneal shunt surgery*	1 (8.3)	8 (40.0)	0.059
Tonic clonic seizures*	2 (16.7)	6 (25.0)	0.455
Myocardial infarctions*	1 (8.3)	2 (8.3)	1
Red blood cell transfusions*	7 (58.3)	11 (45.8)	0.479
Thrombocytes $<100 \times 10^3$*	2 (16.7)	1 (4.3)	0.536
International normalized ratio ≥1.5*	1 (8.3)	1 (4.2)	1
Bradycardia (HF <40)*	4 (33.3)	5 (20.8)	0.685
Osmotherapy*	11 (91.7)	21 (87.5)	0.592
Length of stay†, days	21.8±9.2	32.4±23.5	0.090
In-hospital mortality*	2 (16.7)	4 (16.7)	1

* n (%); † mean ± SD; ‡ median (IQR 25–75th percentile).

Occurrence of DCI

As shown in table 2, a significantly reduced rate of DCI was observed in TH-treated patients (TH: 50% (n = 6 of 12) vs. Ø-TH: 87.5% (n = 21 of 24); p = 0.036). This translated into a significant relative risk reduction of 43% and preventive risk ratio of 0.33 (95% CI 0.14–0.77, p = 0.036) for the development of DCI. No statistical differences were however seen for new demarcated lesions (median 2 (1–4) per patient) nor its duration until occurrence between the 2 compared groups (p = 0.604, p = 0.942). DCI developed predominantly within the vascular territory of peak spastic vessels in all patients at a rate of 85.2% (n = 23 of 27). Figure 3 displays the chronology of DCI occurrence and compares the influence of TH treatment on mean flow velocities in peak spastic vessels. Early TH significantly reduced peak flow velocities starting at day 5 lasting intermittently until day 20 (p < 0.05; fig. 3).

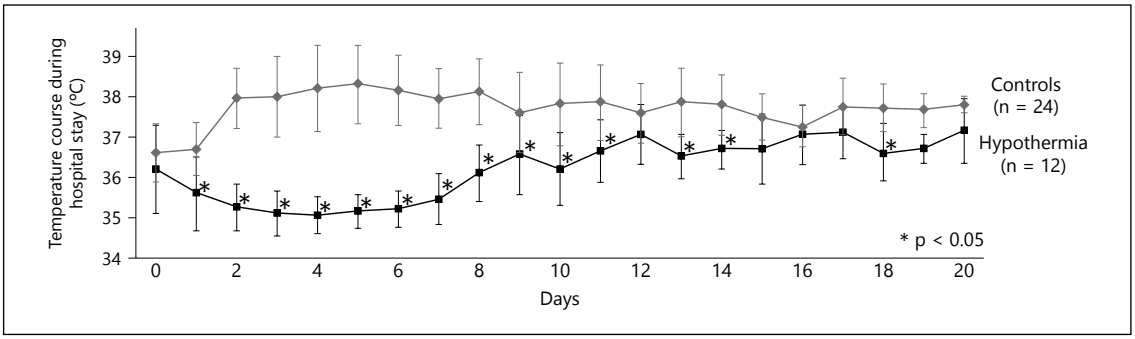

Fig. 1. Comparison of temperature course in TH vs. non-TH patients. Significantly different mean (±SD) body core temperature values are marked by asterixis.

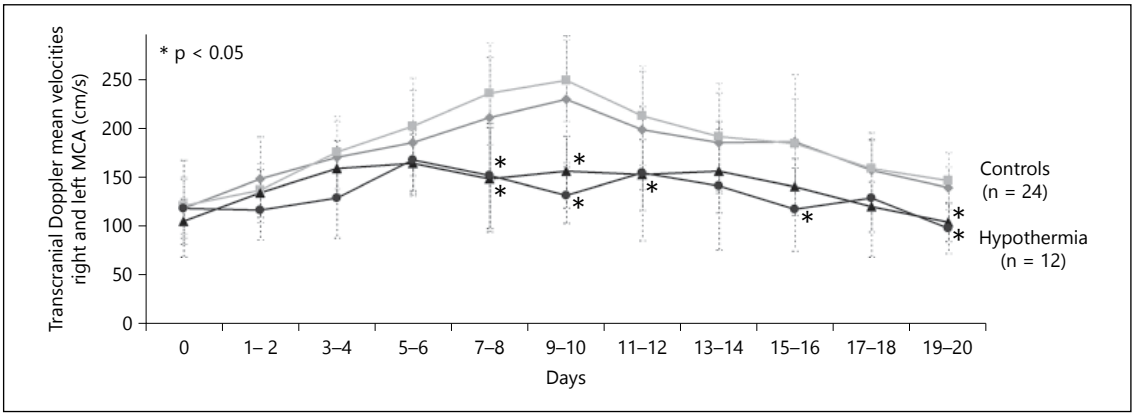

Fig. 2. Comparison of left and right MCA mean Doppler velocities in TH vs. non-TH patients. Significant differences in MCA mean (±SD) velocities are marked by asterixis.

Table 2. Frequency of macrovascular spasm and characteristics of DCI in TH vs. non-TH patients

SAH (n = 36)	TH (n = 12)	Ø-TH (n = 24)	p value
Macrovascular spasm on TCD*	10 (83.3)	21 (87.5)	1
Duration of macrovascular spasm†, days	13.3±5.4	16.1±3.5	0.108
Vasospasm on angiography*	6/10 (60.0)	16/21 (76.2)	0.302
Delayed cerebral infarction*	**6 (50.0)**	**21 (87.5)**	**0.036**
Total infarctions per patient with DCI‡	2.2 (1–4)	1.9 (1–3)	0.604
Mean duration until DCI†, days	7.8±3.8	8.0±4.2	0.942
Infarction over peak spastic vessel*	5/6 (83.3)	18/21 (85.7)	0.659

Significant parameters are expressed in bold. * n (%); † mean ± SD; ‡ median (IQR 25–75th percentile).

Mortality and Functional Outcome

No differences were seen for in-hospital mortality (TH: 16.7% (n = 2 of 12) vs. Ø-TH: 16.7% (n = 4 of 24); p = 1) but, as shown in figure 4, the rate of favorable functional outcome (mRS score 0–2) at 6 months was doubled in TH-treated patients (TH: 66.7% (n = 8 of 12) vs. Ø-TH: 33.3% (n = 8 of 24); p = 0.06).

Discussion

The present investigation on early and prolonged TH in poor-grade SAH patients shows a reduced degree of macrovascular spasm, fewer occurrence of DCI and a possible association with improved functional outcome in treated patients. Two questions emerge from the data:

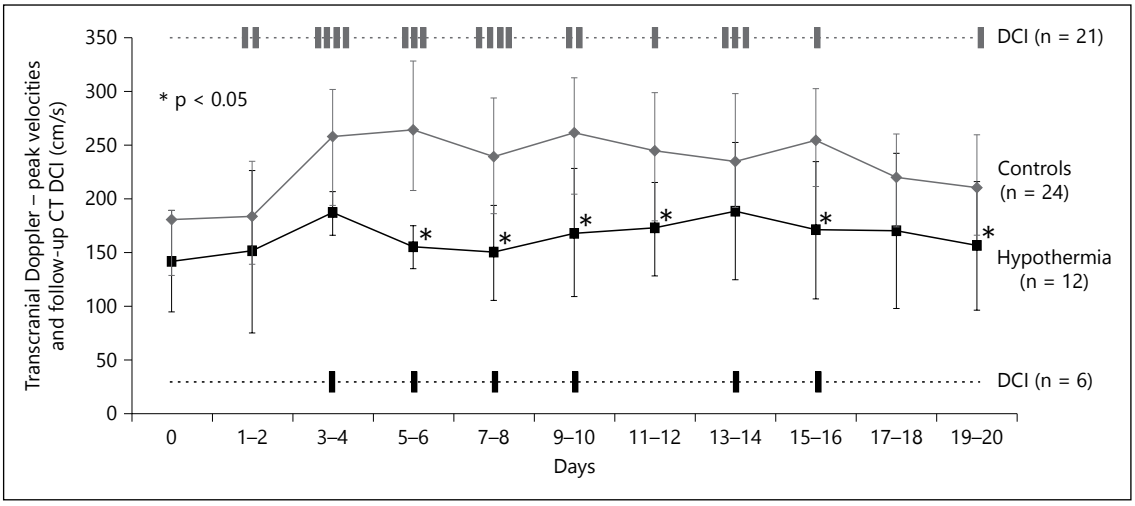

Fig. 3. Comparison of Doppler peak velocities (mean ± SD) of all insonated vessels and chronological distribution of DCI over 21 days.

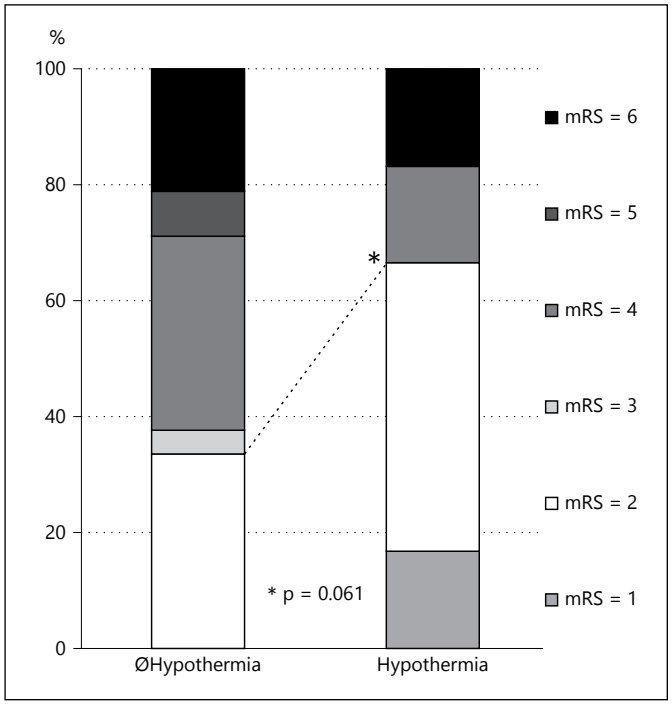

Fig. 4. Distribution of functional outcome as assessed by the mRS at 6 months comparing TH vs. non-TH patients.

how may TH modulate the degree of macrovascular spasm? and why is the occurrence of DCI reduced?

Angiographic vasospasm occur in up to 70% of patients after SAH, yet less than half develop ischemic neurologic symptoms [2]. RCTs within the last decades investigating vasospasm treatment have failed to prevent DCI or to improve outcome [26, 27] questioning the causal relationship of vasospasm as sole contributor to DCI development [2–4]. The present data show that DCI occurred predominantly in the vascular territory of peak spastic vessels supporting the role of vasospasm. TH was related to significant reductions of MCA and peak spastic velocities, which may resemble a decreased degree of macrovascular spasm [23]. As previously suggested, TH mediates its neuroprotective effects by modulations of molecular, metabolic and inflammatory processes, possibly supporting associations with cerebral blood flow velocities [6, 12, 28–30]. Such a mechanistic association of TH seems likely, yet its influence on actual peak spasm and its clinical significance warrant further investigations [31]. Available clinical studies have investigated TH rather as acute treatment strategy for increased ICP than for its effects on vasospasm and DCI [12–14, 29, 31]. To date, no study has evaluated this novel approach of early and prolonged TH and its influence on those complications after poor-grade SAH.

Results here provide associations of early TH with a decreased risk and reduced rate of DCI. Possibly, this beneficial association may have translated into a doubled rate of favorable functional outcome in treated patients. All patients who exhibited DCI showed a median of 2 newly demarcated lesions, which may be associated with consecutive neurological deficits potentially influencing functional outcome. The pathogenesis of DCI is intensely debated and a multifactorial process has been proposed – inflammation, microthromboembolism, autoregulatory failure, spreading depolarization and vasospasm [2–5]. These mechanisms may contribute to DCI,

and available data support ameliorating neuroprotective properties of TH [6, 32, 33]. Clinical investigations have identified pro-inflammatory cytokines (IL-6, TNF-α) to be associated with DCI and poor outcome after SAH [5, 30], and experimental data suggest that TH may reduce cytokine levels and induce upregulation of cytoprotective protein expression [33]. Causal relations of spreading depolarization with non-vasospastic DCI have been described [5] and again experimental data propose attenuation of spreading depolarization by TH [32]. Suggested TH-mediated neuroprotective mechanisms, that is, decreased metabolic demand, reduced glutamate toxicity, less free-radical production, decreased neuronal calcium influx, decreased neuronal apoptosis, attenuation of blood-brain barrier and preservation of cerebral autoregulation, may increase ischemic tolerance in patients treated with hypothermia, which hypothetically may lead to fewer cerebral infarctions and potentially improved functional outcome [6, 12, 14, 29].

Limitations of this investigation: Transcranial Doppler instead of duplex examinations was performed by certified physicians; nevertheless, specificity for vasospasm detection remains debated. Reported macrovascular spasm rate may be exaggerated as low Doppler thresholds were applied and hypothermia itself may reduce cerebral blood flow limiting the interpretation of Doppler-based results but reinforce the positive associations of TH for DCI and functional outcome [23, 31]. Within this study, DCI rate was very high as DCI detection was based exclusively on CT findings rather than on apparent neurologic deficits or multimodal imaging since assessment and executability in critically ill, mechanically ventilated SAH patients are limited. This methodology possibly overestimates DCI count and limits interpretation of causal and clinically meaningful cerebral infarctions [25]. The present study was not designed as randomized trial; low patient numbers, single center, matched controlled design and the validity of follow-up mRS assessment make it difficult to interpret the outcome findings, thus residual confounding by indication cannot be completely excluded. Importantly, this investigation has a pilot study character, which is exploratory in nature and associations of TH may be influenced by the small sample size demanding appropriately designed future trials.

Conclusion

This pilot study seems to indicate that early and prolonged TH may be beneficial for patients with severe SAH by reducing macrovascular spasm, DCI and possibly affecting functional outcome. Future randomized controlled studies investigating TH in selected SAH patients with a high DCI risk seem warranted.

Acknowledgments

We like to thank Jonathan Reichl and Henning Abel for helping with logistics and clinical data acquisition as well as Dr. Inken Martin for valuable discussions.

Contributions

J.B.K., R.K. and H.B.H. designed the study and wrote the manuscript. J.B.K., S.T.G. and D.M. evaluated clinical data. A.D. and S.P.K. obtained all neuroradiological data. J.B.K., A.P. and D.S. performed ultrasonography examinations. S.S. and I.Y.E. helped with statistical analyses and critically revised the manuscript.

Disclosure Statement

J.B.K. has received travel grants from EMSCools and D.S. from Zoll medical and Bard medical. R.K. and S.S. have received travel grants and speaker's honoraria from Zoll medical, Bard medical, Seiratherm and EMSCools. The other authors have nothing to disclose. All authors have read the manuscript, agreed with the contents and have approved the final version of the manuscript.

Financial Support

The study was partially funded by the ELAN program (12-01-04-1; FSt 56610036) of the Friedrich-Alexander University Erlangen-Nuremberg.

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