Effects of hypertonic/hyperoncotic treatment and surgical evacuation after acute subdural hematoma in rats*

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Objective: The treatment of acute subdural hematoma (ASDH) consists mainly of surgical evacuation of the hematoma. It is conceivable that early preoperative neuroprotection with hypertonic/hyperoncotic treatment (HHT) can improve survival rates. The present study investigated the benefit of treatment with hypertonic/hyperoncotic solution on functional and histologic outcome as supportive therapy accompanying surgical intervention.

Design: Laboratory experiment.

Setting: University laboratory.

Subjects: Male Sprague-Dawley rats weighing 296–350 g (n = 56).

Interventions: ASDH was induced through subdural infusion of 400 μL of autologous venous blood. Thirty minutes after subdural blood infusion, the rats received either HyperHAES (7.2% saline/6% hydroxyethyl starch) or vehicle (NaCl 0.9%) intravenously, followed by surgical evacuation of the hematoma 1 hr after ASDH induction in those rats scheduled for surgical treatment. The experiment was divided into two parts: an acute study, which explored acute effects of HHT on blood variables, ASDH-induced changes of intracranial pressure (ICP), and cerebral perfusion pressure (CPP), and a chronic study, which investigated the chronic effects of HHT, surgical blood clot evacuation, and the combination of both on the functional and histologic outcome following ASDH (12 days).

Measurements and Main Results: In the acute study, HHT expectedly raised the serum sodium concentration and lowered hematocrit. ASDH increased ICP and decreased CPP in all groups. HHT improved CPP by reducing ICP. In the chronic study, all treated groups showed a better recovery with respect to neurologic function and neuronal cell death compared with the vehicle-treated ASDH group. HHT with surgical evacuation or HHT alone improved functional and histologic outcome slightly more than surgical evacuation alone.

Conclusions: In this rat model, HHT led to a decrease of ICP after ASDH. This significantly improved functional and histologic outcome, which was comparable to the effects after blood evacuation alone. The combination of evacuation of subdural blood and early HHT improved histologic outcome further but not significantly, which was due to the strong effects of single treatments and a ceiling effect of the combined treatment in this model. (Crit Care Med 2008; 36:●●●–●●●)

KEY WORDS: rats; acute subdural hematoma; hypertonic hyperoncotic treatment; neurologic deficit; surgical evacuation; intracranial pressure

Many studies have shown the serious consequences of acute subdural hematoma (ASDH) after traumatic brain injury (1–3). With current conventional treatment, consisting of early surgical intervention with blood clot evacuation and intensive care, the mortality of patients treated within 4 hrs after ASDH is still extremely high. Up to 30% die and only 65% have a good functional recovery. With treatment starting after 4 hrs, the mortality rate increases to as high as 85% (2). Also, in a more recent survey, the rate of full functional recovery 6 months after traumatic brain injury remained low at 30% (4). The positive effect of surgery is partially based on improved cerebral hemodynamics and tissue oxygenation and reduced intracranial pressure (ICP) associated with a better functional outcome (5–8). Thus, additional treatment strategies are needed. One such involves treating ASDH by influencing the microcirculation in the traumatized brain. No-flow/low-flow areas after global ischemia can be reduced with hypertonic/hyperoncotic treatment (HHT) (9). HHT improves histologic outcome after cortical vein occlusion (10), controlled cortical impact (11), cerebral ischemia (12), and subarachnoid hemorrhage (13) by restoring microcirculation through improved rheology. Swelling of endothelial cells is reduced, capillary diameters are increased, and leukocyte-endothelium interactions are reduced (14–17). A predictable reduction of ICP in patients after therapy with hypertonic saline containing hydroxyethyl starch has also been shown (15, 18–20). Guidelines for the management of severe head injury recommend mannitol as a first-line option to treat elevated ICP (21). In a more recent study, however, HHT seemed to be superior to mannitol in controlling intracranial hypertension (22). In contrast to surgery, which can only be performed in the operating room, HHT can be applied much earlier. Thus, HHT administered early after traumatic brain injury might improve microcirculation and protect cerebral tissue until evacuation of the hematoma can be performed. We therefore examined whether the protective effect of surgery with blood clot evacuation after ASDH can be further improved by early

HHT in a rat model of ASDH. For this purpose we studied the effects of early HHT on functional and histologic outcome.

MATERIALS AND METHODS

Subjects. All experiments were performed under the Animal Care and Welfare Guidelines and were approved by the local ethics committee. Male Sprague-Dawley rats, weighing 296–350 g (Charles River, Germany) were used for this experiment (n = 56).

Surgical Preparation. Rats were briefly anesthetized with isoflurane (1 mL) in a glass cylinder and then given chloral hydrate by intraperitoneal injection (initial dose, 1 mL/100 g of body weight of 36 mg/mL; maintenance dose, 1 mL/hr) and premedicated with 1 mg of atropine subcutaneously. Body temperature was maintained constant at 37°C with a feedback-controlled homeothermic blanket (Harvard, South Natick, MA). The rats were allowed to breathe spontaneously. The tail artery was cannulated with polyethylene tubing for continuous monitoring of mean arterial blood pressure (MABP) and withdrawal of blood samples for blood gas analysis. A jugular vein was cannulated to obtain blood for subdural infusion and for the venous infusion of drugs. The volume needed for each blood gas analysis was 210 µL (ABL615/EML105, Radiometer, Copenhagen, DK). The animals were placed into a stereotactic frame. After skin incision to expose the skull, a 3 × 5 mm craniotomy for ASDH induction was performed 2 mm left of and 2 mm posterior to the bregma. Depending on the study, a burr hole was drilled for ICP catheter insertion, or a small area of the skull on the contralateral side was thinned out for laser Doppler flowmetry (Fig. 1).
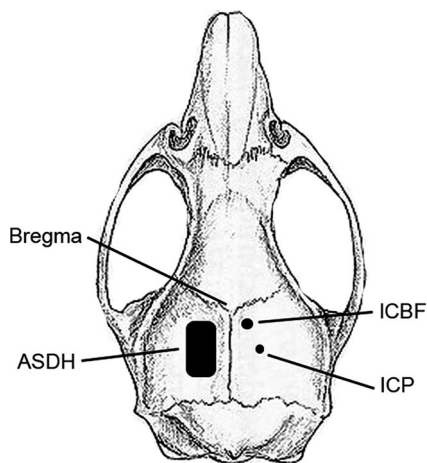

Figure 1. Schematic representation of the locations of the craniotomy for acute subdural hematoma infusion (*ASDH*), the laser Doppler probe for measurement of local cerebral blood flow (*lCBF*), and the intracranial pressure probe (*ICP*) for measurement of intracranial hypertension.

Subdural Hematoma. After craniotomy, a 23-gauge L-shaped blunted needle (Sterican, B. Braun, Melsungen, Germany) was inserted under the dura mater, and the craniotomy was sealed again with tissue glue (Histoacryl, B. Braun). A baseline of 15 mins of stable monitoring values was achieved, and 400 µL of autologous venous blood was infused at a rate of 50 µL/min (23). Animals were monitored for 1 hr from that time onward (Fig. 2). The craniotomy remained closed in all animals for the whole time of the experiment. Subdural blood was left in the skull except for animals scheduled for surgical evacuation of the hematoma, which was performed only in the chronic study. In these animals, the craniotomy was opened for a maximum of 6 mins to allow evacuation of the hematoma and then closed again with the bone flap and tissue glue.

Fluid Administration and Treatment Arms. The animals were treated with either 0.9% NaCl or hypertonic/hyperoncotic solution (HyperHAES, Fresenius, Bad Homburg, Germany) consisting of 60 g of hydroxyethyl starch and 72 g of NaCl in 1000 mL resulting in 1232 mmol Na$^+$ and 1232 mmol Cl$^-$ with a pH between 3.5 and 6.0 and a theoretical osmolarity of 2640 mosm/L. NaCl and HyperHAES were administered intravenously as a 4-min bolus (4 mL/kg body weight) as small-volume resuscitation (24) 30 mins after ASDH. The subdural blood was evacuated in animals assigned to the surgical evacuation group 60 mins after ASDH by opening the craniotomy, removing the needle, and then opening the dura mater. The clotted blood was removed as completely as possible, and the craniotomy was closed again with the bone flap and sealed with tissue glue (Fig. 2). The animals were assigned to two different experimental studies: An acute study concerned the acute effects of HHT on blood variables, MABP, ICP, and cerebral perfusion pressure (CPP; CPP = MABP − ICP) after ASDH. A chronic study concerned the long-term effects

Figure 2. Graphic depiction of the timeline of the experiments. After 15 mins of baseline monitoring, acute subdural hematoma (*ASDH*) was induced. Thirty minutes after ASDH, either NaCl 0.9% or HyperHAES was administered. Another 30 mins later, acute monitoring was ended. In some animals of the chronic study, the ASDH was evacuated surgically. Subsequently, behavioral tests were performed, and after 11 days the rat brain was removed for histologic examination. *HHT,* hypertonic/hyperoncotic treatment.

of HHT, surgical evacuation of the blood clot, and the combination of both on histologic and functional outcome after ASDH.

Acute Study: Acute Effect of HHT on Blood Variables, ICP, MABP, and CPP. To ensure that HHT produced effects on blood variables as found in a previous study (10), frequent blood samples were taken from sham animals before and 0.5, 2, 5, 10, 15, 20, 30, and 45 mins after bolus therapy (n = 3).

Further on we established the effect of HHT on the clinically relevant variables MABP, ICP, and CPP (n = 20). For this purpose, an ICP probe (Neurovent 3-Fr; Raumedic, Helmbrechts, Germany) was inserted through a burr hole at 3 mm lateral to the sagittal suture and 5 mm posterior to the bregma and was advanced 2 mm into the contralateral cortex. Variables were monitored at baseline, during blood infusion, and over a 1-hr postinfusion period. NaCl and HHT were infused 30 mins after ASDH. Animals were assigned to the following groups: 1) sham (n = 4); 2) vehicle (NaCl 0.9%) (n = 9); 3) HHT (HyperHAES) (n = 7).

Chronic Study: Chronic Effects of HHT, Surgical Evacuation, and the Combination of Both on Histologic and Functional Outcome After ASDH. To avoid an effect of intraparenchymal damage or possible inflammation on the chronic outcome variables, no ICP probe was inserted into the brain in the chronic study. However, to ensure the quality of subdural blood infusion, local cerebral blood flow was monitored by laser Doppler flowmetry (Vasamedics BPM 403a, St. Paul, MN; 0.8-mm needle probe). The probe was placed <100 µm from the surface of the thinned-out skull area above the contralateral hemisphere (about 1 mm right and 1 mm posterior to the bregma) and was kept wet at all time. Local cerebral blood flow values were collected during a baseline period and until blood clot removal.

The following groups were tested: 1) sham (n = 4); 2) vehicle (NaCl 0.9%) (n = 8); 3) HHT (HyperHAES) (n = 8); 4) vehicle + surgical evacuation (n = 8); 5) HHT + surgical evacuation (n = 8).

As described previously, fluids were infused 30 mins after ASDH, and the blood clot was removed 60 mins after the onset of ASDH in animals assigned to groups 4 or 5.

Evaluation of Behavioral and Neurologic Deficits. Neurologic and behavioral testing was performed in a quiet room in dim light. Starting 3 days before sham-operation or injury, all animals were trained daily to walk along a beam (diameter 1.8 cm, length 1 m, 2.5 cm between bars, 50 cm above ground) while their missteps were counted and the time it took to reach a black box was measured (25). Sensory and motor integrity was tested with a neuroscore by evaluating motor activity, orientation, and reaction to tactile, visual, and auditory stimuli. The points obtained in the individual tests were then added together to yield an overall score ranging from 0 points (no deficit) to 100 points (most severe deficit)
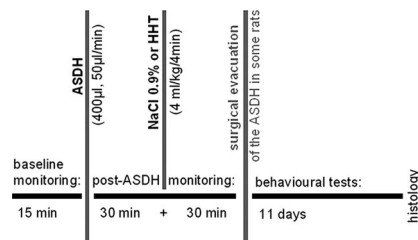
(25, 26). These tests were performed on days −3, −2, −1, 1, 2, 3, 4, 5, 7, 9, and 11. Spontaneous locomotor activity was tested in an open field (75 × 75 × 40 cm). The path was tracked and analyzed using a video camera connected to computer running the tracking software Ethovision (Noldus Ethovision 3.1, Utrecht, The Netherlands) (25, 27).

Neurohistological Evaluation. Twelve days after sham operation or ASDH, the animals were transcardially perfused with 4% buffered paraformaldehyde, and their brains were carefully removed and postfixed for 24 hrs. Coronal sections spaced 250 μm apart were made through the paraffin-embedded brains and stained with hematoxylin and eosin to delineate the injury. The damaged area on each section was photographed with a CCD camera (SSC-C370P, Sony) connected to a light microscope (Zeiss, Oberkochen, Germany) and a computer. The areas of ischemic brain damage underlying the subdural hematoma and hemisphere were surveyed with image analyzing software (Optimas 6.51, VSG, UK). Infarct volume is expressed as percentage of contralateral hemisphere in order to correct for swelling.

Statistical Analysis. Data are expressed as mean ± SEM. Comparison of the different groups was performed with one-way analysis of variance with *post hoc* comparisons for individual differences (Student-Newman-Keuls' test) or by analysis of variance for repeated measures with Bonferroni correction for multiple comparisons. Data that were not distributed normally were analyzed by analysis of variance on ranks followed by the Dunn *post hoc* test (SigmaStat 3.1, SPSS, Chicago, IL). Differences were considered statistically significant at $p < .05$.

RESULTS

Acute Study: Acute Effect of HHT on Blood Variables, ICP, MABP, and CPP. The administration of HHT resulted in significantly elevated sodium and decreased potassium and significantly decreased hematocrit levels in the plasma (Fig. 3). ICP, MABP, and CPP developed as follows: Starting at normal levels (sham, 8 ± 2 mm Hg; vehicle, 10 ± 1 mm Hg; HHT, 12 ± 1 mm Hg), ICP reached its maximum values at the end of subdural blood injection (sham: 9 ± 2 mm Hg; vehicle, 52 ± 6 mm Hg; HHT: 61 ± 6 mm Hg). Twenty minutes later, shortly before fluid administration, ICP had settled down to values that were still significantly above normal levels in both blood infusion groups (sham, 9 ± 2 mm Hg; vehicle, 21 ± 2 mm Hg; HHT, 22 ± 2 mm Hg). HHT significantly reduced ICP compared with rats receiving NaCl (sham, 9 ± 2 mm Hg; vehicle, 21 ± 1 mm Hg; HHT, 17 ± 1 mm Hg). While the ICP of
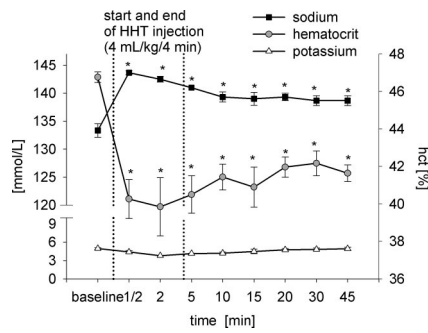
Figure 3. Acute study: Effects of hypertonic/hyperoncotic treatment (*HHT*) on sodium, potassium, and hematocrit (*hct*) before and after drug treatment. Blood samples for analysis were taken during a baseline and 0.5, 2, 5 10, 15, 20, 30, and 45 mins after HHT. Values are given as mean ± SEM, and each time point was compared with baseline conditions using one-way analysis of variance for repeated measures with Bonferroni correction for multiple comparisons (*$p < .05$).

the vehicle group remained significantly increased after saline infusion compared with baseline, HHT-treated animals no longer displayed any significant differences after treatment compared with baseline. CPP had a similar course. Starting at normal perfusion pressures (sham, 71 ± 3 mm Hg; vehicle, 64 ± 3 mm Hg; HHT, 64 ± 2 mm Hg), CCP was critically low at the end of the blood injection (sham, 69 ± 2 mm Hg; vehicle, 29 ± 5 mm Hg;, HHT, 21 ± 6 mm Hg). Shortly before fluid administration, CCP had recovered to almost normal levels (sham, 69 ± 2 mm Hg; vehicle, 56 ± 2 mm Hg; HHT, 56 ± 2 mm Hg). HHT significantly ameliorated the slightly reduced CPP, so that at the end of the acute experiment the vehicle group still showed a lower CPP than the other groups (sham, 66 ± 3 mm Hg; vehicle, 55 ± 2 mm Hg; HHT: 63 ± 3 mm Hg) (Fig. 4). Physiologic variables showed similar values as in the chronic study (see below).

Chronic Study: Chronic Effects of HHT, Surgical Evacuation, and the Combination of Both on Histologic and Functional Outcome After ASDH. Arterial blood gases taken before and after infusion of blood remained stable over the course of the experiment (Table 1).

Cerebral Blood Flow Measurement. After ASDH, contralateral local cerebral blood flow (CBF) was reduced from 100% (△33.2 ± 0.3 LDU) to approximately 27% (△9.2 ± 0.9 LDU) and returned to 54% (△18.2 ± 1.4 LDU) of baseline levels 1 hr afterward. There were no statistically significant differences between blood infusion groups (Fig. 5).
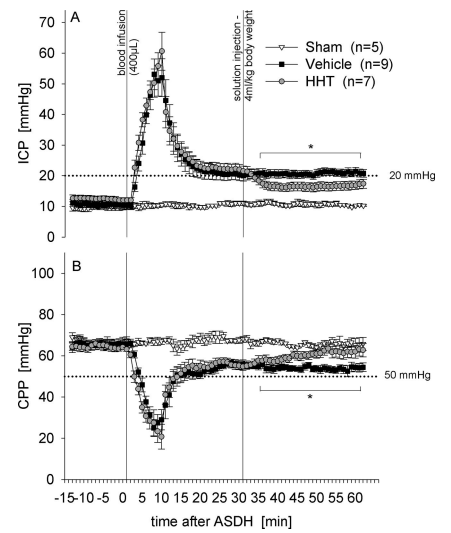
Figure 4. Acute study: (*A*) Mean (±SEM) intracranial pressure (*ICP*) and (*B*) cerebral perfusion pressure (*CPP*) expressed in mm Hg throughout the experimental procedure. Hypertonic/hyperoncotic treatment (*HHT*) significantly lowered ICP and ameliorated reduced CPP. The horizontal bar indicates a statistical difference between HHT and vehicle after the start of treatment (*$p < .05$ comparison area under curve using one-way analysis of variance on ranks with Dunn *post hoc* pair-wise comparison). *ASDH*, acute subdural hematoma.

Functional Outcome. In all trauma groups, the neurologic deficit, as expressed by the neuroscore, was significantly increased as early as the first day after operation (sham, 0 ± 0 points; vehicle, 27 ± 2 points; surgical evacuation, 21 ± 3 points; HHT, 13 ± 2 points; HHT + surgical evacuation, 13 ± 3) but improved throughout the observation period. Baseline levels were not regained in any injury group. HHT and surgical evacuation of the hematoma as well as combination therapy were associated with a significantly better functional outcome (Fig. 6). On day 11, the best results were seen after treatment with HHT and HHT + surgical evacuation, but combination therapy had no additional beneficial effect. The beam-walk test showed similar results. Rats that received therapy crossed the parallel bars faster and made fewer missteps than those that had not. On day 11 after ASDH, rats receiving HHT alone performed significantly better than the two other treatment groups (Fig. 7). Spontaneous locomotion assessed in an open field was affected neither by injury nor by the type of therapy (results not shown).

Morphometric Analysis. All therapies had a significant neuroprotective effect

Table 1. Physiological variables

Group	pH	P_{CO_2}, mm Hg	P_{O_2}, mm Hg	Na^+, mmol/L	K^+, mmol/L	Hct, %
Baseline						
Sham	7.33 ± 0.03	53 ± 3.8	90.3 ± 8.1	133 ± 1.1	5.5 ± 0.2	45 ± 2.1
Vehicle	7.36 ± 0.01	51.8 ± 1.8	120.4 ± 14.1	134.8 ± 0.6	5.2 ± 0.2	45.1 ± 1.2
HHT	7.33 ± 0.01	55.9 ± 1.7	132.3 ± 10.6	132.7 ± 0.4	5.3 ± 0.2	45.1 ± 1.0
SE	7.35 ± 0.01	52.8 ± 1.9	145.5 ± 10.1[a]	132.6 ± 0.8	5.3 ± 0.2	44.5 ± 0.8
HHT + SE	7.34 ± 0.01	56.9 ± 1.1	142.8 ± 7.0[a]	133.3 ± 0.5	5.4 ± 0.2	45.1 ± 0.8
45 mins after ASDH						
Sham	7.31 ± 0.01	54.0 ± 2.1	89.2 ± 18.6	135.7 ± 2.2	4.9 ± 0.2	46.5 ± 0.4[a]
Vehicle	7.35 ± 0.01	51.9 ± 1.9	129.0 ± 11.8	135.1 ± 0.6	5.2 ± 0.1	41.9 ± 1.1[a]
HHT	7.32 ± 0.01	54.9 ± 1.4	131.9 ± 10.4	140.1 ± 0.5[a,b]	4.5 ± 0.2[b]	39.0 ± 0.5[a,b,c]
SE	7.33 ± 0.01	53.5 ± 1.7	154.3 ± 5.1[a]	133.1 ± 0.6	5.4 ± 0.2	42.8 ± 0.6[a]
HHT + SE	7.31 ± 0.01	56.4 ± 1.3	153.6 ± 10.6[a]	140 ± 0.5[a,b]	4.7 ± 0.1	39.2 ± 0.6[a,b,c]

Hct, hematocrit; HHT, hypertonic/hyperoncotic treatment; SE, surgical evacuation; ASDH, acute subdural hematoma.

[a] $p < .05$ vs. sham; [b] $p < .05$ vs. vehicle; [c] $p < .05$ vs. surgical evacuation group using one-way analysis of variance with Student-Newman-Keuls' *post hoc* test for analysis of individual group differences.
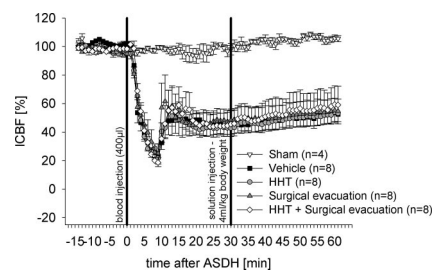

Figure 5. Chronic study: Contralateral local cerebral blood flow (*lCBF*) expressed as percentage change from baseline throughout the experimental procedure. There were no differences between treated groups. Decompression was initiated only at 60 mins after acute subdural hematoma (*ASDH*), that is, after the end of the lCBF monitoring. Values are given as mean ± SEM. *HHT*, hypertonic/hyperoncotic treatment.

Figure 6. Chronic study: Neuro-deficit score expressed in points (mean ± SEM) throughout the observation period of 11 days. Acute subdural hematoma (*ASDH*) at the vertical line marks day of injury with subdural blood infusion. *Significant difference between the vehicle group and all other groups ($p < .05$). Statistical analysis was performed with one-way analysis of variance on ranks with pair-wise multiple comparison (Dunn *post hoc* test). *HHT*, hypertonic/hyperoncotic treatment.

compared with the vehicle group, but there were no statistically significant differences among the treated groups. The percentage of hemispheric infarction volume in correlation with ipsilateral hemispheric volume was 13.3% ± 4.8% in the vehicle group, 4.4% ± 1.6% in the surgical evacuation group, 1.9% ± 0.6% in the HHT group, and 1.4% ± 0.3% in the group that received combination therapy (Fig. 8).

DISCUSSION

In our study, an acute subdural hematoma induced long-lasting behavioral deficits. Surgical evacuation of the hematoma was a protective measure following acute subdural hemorrhage. Furthermore, we were able to demonstrate a marked protective effect of blood evacuation in combination with early HHT
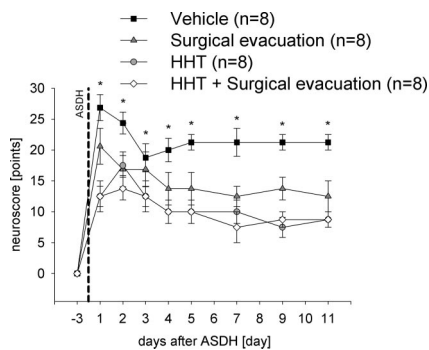
(HyperHAES) on functional and histologic outcomes, which was similar to that of early HHT alone. These protective effects were associated with a positive influence of HHT on ICP.

Pathophysiology of ASDH. After traumatic brain injury with acute subdural hemorrhage, lesions continue growing even if the CPP is normalized (23). Increased energy metabolism, massive glutamate release, and reduced tissue oxygen levels lead to necrotic cell death (28–30). Some of this secondary cell death can be explained by a secondary ischemic effect due to prolonged intracranial hypertension causing prolonged CBF reduction (30–32). There is a loss of coupling

of blood flow and metabolism as a mechanism for infarct recruitment (33). Most studies of the pathophysiological mechanisms after acute subdural hemorrhage have been performed without including traumatic brain injury in order to single out processes induced by the blood mass. The model used in this study was first described by Miller et al. (23) in 1990. A number of observations support the utility of this model. In this model, ischemic damage appears to be mainly due to the local effects of blood overlying the cortex. In humans too, the ischemic damage is mainly ipsilateral (34). Also, the slow rate of hematoma formation may accord with findings in humans, in which posttraumatic bleeding is usually from a vein or a very small cortical artery (35). The blood infusion in this experimental setup leads to an initially high ICP peak followed by prolonged intracranial hypertension around 20 mm Hg. This was easily reproduced in the past in different studies employing this model, including our study (23, 36, 37). The ICP peak can lead to herniation with wide pupils and cessation of spontaneous breathing due to intracranial hypertension mainly around the time of blood infusion, but less frequently at later times. Subsequently, however, the model produces only moderate intracranial hypertension, but vasogenic edema develops and reaches a peak 48 hrs after blood infusion (30). The rat model results in mortality rates similar to those found in humans (23). Moreover, the pathophysiological processes induced in this model can be successfully treated. This model is used to test the effects of putative neuroprotective, recovery-supporting, and cognition-enhancing drugs (38). The administration of glutamate receptor antagonists (29, 39–41) and surgical evacuation (36, 42), as performed in our studies, was previously shown to be helpful in the rat model. Blood evacuation and a glutamate receptor antagonist also seem to be neuroprotective in human patients (2, 8, 43).

Thus, this ASDH model is useful and valid for testing novel therapies. In the present studies, HHT reduced ICP immediately after application and markedly improved functional and histologic outcome significantly. The combination of HHT and blood evacuation could not improve the outcome variables any further. In order to overcome this ceiling effect and better simulate clinical conditions, using a model of more severe injury might en-
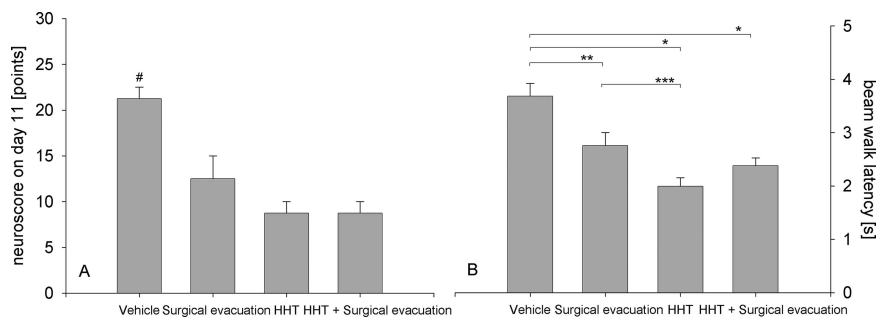
Figure 7. Chronic study: Neuroscore points (*A*) and beam-walk latency (*B*) on day 11 (mean ± SEM). #Significant difference of vehicle to all other groups. For the beam walk, performance differences were as follows: *$p < .001$ vs. hypertonic/hyperoncotic treatment (*HHT*) and HHT + surgical evacuation; **$p < .05$ vs. surgical evacuation; ***$p < .05$ vs. HHT. Statistics: one-way analysis of variance on ranks with Dunn *post hoc* comparison (*A*) and one-way analysis of variance with Student-Newman-Keuls' *post hoc* test (*B*).
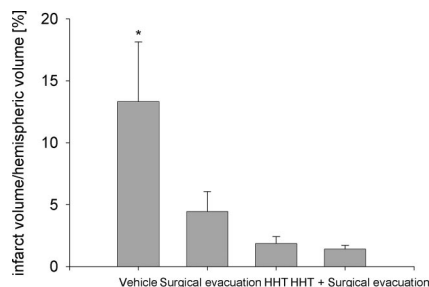

Figure 8. Chronic study: Infarction size displayed as percentage of hemispheric damage measured on day 12. The results are expressed as mean ± SEM and as percentage of contralateral hemisphere in order to correct for swelling. *$p < .05$ vs. surgical evacuation, hypertonic/hyperoncotic treatment (*HHT*), and HHT + surgical evacuation group using one-way analysis of variance on ranks. *Post hoc* tests revealed no significant difference between HHT-treated and surgical evacuation groups.

able us to establish an additional benefit of combined treatment.

Sawauchi et al. (36, 37) combined ASDH with diffuse brain injury or hypoxemia and demonstrated that this leads to more pronounced, long-term elevation of ICP and severe brain swelling. This ensured a prolonged ICP elevation due to massive swelling. Thus, a more severe injury might overcome the ceiling effect in our model and might reveal the full effect of a combination therapy. Other studies using larger animals might better mimic the neuroanatomical situation in humans.

Issue of Surgical Intervention. The beneficial effect of surgical intervention in the treatment of head trauma patients is controversial. Many criteria describe the indication or timing for surgery (44). Interventions with no beneficial effects have been described (45). Other studies show positive but still less than satisfactory effects (5, 45, 46). Current guidelines state that in patients with acute subdural hematoma and with indications for surgery, surgical evacuation should be performed as soon as possible (44). In many medical centers this is done by unilateral craniotomy and evacuation of the acute subdural hematoma.

Experimental facts, such as a decrease of ICP, improvement of circulation, increase of ptiO₂, and reduction of brain edema formation, support the surgical approach (5–8, 31, 37). Our data for blood clot evacuation are in line with the reported results in the literature. The mechanisms underlying the neuroprotective effect, however, are not well understood. Kuroda and Bullcok (42) found an increased CBF after removal of blood, but surgery had no effect on CBF in some cases. Hyperemia was patchy and infrequent. In their study, focal progression of ischemia and edema was not reversed by removal of the hematoma, although CBF in the contralateral hemisphere was restored to near control values (42). Measurements of cortical CBF and ICP before and after the evacuation of 300 μL of venous blood in rats demonstrated improved CBF and reduced intracranial hypertension (36), in accordance with clinical experience (5, 6, 36). The failure of some patients with traumatic brain injury (as well as laboratory rats) to respond to evacuation of a subdural hematoma is influenced not only by the magnitude of the primary traumatic brain injury but also by factors like intravascular coagulation. Early studies using the ASDH model reported microcoagulation in small vessels (47). Occlusion of cortical vessels under the subdural hematoma by clotted red cells and platelets and massively enlarged perivascular spaces due to swelling of astrocytes were reported. In addition, thromboxane A2 (48), free radicals, (49) nitric oxide (50), endothelin (51), and oxyhemoglobin (52) have been associated with vascular reactivity to subarachnoid hemorrhage. These microcirculatory disturbances initiate ischemic cell damage with release of glutamate, resulting in severe ischemic necrosis and progressive brain edema. Therefore, we suggest very early use of HHT to prevent microcirculatory disturbances and forestall further damage.

Mechanisms of Action of HHT. In pathologic situations with extensive microvascular damage, hypertonic saline seems to reduce microvascular collapse, restore vital nutritional blood flow, and diminish leukocyte-endothelium interactions (14, 17). Moreover, a significant decrease in ICP has been observed in various studies (15, 18–20). Other studies (10–12) have reported an improvement of cerebral perfusion. Our data support the finding of an improvement of intracranial hypertension after ASDH. However, we did not find strong evidence of improved CBF, except for an improved CPP after HHT. An explanation for the lack of reaction of cortical CBF to HHT might be the location of the laser Doppler probe. Cortical CBF could only be monitored over the contralateral cortex in which swelling is in general not a major factor (37, 42). Changes of no-flow and low-flow areas that can be followed easily using laser Doppler scanning and are influenced by HHT (12) might not be picked up by a stationary measurement. Finally, the period of measurements may have been too short to reveal the temporal course of the CBF reaction, as other studies with HHT have revealed reactions beginning ≥24 hrs after drug administration (11). Despite the lack of global CBF changes after HHT, this treatment improved outcome slightly more than blood evacuation alone. Duhaime et al. (53) and Yilmazlar et al. (54) reported that the blood mass is not solely responsible for the entire damage after ASDH in rats. Blood products from extravasated blood also play an important role (53, 54). A fact supporting this is that after blood clot removal. CBF remains decreased in some animals (36, 42). Our own studies show that CBF recovers quicker and parenchymal damage is smaller after subdural paraffin oil infusion than after blood infusion despite almost identical ICP changes (55). We hypothesize that the early treat-

ment with hyperoncotic/hypertonic solution after ASDH or subarachnoid hemorrhage helps to reduce ischemic areas underlying the blood clot and improves the glucose and oxygen supply to the tissue at risk. Consequently, the duration of ischemia is shortened and cells might be able to react better to toxic products of extravasated blood. In a study of subarachnoid hemorrhage performed by Zausinger et al. (13), HHT was found to reduce histologic and functional deficits dramatically despite high ICP levels and the fact that the blood clot was not removed. The authors related these effects of early HHT to a reduction of capillary resistance, endothelial cell swelling, and leukocyte-endothelial interactions. These effects improve energy status of cells, which resembles a protective mechanism following subdural blood removal. Thus, it seems that early application of HHT with effects on microcirculation and energy status may have caused its powerful effect in comparison to blood removal, which was performed much later after injury in this animal model.

Clinical Implications. Clinically relevant treatments, such as evacuation of subdural blood, are as effective in humans as in animals to reduce induced tissue damage and to restore blood flow if performed early after injury. As Seelig et al. showed (2), the time frame for curative therapy is very narrow. HHT is a well-established treatment of hemorrhagic shock and is readily available as a safe and minimally invasive therapy (24). Because of its known effects on brain swelling, microcirculation, and inflammatory responses, HHT given before surgery for ASDH might be an ideal ultraearly presurgical treatment strategy to protect brain tissue at risk before access to evacuation surgery. Our model and other animal models and patient studies examining similar coherences have shown a clear benefit of HHT in cerebral ischemia, controlled cortical impact injury, or subarachnoid hemorrhage (11–13). Unfortunately, there are yet too few clinical studies in traumatic brain injury with patient survival as an end point. A double-blinded, randomized, multicenter trial examining patients with head trauma in association with systemic hypotension revealed an advantage of HHT with increased survival (56). Given the safety and efficacy of HHT in the treatment of shock, prospective randomized clinical trials examining its preoperative effect as an adjunct to surgical evacuation

might uncover the potential of preoperative HHT. The data shown here should not be taken to imply that surgical evacuation is not necessary in the clinical setting, but animal studies, including ours, indicate that early HHT has a great potential in traumatic brain injury.

CONCLUSION

We assume that the most important mechanisms of HHT and surgical evacuation of subdural blood clot are linked to the reduction of ICP and improvement of microcirculatory blood flow. In our study, both treatments significantly improved the histologic and functional outcome when applied individually, while combined treatment was only slightly more efficient than blood clot evacuation alone. As revealed by ICP monitoring, but not by contralateral CBF monitoring, early HHT induced strong effects on outcome variables. HHT was very effective in this model of acute subdural hematoma in rats. However, a more severe traumatic ASDH model in rats, perhaps a large animal model, and clinical trials will be necessary to support the introduction of a combined treatment strategy into the clinical setting.

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