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ORIGINAL ARTICLE

Cerebral Hemodynamic and Metabolic Effects of Equi-Osmolar Doses Mannitol and 23.4% Saline in Patients with Edema Following Large Ischemic Stroke

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Abstract
Introduction Cerebral edema after ischemic stroke is frequently treated with mannitol and hypertonic saline (HS); however, their relative cerebrovascular and metabolic effects are incompletely understood, and may operate independent of their ability to lower intracranial pressure.
Methods We compared the effects of 20% mannitol and 23.4% saline on cerebral blood flow (CBF), blood volume (CBV), oxygen extraction fraction (OEF), and oxygen metabolism ($CMRO_2$), in nine ischemic stroke patients who deteriorated and had >2 mm midline shift on imaging. ^{15}O-PET was performed before and 1 h after administration of randomly assigned equi-osmolar doses of mannitol (1.0 g/kg) or 23.4% saline (0.686 mL/kg).
Results Baseline CBF values (ml/100g/min) in the infarct core, periinfarct region, remaining ipsilateral hemisphere, and contralateral hemisphere in the mannitol group were 5.0 ± 3.9, 25.6 ± 4.4, 35.6 ± 8.6, and 45.5 ± 2.2, respectively, and in the HS group were 8.3 ± 9.8, 35.3 ± 10.9, 38.2 ± 15.1, and 35.2 ± 12.4, respectively. There was a trend for CBF to rise in the contralateral hemisphere after mannitol from 45.5 ± 12.2 to 57.6 ± 21.7, $P = 0.098$, but not HS. CBV, OEF, and $CMRO_2$ did not change after administration of either agent. Change in CBF in the contralateral hemisphere after osmotic therapy was strongly correlated with baseline blood pressure ($R^2 = 0.879$, $P = 0.002$).
Conclusions We conclude that at higher perfusion pressures, osmotic agents may raise CBF in non-ischemic tissue. We conclude that at higher perfusion pressures, osmotic agents may raise CBF in non-ischemic tissue.

Keywords Osmotic · Hypertonic saline · Mannitol · Cerebral blood flow · Cerebral blood volume · Blood pressure

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Introduction

Following ischemic stroke, patients with large hemispheric infarction are at particularly high risk for neurological deterioration from cerebral edema [1]. The mortality for middle cerebral artery (MCA) infarction with massive brain edema (malignant MCA infarction) can be as high as 80% with conservative therapy [2]. While mortality may be reduced by early hemicraniectomy in selected patients [3], medical therapy aimed at lowering intracranial pressure (ICP), reversing edema and maintaining cerebral perfusion, remains a key component in management of these patients.

Osmotic agents such as mannitol and hypertonic saline (HS) are frequently administered to patients with post-stroke edema and are recommended by the American Heart Association (AHA) guidelines [4]. Mannitol and HS are effective at lowering ICP [5, 6], although data regarding their effect on outcome are limited [7].

Conflicting theories exist as to how osmotic agents act to reduce ICP. One hypothesis is that osmotic agents act primarily by reducing brain water [8]. However, an alternate hypothesis is that they act by reducing viscosity, lowering

cerebrovascular resistance, leading to compensatory vasoconstriction and a fall in cerebral blood volume (CBV) [9].

In addition osmotic agents may have cerebrovascular and metabolic effects independent of their effect on ICP. These effects may be as important as their ability to lower ICP following stroke. It is well known that herniation in stroke patients usually occurs when ICP is normal [10]; yet, osmotic agents are effective at reversing clinical herniation [11]. In experimental models of stroke and cerebral edema, mannitol improves CBF even when ICP is not elevated [12–14]. Few data exist in humans, limiting our ability to understand how to optimally utilize osmotic therapy. Furthermore, the relative efficacy of different agents has rarely been studied in randomized head-to-head comparisons using equi-osmolar doses, which has hampered our ability to select an optimal agent to both control ICP and maintain cerebral perfusion.

To understand the relative cerebrovascular and metabolic effects of mannitol and HS, we measured CBF, CBV, oxygen extraction fraction (OEF), and cerebral metabolic rate for oxygen ($CMRO_2$) using ^{15}O positron emission tomography (PET) before and after administration of a large equi-osmolar dose of either 20% mannitol or 23.4% saline in patients who had deteriorated secondary to cerebral edema following an ischemic stroke. We sought to determine whether (1) equi-osmolar doses of mannitol and 23.4% saline had similar effects on regional CBF, CBV, and $CMRO_2$ and (2) further understand the mechanism by which osmotic agents act by determining whether they reduce CBV.

Methods

Eligible Patients

Adult ($\geq$18 years old) patients with acute hemispheric ischemic stroke were screened to identify those at risk for edema (NIH Stroke Scale [NIHSS] score $\geq$11). Those who developed clinical worsening (fall of $\geq$2 points on the Glasgow Coma Scale [GCS] or $\geq$4 points on the NIHSS) and/or repeat imaging demonstrating midline shift of $>$2 mm at the pineal gland or septum pellucidum were eligible to be enrolled in the study. Exclusion criteria included renal failure (serum creatinine $>$1.5 mg/dl), congestive heart failure, cardiac ischemia, and pregnancy. The Human Research Protection Office and Radioactive Drugs Research Committee of Washington University approved the study.

Clinical Management

Patients with large hemispheric stroke were monitored closely for signs of clinical deterioration. The decision to initiate osmotic therapy was made based on neurological deterioration associated with cerebral edema and radiographic evidence of increased midline shift. Patients who failed to respond to osmotic therapy were considered for hemicraniectomy based on age, co-morbidities, and wishes of the patient and family. Intubation was performed in patients with marked impairment of consciousness (typically GCS $<$9), inability to maintain an adequate airway or mange secretions.

The patients were treated in a consistent manner by a single neurointensive care team. Mannitol (20%) was administered intravenously by intermittent boluses (starting at a dose of 1 gm/kg every 6 h). Patients were weighed daily; fluid balances were assessed frequently; and intravenous fluids were adjusted to keep the overall fluid balance even. Additional adjustments were made in patients with large insensible losses of fluid, with the aim of maintaining a constant intravascular volume. Measurements of serum electrolytes, osmolality, the osmotic gap were performed two to four times a day during osmotic therapy.

Study Protocol

Using sealed envelopes, patients were randomized to receive either mannitol or HS. The study was timed so that the osmotic agent given for the PET study would be administered at the same time they would normally have received their next dose of osmotic agent.

Baseline measurements of NIHSS score, GCS, osmolality, and electrolytes, and PET imaging were performed. Then 1.0 g/kg of 20% mannitol or 0.686 ml/kg of 23.4% saline (equi-osmolar doses) was infused over 15 min. One hour after beginning the infusion, measurement of NIHSS, GCS, and PET imaging were repeated.

In order to maintain stable volume status, patients had urine output measured and any net negative fluid balance (the difference between the urine output and the volume of infused intravenous fluids and mannitol) was corrected by infusing an equivalent amount of isotonic saline prior to the PET imaging. Serum osmolality and electrolytes were measured again 4 h after completion of mannitol or HS infusion.

PET Methods

All patients were studied on the Siemens CTI ECAT EXACT HR 47 PET Scanner located in the Neurology-Neurosurgery Intensive Care Unit (NNICU). A neurointensivist was present throughout the study, and all ongoing therapies were continued throughout the duration of the study. During the PET study, every effort was made to maintain a constant physiological state. At the time of each image acquisition, physiological data were recorded.

Each scan was acquired in the two-dimensional mode. An individual transmission scan was obtained and used for subsequent attenuation correction of emission scan data. All scans were calibrated for conversion of PET counts to quantitative radiotracer concentrations, as previously described [15].

Regional CBF was measured by bolus injection of ^{15}O-labeled water using an adaptation of the Kety autoradiographic method [15, 16]. Regional CBV was measured using a brief inhalation of ^{15}O-labeled carbon monoxide [17, 18] while $CMRO_2$ and oxygen extraction fraction (OEF) were derived from the CBF and CBV measurements and an inhalation of ^{15}O-labeled oxygen [19]. Quantitative measurements of arterial oxygen content (CaO_2) were obtained by oximetry.

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). In five patients (three mannitol and two hypertonic saline), CT images obtained within 12 h of the PET study were available for analysis and were realigned with the PET images. Using the individual CT images, an image mask was created that included the brain below the superior sagittal sinus down to the level of the pineal gland. In addition, regions were hand drawn on the CT images to correspond to the following: infarct core—center of the hypodensity; peri-infarct region—an approximately 1 cm wide band adjacent to the edge of the infarct; ipsilateral—remaining ipsilateral hemisphere after removal of infarct and peri-infarct regions, and the entire contralateral hemisphere. These regions were superimposed on aligned PET images for analysis. In four subjects CT images were no longer available and regions were identified on the PET CBF images. In those cases the regions identified were limited to the infarct and contralateral hemisphere.

Data Analysis

Continuous clinical and physiological variables and regional PET values were compared using 2-tailed paired t-tests. The relationship between physiological variables and change in CBF following osmotic therapy was tested with Pearson's correlation coefficient.

Results

The clinical characteristics of the nine patients are summarized in Table 1. All had suffered large hemispheric infarction (left sided in eight) involving most or all of the MCA territory and had received mannitol following clinical deterioration attributed to cerebral edema. All but one (eight of nine) received mannitol therapy prior to the PET study. The average dose of mannitol for the 24 h prior to the PET study was 2.5 ± 0.9 g/kg. None had received hypertonic saline.

The NIHSS had deteriorated from a median of 22 (range 15–30) at the time of admission to 25 (range 15–35) at the time of the PET study. The range of the individual changes in NIHSS was +18 to −2, and four patients had developed pupillary asymmetry. Average midline shift on the CT performed closest to the time of the PET study was 7.9 ± 7.3 mm. Two patients had undergone a hemicraniectomy. During the PET study all were intubated, none were on vasoactive agents, and eight of nine were sedated with intermittent boluses of fentanyl.

Blood pressure, arterial pCO_2, arterial oxygen content, temperature, and renal function at baseline were not significantly different and remained stable in both groups following administration of either mannitol or HS (Table 2). At 4 h osmolality rose in both groups, but sodium concentration rose significantly only in the HS group in response to the single dose administered during the PET study.

There were no significant changes in CBF, CBV, OEF, or $CMRO_2$ in the infarct core, peri-infarct or ipsilateral regions following administration of either mannitol or HS. In the contralateral hemisphere there was a trend for CBF to increase following mannitol (Table 3), although the differences were not statistically significant. No such trend was evident following HS.

Examination of individual patient values of change in CBF in the non-ischemic ipsilateral and contralateral hemispheres revealed a range of responses with no effect in some patients and CBF rising more than 50% in others. There was an obvious relationship between baseline mean blood pressure at the time of the PET study and change in CBF following osmotic therapy in non-infarcted tissue. The percentage change in CBF in the contralateral and non-ischemic ipsilateral hemispheres following osmotic therapy was highly correlated with mean blood pressure at the time of the study ($R^2 = 0.787$, $P = 0.001$, see Fig. 1).

Discussion

When blood flow is restored to infarcted brain tissue, the dead cells swell, causing an increased mass within the brain. Edema starts to develop within hours of stroke onset, peaks at 2–5 days, and then gradually resolves [20]. With large infarcts, the swelling can damage and displace brain structures and compromise CBF. This can cause additional brain injury, herniation, and is a primary cause of early death after MCA stroke.

Table 1 Clinical characteristics

	Mannitol	Hypertonic (23.4%) saline	Total
N	5	4	9
Age (years)	64 ± 12	62 ± 11	63 ± 12
Male	3	2	5
White/African American	2/3	2/2	4/5
Admission NIHSS	23 (15–30)	22 (17–28)	23 15–30
% MCA territory involved	75 ± 10	60 ± 10	68 ± 10
Midline shift (mm)	5.6 ± 5.2	10.5 ± 9	7.9 ± 7.3
Hemicraniectomy	2	0	2
Interval from ictus (h)	65.5 ± 15.2	74.3 ± 17.0	69.9 ± 15.6

NIHSS NIH Stroke Scale score, *MCA* middle cerebral artery

Table 2 Physiological and laboratory characteristics during the PET study

	Mannitol		Hypertonic (23.4%) saline	
	Baseline	After mannitol	Baseline	After HS
MAP (mm Hg)	113 ± 19	113 ± 14	98 ± 11	103 ± 11
$PaCO_2$ (mm Hg)	38 ± 8	40 ± 6	32 ± 7	30 ± 8
PaO_2 (mm Hg)	103 ± 21	98 ± 25	135 ± 11	115 ± 5
CaO_2 (mm Hg)	16.0 ± 1.9	15.9 ± 1.7	16.3 ± 3.2	15.9 ± 3.4
Hemoglobin (gm/dl)	11.9 ± 1.4	12.0 ± 1.5	12.1 ± 2.4	11.1 ± 2.4
Temperature (°C)	37.8 ± 0.7	37.8 ± 0.6	37.9 ± 0.5	38.0 ± 0.6
[a]Na (mEq/L)	144.5 ± 9.3	146.5 ± 8.4	139.8 ± 6.1	147.3 ± 4.8*
[a]Glucose (mg/dL)	130.5 ± 33.1	177.8 ± 52.3	167.0 ± 71.3	171.0 ± 84.2
[a]BUN (mg/dL)	7.3 ± 2.5	9.3 ± 3.2	14.5 ± 7.7	14.5 ± 4.8
[a]Creatinine (mg/dL)	0.67 ± 0.10	0.70 ± 0.08	1.0 ± 0.41	0.93 ± 0.45
[a]Osmolality (mOsm/L)	301.3 ± 14.1	309.8 ± 19.8*	304.5 ± 16.3	317.0 ± 14.8*

MAP mean arterial pressure, $PaCO_2$ partial pressure of carbon dioxide, PaO_2 partial pressure of oxygen, CaO_2 arterial oxygen content, *Na* sodium concentration, *BUN* blood urea nitrogen

* $P < 0.05$ compared to baseline

[a] Four hours after osmotic agent

In some experimental models of ischemic stroke, mannitol reduces infarct size, edema, and neurological deficit [21, 22]. Mannitol and hypertonic saline reduce elevated ICP in stroke patients [23–25]; yet, their impact on outcome is less clear. While noting the lack of convincing evidence of efficacy, the AHA guidelines [4] and others recommend the use of osmotic agents to treat post-stroke edema.

There are two proposed mechanisms through which osmotic agents may act to lower ICP: (1) by reducing brain water or (2) by reducing CBV. Mannitol doses of 0.75–1.25 g/kg reduce brain water from 79.61 to 77.96% in normal rabbits [26]. In a model of head injury, mannitol and 7.5% saline produced similar reductions in brain water [27]. In a series of ischemic stroke patients, we previously reported shrinkage of the contralateral hemisphere (reduction of 8.0 ± 0.4%) following mannitol [28]. These studies, however, did not allow us to determine whether the fall in brain volume was due to a reduction in brain water or blood volume.

The alternate theory is based on the observation that mannitol produces a rapid constriction of both arterioles and venules on the surface of the brain [9]. Mannitol shrinks red blood cells and increases their deformity, reducing viscosity [29, 30], an effect that is independent of changes in hematocrit [31]. The reduced viscosity leads to compensatory vasoconstriction to maintain stable CBF a fall in CBV and thus ICP.

In this study of osmotic agents in patients with post-stroke edema we found that osmotic agents produce a variable effect on CBF, which appears to be modulated by blood pressure. At normal blood pressures osmotic agents had minimal effect on CBF, but when blood pressure was elevated, osmotic agents resulted in an impressive rise in CBF. In addition, our data indicate that neither mannitol nor 23.4% saline led to a fall in CBV, arguing against

Table 3 Regional cerebrovascular and metabolic response to mannitol and hypertonic saline

Stroke	Mannitol			Hypertonic Saline (HS)		
	Baseline	After mannitol	*P* value	Baseline	After HS	*P* value
Infarct core						
CBF (ml/100 g/min)	5.0 ± 3.9	6.3 ± 5.2	0.213	8.3 ± 9.8	9.7 ± 11.2	0.344
CBV (ml/100 g/min)	1.55 ± 0.56	1.91 ± 1.05	0.196	1.58 ± 0.74	1.64 ± 0.81	0.612
OEF	0.19 ± 0.07	0.18 ± 0.14	0.974	0.27 ± 0.01	0.39 ± 0.13	0.362
$CMRO_2$ (ml/100 g/min)	0.17 ± 0.11	0.15 ± 0.17	0.829	0.22 ± 0.37	0.38 ± 0.49	0.216
Peri-infarct						
CBF (ml/100 g/min)	25.6 ± 4.4	30.2 ± 5.6	0.049	35.3 ± 10.9	37.2 ± 6.0	0.678
CBV (ml/100 g/min)	3.48 ± 0.25	4.45 ± 0.90	0.171	3.95 ± 1.60	4.23 ± 1.87	0.375
OEF	0.29 ± 0.08	0.21 ± 0.05	0.313	0.33 ± 0.09	0.52 ± 0.10	0.395
$CMRO_2$ (ml/100 g/min)	1.11 ± 0.40	0.94 ± 0.21	0.571	1.63 ± 0.26	2.85 ± 1.32	0.352
Ipsilateral hemisphere (minus infarct and peri-infarct)						
CBF (ml/100 g/min)	35.6 ± 8.6	43.0 ± 12.7	0.114	38.2 ± 15.1	40.1 ± 10.0	0.59
CBV (ml/100 g/min)	4.57 ± 0.41	6.07 ± 1.51	0.163	4.92 ± 1.86	5.29 ± 2.31	0.441
OEF	0.27 ± 0.004	0.18 ± 0.07	0.244	0.35 ± 0.07	0.53 ± 0.13	0.414
$CMRO_2$ (ml/100 g/min)	1.46 ± 0.44	1.10 ± 0.28	0.412	1.92 ± 0.63	3.27 ± 1.89	0.373
Contralateral hemisphere						
CBF (ml/100 g/min)	45.5 ± 12.2	57.6 ± 21.7	0.098	35.2 ± 12.4	36.9 ± 7.27	0.574
CBV (ml/100 g/min)	4.30 ± 0.50	5.29 ± 1.42	0.104	3.49 ± 0.85	3.41 ± 1.26	0.791
OEF	0.39 ± 0.15	0.31 ± 0.10	0.209	0.33 ± 0.09	0.46 ± 0.15	0.220
$CMRO_2$ (ml/100 g/min)	2.55 ± 0.58	2.61 ± 0.60	0.802	1.82 ± 0.69	2.81 ± 1.49	0.105

CBF cerebral blood flow, *CBV* cerebral blood volume, *OEF* oxygen extraction fractions, *$CMRO_2$* cerebral metabolic rate for oxygen

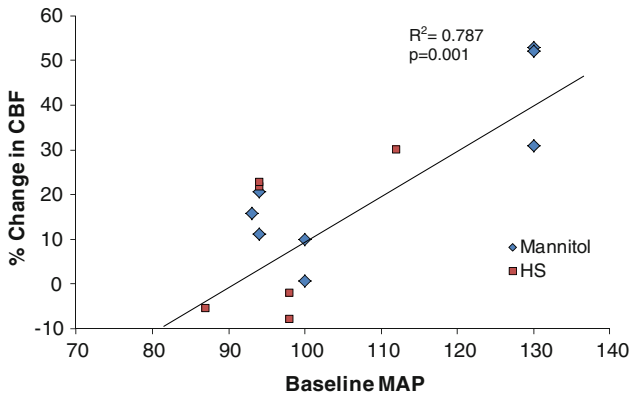

Fig. 1 Correlation between baseline mean arterial blood pressure and percent change in CBF in contralateral hemisphere CBF after osmotic therapy

the theory that they reduce ICP by producing cerebral vasoconstriction.

Few studies (none in patients with ischemic stroke) have assessed the CBF and metabolic response to osmotic therapy. In experimental models of head injury, intravenous boluses of 0.5 g/kg of mannitol led to a consistent rise in CBF and metabolism that was out of proportion to the reduction in ICP [32]. In head injury patients, mannitol either had no effect or slightly increased CBF [33, 34], but did not improve metabolism. In another study 0.5 gm/kg of mannitol resulted in a modest increase in CBF but no change in oxygen or glucose metabolism [35]. While mannitol reduces ICP and improves cerebral perfusion pressure, this does not necessarily lead to improved jugular venous saturation or brain tissue oxygen tension [36].

The relationship we found between blood pressure and change in CBF has not been previously reported and might explain some of the variability in the literature. That it occurred in the non-infarcted ipsilateral and contralateral hemispheres is of particular importance since it involved presumably normal brain regions. There was no change in blood pressure as a result of the administration of the osmotic agent to account for the rise in CBF. This suggests that with high perfusion pressures (a mean blood pressure of ~130 mm Hg in these patients), the vasoconstrictive response to a fall in viscosity is lost. At moderate perfusion pressures, reduced viscosity is compensated for by vasoconstriction. However, when CPP is near the upper limits of autoregulation cerebral resistance arterioles are close to maximally constricted and the ability to respond to the rise in CBF due to reduced viscosity is limited. This observation is preliminary and should be interpreted with caution. Further study is needed to better define the relationship and understand its therapeutic implications.

This article has a number of weaknesses. The number of subjects is small and we did not study the time course of the cerebrovascular response to osmotic agents, which may change dynamically over time. However, strengths of this study include random allocation of eligible patients to equi-osmolar doses of the two agents and evaluation of regional effects using PET. We were also able to address, for the first time in humans, the mechanism of action (effect on CBV) of these agents. Finally through this approach we were able to identify a previously unreported potential relationship between blood pressure and cerebrovascular response to osmotic therapy.

In summary, we found that the degree of rise in CBF in the contralateral hemisphere in ischemic stroke patients following osmotic therapy appears to be mediated by blood pressure. We found no support for the theory that osmotic agents reduce CBV.

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