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Effect of Osmotic Agents on Regional Cerebral Blood Flow in Traumatic Brain Injury

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Abstract

Purpose—Cerebral blood flow (CBF) is reduced after severe traumatic brain injury (TBI), with considerable regional variation. Osmotic agents are used to reduce elevated intracranial pressure (ICP), improve cerebral perfusion pressure (CPP), and presumably improve CBF. Yet, osmotic agents have other physiological effects that can influence CBF. We sought to determine the regional effect of osmotic agents on CBF when administered to treat intracranial hypertension.

Materials and Methods—In eight acute TBI patients we measured regional CBF with PET before and 1 hour after administration of equi-osmolar 20% mannitol (1 g/kg) or 23.4% hypertonic saline (0.686 ml/kg) in regions with focal injury and baseline hypoperfusion (CBF < 25 ml/100g/min).

Results—ICP fell (22.4 ± 5.1 to 15.7 ± 7.2 mm Hg, $p=0.007$) and CPP rose (75.7 ± 5.9 to 81.9 ± 10.3 mm Hg, $p=0.03$). Global CBF tended to rise (30.9 ± 3.7 to 33.1 ± 4.2 ml/100g/min, $p=0.07$). In regions with focal injury, baseline flow was 25.7 ± 9.1 ml/100g/min and was unchanged; in hypoperfused regions (15% of regions), flow rose from 18.6 ± 5.0 to 22.4 ± 6.4 ml/100g/min ($p < 0.001$). Osmotic therapy reduced the number of hypoperfused brain regions by 40% ($p < 0.001$).

Conclusion—Osmotic agents, in addition to lowering ICP, improve CBF to hypoperfused brain regions in patients with intracranial hypertension after TBI.

Keywords

osmotic agents; cerebral blood flow; traumatic brain injury; intracranial hypertension

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Introduction

Patients with traumatic brain injury (TBI) may have mass lesions or develop cerebral edema, which can lead to increased intracranial pressure (ICP) ¹. Elevations in ICP can decrease cerebral perfusion pressure (CPP) to the point where cerebral blood flow (CBF) may fall to levels that produce ischemia and secondary brain injury. Ischemic neuronal changes have been identified in postmortem examinations of patients dying from TBI, with extent of ischemic brain damage correlated with extent/severity of intracranial hypertension ⁴. Control of ICP and maintenance of adequate cerebral perfusion forms the major focus in the management of TBI patients.

Yet, disturbances in CBF following TBI are heterogeneous and not globally uniform, with some regions being particularly vulnerable, having CBFs below traditional ischemic thresholds ⁷. PET studies indicate that even in the setting of adequate CPP, regional hypoperfusion may lead to inadequate oxygen delivery and ischemia ⁸.

Osmotic therapy is a key component in the medical management of elevated ICP. Both mannitol and hypertonic saline (HS) are effective in decreasing ICP and improving CPP. While this increase in perfusion pressure (CPP) is thought to result in increased CBF, this potentially beneficial effect of osmotic therapy has not been adequately verified in TBI patients. In addition, osmotic agents have a number of physiologic effects including changes in blood pressure, volume and viscosity that may influence its effect on CBF. This may lead to a heterogeneous CBF response to osmotic agents depending on the physiologic state of different brain regions. Thus it is likely that the effect of osmotic agents on CBF differs regionally, either as a result of focal injury (contusion or edema) or because of regional hypoperfusion.

In order to determine the regional effects of osmotic therapy we used quantitative 15-oxygen positron emission tomography (¹⁵O-PET) to measure regional CBF and metabolism in patients with severe TBI. In order to study the effects of osmotic agents in clinical use, these studies were performed in patients being clinically treated for intracranial hypertension. We primarily evaluated whether these agents improve CBF in hypoperfused or injured tissue when given to lower ICP.

Materials and Methods

Eligible Patients

A convenience sample of adult patients with traumatic brain injury who were receiving osmotic therapy for elevated ICP was enrolled in the study. Exclusion criteria included renal failure (serum creatinine >1.5mg/dl), age < 18 years, congestive heart failure, cardiac ischemia and pregnancy. The Human Research Protection Office and Radioactive Drugs Research Committee of Washington University School of Medicine approved the study. Written informed consent was obtained from each patient's legally authorized representative.

Clinical Management and Data Collection—TBI patients were evaluated in the Emergency Department by the Neurosurgery and Trauma services and underwent standard resuscitation and trauma management following the Brain Trauma Foundation guidelines¹⁵ and transferred to the Neurology/Neurosurgery Intensive Care Unit (NNICU). After initial stabilization, patients meeting recommended guidelines¹⁶ had an ICP monitor placed with either a Camino implantable transducer or intraventricular catheter. Surgery was performed if mass lesion required evacuation. ICP was treated, independent of CPP, if it exceeded 25 mm Hg for 5 minutes using a stepwise approach beginning with sedation followed by

osmotic agents. CPP was maintained above 60 mm Hg with vasopressors, if necessary. Data collected on each patient included demographics, Marshall grade ¹⁷ based on admission CT, degree of midline shift at the level of the third ventricle and GCS score at the time of admission and study.

Experimental Protocol

Physiologic, laboratory and PET data were recorded at baseline, including ICP, CPP and serum sodium/osmolality. After the baseline PET scan, patients were randomly assigned to receive either 1.0 g/kg of 20% mannitol or 0.686 ml/kg of 23.4% saline (i.e., equi-osmolar doses) infused over 15 minutes. One hour after initiation of infusion, measurements of all physiologic and PET data were repeated. Total fluid intake and urine output between the two PET studies was recorded. Repeat laboratory values were obtained at 4 hours after osmotic agent administration.

PET Methods

All PET studies were performed on the Siemens/CTI ECAT EXACT HR 47 located in the NNICU. The NNICU PET Research Facility is equipped with the same life support and monitoring equipment available at each patient bed in the NNICU (i.e., continuous electrocardiography, mean arterial pressure (MAP), O₂ saturation monitoring and ICP monitoring). A neurointensive care physician was present throughout each study and all ongoing therapies (vasopressors and fluids) were continued throughout the study. Every effort was made to maintain a constant physiologic state between the two scans. Image acquisition was performed as detailed previously to measure CBF, cerebral blood volume (CBV), oxygen extraction fraction (OEF), and cerebral metabolic rate for oxygen (CMRO₂) ¹⁸.

PET Processing

All PET scans for each patient were co-registered and aligned to the initial baseline CBF study using Automated Image Registration software (AIR, Roger Woods, University of California, Los Angeles, CA) ¹⁹. Radioactivity in arterial blood was measured using an automated blood sampler. The arterial time-radioactivity curve recorded by the sampler was corrected for delay and dispersion using previously determined parameters. Images were then co-registered to a reference brain image and resampled into Talairach atlas space. Global values for CBF, CBV, OEF and CMRO₂ were obtained using a standard image mask covering the brain from below the superior sagittal sinus down to the level of the pineal gland.

In the five subjects with focal injuries (Marshall grade 5), CT images obtained within 12 hours of the PET study were aligned with the PET images using Automated Image Registration software (AIR, Roger Woods, University of California, Los Angeles, California). In regions with contusion or edema (i.e. focal injury), regions were hand drawn on CT images to correspond to hypo/hyper-intensity. These regions were then superimposed on the aligned PET images for analysis. These focal injury regions were also subtracted from the brain mask for adjusted global analysis of uninjured brain.

For analysis of regions with hypoperfusion at baseline, we used an automated search routine to identify non-overlapping spherical regions of 2-cm diameter ¹⁸. This size of ROI was chosen to provide a reasonable balance between spatial resolution and counting statistics. Calculations were performed using the mean PET counts within each sphere and converted to CBF values. Regions were identified in order of CBF magnitude beginning with the lowest CBF. The mean hemodynamic and metabolic values for all regions in which CBF was below 25 ml/100g/min was determined for each patient at baseline and after

administration of the osmotic agent. To evaluate frequency of resolution of hypoperfusion with osmotic therapy, we compared the number of regions below this threshold prior to and after treatment.

Data Analysis

Continuous clinical, physiologic, and mean global and regional PET values are presented as mean $\pm$ SD and were compared using 2-tailed paired t-tests. Correlation between change in CPP and change in global CBF was analyzed using Pearson's correlation coefficient. We compared the number of hypoperfused regions before and after osmotic therapy using McNemar's test. No separate analysis comparing mannitol and HS was performed due to inadequate power from limited sample size in each treatment group.

Results

The eight patients were 37.4 ± 17.4 years of age, 7 were male and 7 Caucasian. Median admission GCS was 7 (range 3–13). Three patients had Marshall Type 2 (diffuse) injury, one patient was Type 5 and four were Type 6. Patients were studied a median of 3 days (range 1–4) after TBI, all while already on osmotic therapy for intracranial hypertension. At the time of the PET study median GCS was 5 (range 5–12) and three of the patients had midline shift (median 7, range 0–8 mm) on the CT performed closest to the time of PET study. Six were studied after administration of mannitol and two after hypertonic saline. None of the patients were treated with hyperventilation, hypothermia or barbiturates.

Results from patients who received HS and mannitol were not different and combined for all analyses. Osmotic therapy resulted in a significant reduction in ICP, stable MAP, and increase in CPP (Table 2). Osmotic therapy had no effect on arterial partial pressure of oxygen or carbon dioxide. There was no hemodilution or change in arterial oxygen content (Table 1). There was minimal volume loading with the fluid balance between the first and second PET studies being only 139 ± 72 ml net positive. Serum sodium concentration rose four hours after osmotic therapy ($p < 0.05$), while renal function and other laboratory/physiologic parameters were stable (Table 1).

PET Measurements

There was a trend toward higher CBF ($p=0.07$) but no change in global CBV, OEF or CMRO₂ (Table 2) after osmotic therapy. There was no correlation between change in CPP and change in global CBF ($r=0.436$, $p=0.42$). In regions with focal injuries, there was also no change in cerebrovascular data after osmotic treatment (Table 4).

A total of 677 ROIs (mean 85 ± 13 regions per patient) were created by the automated search algorithm and used to identify hypoperfused regions (Table 2). CBF < 25 ml/100g/min was present in 104 (15%) of these at baseline. Following intervention, CBF in those regions increased by 20% ($p < 0.001$) while CBV increased and OEF decreased (both $p < 0.05$). Figure 1 shows the change in the number of hypoperfused regions from baseline to after osmotic therapy. The number of regions with CBF < 25 ml/100g/min decreased by 40% from a mean of 13 per patient to 8 per patient ($p < 0.001$). The effectiveness of osmotic therapy in reducing the number of hypoperfused regions was evident in every patient studied (Figure 2).

Discussion

Using PET to determine the effects of osmotic agents on CBF in TBI patients with intracranial hypertension, we found that administration of mannitol or hypertonic saline

increased CBF specifically in regions with baseline hypoperfusion (without increasing global CBF), resulting in fewer hypoperfused regions after therapy.

While osmotic agents may both lower ICP and improve CBF they may do so via difference mechanisms and not necessarily in parallel. The ability of osmotic agents to lower ICP is generally believed to result from their capacity to decrease brain water²⁰. In a head injury model, Freshman and colleagues found that mannitol and HS produced similar reductions in brain water²¹. Previously our group has shown in a series of ischemic stroke patients that mannitol decreases total brain volume²². An alternative hypothesis has been proposed based on the observation that in experimental animals mannitol produces vasoconstriction of pial vessels observed through a cranial window²³. This argues that as a result of the fall in viscosity CBF would rise were it not for the reactive vasoconstriction that occurs in response to the change in viscosity. This vasoconstriction reduces cerebral blood volume, which accounts for the reduction in ICP.

In addition to changing perfusion pressure osmotic agents induce changes in viscosity that may influence its effect on CBF. Thus, while global CBF may change little, local effects may vary depending on the physiologic state of different brain regions. Several studies have shown that mannitol administration decreases blood viscosity. This is believed, in part, to be a result of mannitol shrinking red blood cells, which improves their deformability and thereby lowers viscosity²⁵. While less is known about the effect of hypertonic saline on blood viscosity, it likely works by the same mechanism as mannitol²⁶. It is this decrease in blood viscosity which may account for the increase in blood flow, especially in hypoperfused regions where flow is already reduced and vessels maximally dilated.

If all other influences on CBF remain stable, a drop in blood viscosity will reduce cerebrovascular resistance and improve flow. Normally compensatory vasoconstriction is triggered to maintain constant CBF. The explanation for the rise CBF is seen in hypoperfused regions relates to the effects of osmotic agents on blood viscosity coupled with the failure of cerebrovascular vasomotor response in the setting of ischemia. Multiple factors influence regional vasomotor tone simultaneously: perfusions pressure, metabolic demand, oxygen delivery, brain acid-base status and neuronal activity²⁷. It follows that under certain conditions a very potent stimulus from one of those factors could override the others. This is the case with ischemia where flow/metabolism mismatch induces vasodilation recalcitrant to other influences; thus the observation that autoregulation and CO₂ reactivity are lost in ischemic tissue. Similarly the vasoconstrictive response to a fall in viscosity may be lost, resulting in improved CBF to such regions.

These results are very similar to the data of Muizelaar and colleagues who studied the effect of mannitol on global CBF in patients with severe head injury³⁰. The investigators found that mannitol had no effect on CBF in patients with intact autoregulation but CBF rose in patients with defective autoregulation. Interestingly in almost half of the patients with defective autoregulation the baseline CBF was <25 mm Hg, similar to the hypoperfused regions in our study. Thus it is likely that in Muizelaar's study defective autoregulation and the rise in CBF following mannitol were both manifestations of a state of "vasoparalysis" due to hypoperfusion and inadequate oxygen delivery, as seen in our patients. It likely that the rise in CBF in hypoperfused regions is primarily due to a fall in viscosity distinct from any changes in CPP and ICP; hematocrit, blood pressure, arterial partial pressure of carbon dioxide (PaCO₂), arterial oxygen content (CaO₂), cardiac output and blood volume; as in our patients these factors remained quite stable.

This study has several limitations, including the small number of patients studied. As a result, the generalizability of our findings and ability to show small differences in

physiologic parameters could be limited. We also did not study the time course of the cerebrovascular response to the osmotic agents, which could change over time, but only demonstrate their effect acutely (i.e. at one hour). In addition, the study does not allow us to determine if there are any differences between mannitol and hypertonic saline. However, the major strength of this study is the comprehensive regional analysis with PET, which allowed us to determine the effect osmotic agents have on hypoperfused regions (not necessarily evident on CT scan) in TBI patients with established intracranial hypertension.

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CBF=cerebral blood flow (in ml/100g/min)

Figure 1.

Resolution of hypoperfused regions after osmotic therapy

Figure 2.
Individual improvement of regions with baseline hypoperfusion (CBF < 25 ml/100g/min)

Table 1

Physiologic and laboratory data before and after osmotic therapy

	Pre	Post
MAP (mm Hg)	103.3 ± 14.8	102.6 ± 17.0
P _a CO ₂ (torr)	36.8 ± 3.3	35.7 ± 4.8
P _a O ₂ (torr)	121.9 ± 42.1	125.0 ± 33.0
CaO ₂ (ml/dl)	14.2 ± 2.6	14.2 ± 3.0
CPP (mm Hg)	75.7 ± 5.9	81.9 ± 10.3 *
ICP (mm Hg)	22.4 ± 5.1	15.7 ± 7.2 *
Hemoglobin (g/dl)	11.3 ± 2.6	11.2 ± 2.7
Temperature (°C)	37.0 ± 0.5	37.3 ± 0.7
Na (mEq/L)	147.8 ± 7.7	150.1 ± 8.1 *
Glucose (mg/dL)	162.3 ± 44.5	188.6 ± 49.9
BUN (mg/dL)	9.1 ± 2.9	9.0 ± 1.9
Creatine (mg/dL)	0.9 ± 0.2	0.9 ± 0.2
Osmolality (mOsm/L)	315.1 ± 20.8	319.3 ± 23.0

MAP=mean arterial pressure; PaCO₂=partial pressure of carbon dioxide; PaO₂ = partial pressure of oxygen; CaO₂=arterial oxygen content; CPP=cerebral perfusion pressure; ICP= intracranial pressure, Na=sodium concentration, BUN=blood urea nitrogen,

*
p < 0.05

Table 2

Global and regional cerebrovascular and metabolic response to osmotic agent

	Pre	Post
Global (minus focal injury)		
CBF [*]	30.9 ± 3.7	33.1 ± 4.2
CBV ⁺	3.00 ± 0.35	3.15 ± 0.33
OEF	0.33 ± 0.07	0.33 ± 0.10
CMRO ₂ [*]	1.42 ± 0.34	1.48 ± 0.41
Focal injury (CT hypo/hyper-intensity)		
CBF [*]	25.7 ± 9.1	27.3 ± 6.3
CBV ⁺	2.74 ± 0.39	2.74 ± 0.55
OEF	0.38 ± 0.11	0.37 ± 0.08
CMRO ₂ [*]	1.29 ± 0.27	1.36 ± 0.17
Baseline regions with CBF <25 (n=104)		
CBF [*]	18.6 ± 5.0	22.4 ± 6.4 ^a
CBV ⁺	2.42 ± 1.46	2.56 ± 1.79 ^b
OEF	0.48 ± 0.24	0.41 ± 0.22 ^b
CMRO ₂ [*]	1.34 ± 0.70	1.38 ± 0.56

CBF=cerebral blood flow, CBV=cerebral blood volume, OEF=oxygen extraction fraction, CMRO₂=cerebral metabolic rate for oxygen,^{*} mL/100g/min,⁺ ml/100g,^a $p < 0.001$;^b $p < 0.05$