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Hypertonic saline more efficacious than mannitol in lethal intracranial hypertension model

Joacil Carlos da Silva*, Frederico de Melo Tavares de Lima*, Marcelo Moraes Valença† and Hildo Rocha Cirne de Azevedo Filho*

**Department of Neurosurgery, Hospital da Restauração, Recife, Pernambuco, Brazil*
†Department of Neurosurgery, Hospital das Clínicas, Recife, Pernambuco, Brazil

Background: Medical management of brain edema and elevated intracranial pressure (ICP) is a crucial challenge in neurosurgical practice. Depending on the cause, the treatments for brain edema fall into three categories: stabilization of the blood–brain barrier, depletion of brain water and surgical decompression. Although mannitol is the mainstay of hyperosmolar therapy, hypertonic saline (HS) is emerging as an effective alternative to traditional osmotic agents.
Methods: Experimental elevated ICP (50 mmHg) was induced in rabbits using an intracranial balloon. The effects of mannitol and HS (10% NaCl) were compared in this specific physiopathological model. Twelve animals were divided into three groups (control, HS and mannitol) according to intravenous administration of 0·9% NaCl, 10% NaCl or 20% mannitol 5 minutes after the elevation of ICP. The doses of 10% NaCl and 20% mannitol were iso-osmolar. During 90 minutes, continuous recording of ICP, mean arterial pressure (MAP) and cerebral perfusion pressure (CPP) was realized.
Results: The control group had a median survival of only 53 minutes, significantly lower than the treated groups (p=0·0002). There was statistical difference between mannitol and HS; the 10% NaCl group had lower values of ICP (p=0·0116) and higher values of MAP (p<0·0001) and CPP (p<0·0001).
Conclusion: The findings demonstrate higher efficacy of the 10% NaCl treatment in this comparison with 20% mannitol. Further efforts should be directed toward development of clinical studies using iso-osmotic doses of mannitol and HS in specific etiologies of intracranial hypertension.

Keywords: Intracranial pressure, hypertonic saline, mannitol

Introduction

Hyperosmolar therapy is the preferred treatment for intracranial hypertension (IH) after acute cerebral injury[1,2], and mannitol has been the main osmotic agent used, both in human and animal studies[3–9].

Reduction of brain water content has long been theorized to be an effective means of controlling intracranial pressure (ICP). This theoretical goal initially led to the misguided practice of dehydrating patients through fluid restriction and diuretics. Hyperosmolar agents, primarily mannitol, were introduced, as it was understood that establishing an osmotic gradient across the blood–brain barrier (BBB) did not require systemic dehydration. Mannitol also induces an immediate reduction in ICP through changes in blood–fluid dynamics or rheology. The mechanisms underlying these rheological improvements include optimization of blood viscosity and enhanced oxygen delivery resulting in a compensatory cerebral vasoconstriction[10].

However, administration of mannitol has some adverse reactions, like dehydration, hypotension, metabolic disorders, renal failure and rebound IH[11,12]. Because of these limitations, hypertonic saline (HS) solutions have been investigated as an alternative for the treatment of cerebral edema and IH[13].

The main justification for using HS stems from the fact that an intact BBB is less permeable to saline than to mannitol. HS should therefore be a more effective and more durable osmotic agent. Animal and clinical evidences have shown HS to be as effective as mannitol in reducing ICP and cerebral water content even in cases refractory to mannitol[10,13–40].

The present work was performed to compare the efficacy of mannitol (1 g/kg) and an iso-osmotic dose of 10% HS in a lethal balloon compression IH model.

Material and methods

Permission for the study protocol was granted by the institutional ethical committee.

Correspondence and reprint requests to: J. C. da Silva, Department of Neurosurgery, Hospital da Restauração, Agamenon Magalhães, SN, Recife, Pernambuco 51021-110, Brazil. [joacil_carlos@hotmail.com]
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Animal preparation

Twelve male New Zealand albino rabbits (mean body weight, 3·4 ± 0·15 kg) were anesthetized using propofol intravenously (3 mg/kg bolus and 12 mg/kg/h continuously). After the cranium was fixed in a table frame, a burr hole was performed above the parietal portion of the right cerebral hemisphere using a high speed drill. The dura mater was opened, and a subdural balloon was inserted to induce IH. The ICP was measured on the left side using an intraparenchymal microsensor monitoring system (Codman, Johnson & Johnson Medical Ltd, Berkshire, UK). Blood pressure was recorded through a left femoral artery catheter connected to an electronic system (DX2010; Dixtal Biomédica Ltd, Manaus, Brazil). Hematocrit, blood gases and plasma electrolytes were studied before and 30, 60 and 90 minutes after administration of the different treatments. The intracranial balloon was inflated gradually during 5 minutes until the ICP monitor obtain a record of 50 mmHg.

Treatment regimens

Three groups of animals, HS, control and mannitol (n=4/group), were used in the experiments. Each group received 10% NaCl (3·2 ml/kg), 0·9% NaCl (3·2 ml/kg) or mannitol (1 g/kg) 5 minutes after induction of IH.

Measurements of study variables

ICP and mean arterial pressure (MAP) were recorded continuously throughout the experiment. Arterial and venous blood samples were collected before and 30, 60 and 90 minutes after administration of drugs.

Killing of animals

After 90 minutes of observation, animals were killed by injecting KCl intravenously.

Statistical analyses

The values are presented as means ± standard errors of the means. A two-way analysis of variance and *post hoc* multiple comparisons were performed for all variables. $p<0·05$ was considered significant. All analyses were conducted using commercial software (GraphPad Prism 4·0, GraphPad Software Inc.).

Results

Survival

The developed acute IH model was consistently lethal. Both NaCl 10% and mannitol 20% prolonged survival during the observation period. Control group had a median survival of 53 minutes, significantly lower than the treated groups (p=0·0002).

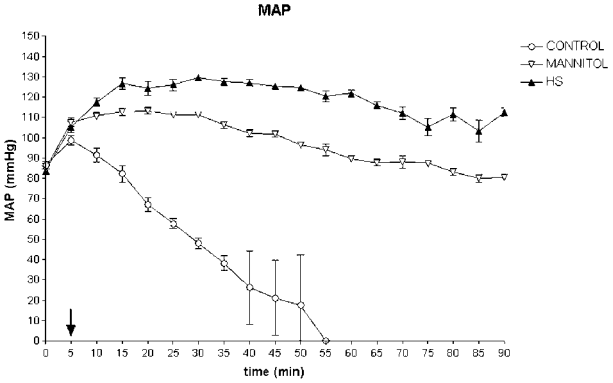

Figure 1 Mean arterial pressure (mmHg) evolution during observation period. Note lethal evolution of control group after 40 minutes. ↓ = drug infusion

Blood analyses

Results are displayed in *Table 1*. After treatment, hematocrit decreased in both groups. Both treatments were associated with a significant decrease of the blood pH, most pronounced in mannitol group. The systemic acidosis was accompanied by an increased arterial pCO_2 and decreased pO_2. The plasma Na^+ level increased after HS infusion and moderately decreased after mannitol. Plasma K^+ moderately decreased in mannitol group.

MAP, ICP and CPP

Results are displayed in *Figures 1–3*.

There was a sustained rise in ICP associated with the balloon inflation in all three groups. After the administration of each treatment regimen, there was an immediate reduction in ICP in NaCl 10% and mannitol groups. The control group maintained higher ICP levels and lower MAP and CPP than the treated groups.

There was statistical difference between mannitol and HS; the 10% NaCl group had lower values of ICP (p=0·0116) and higher values of MAP ($p<0·0001$) and CPP ($p<0·0001$).

Discussion

The use of hyperosmolar agents to treat IH can be traced back to the publication of Weed and McKibben[41]. Their work led to studies of hypertonic

Table 1 Hematocrit, blood gases and plasma electrolytes

Group, time (min)	Hct (%)	Na^+ (mmol/L)	K^+ (mmol/L)	pO_2 (mmHg)	pCO_2 (mmHg)	pH
Control, 0	35·7±1·9	145·3±1·2	4·5±0·2	138±8·0	32·6±1·8	7·41±0·02
Control, 30	35·5±1·7	145·7±1·1	4·4±0·3	139±1·0	31·4±1·5	7·34±0·01
Control, 60	0	0	0	0	0	0
Control, 90	0	0	0	0	0	0
HS, 0	34·5±1·7	144·5±0·2	4·3±0·1	137±6·4	33·4±1·6	7·44±0·03
HS, 30	29·6±0·9	156·8±0·7	4·2±0·9	136±2·7	36·1±1·5	7·34±0·02
HS, 60	30·2±1·2	157·9±0·5	4·3±0·5	135±4·9	33·5±0·9	7·38±0·01
HS, 90	29·7±1·8	160·2±0·1	4·4±0·3	133±5·8	34·4±1·4	7·35±0·01
Mannitol, 0	36·1±1,3	143·9±0·9	4·4±0·3	138±5·5	33·7±1·5	7·40±0·04
Mannitol, 30	36·1±1·1	135·3±0·4	3·8±0·7	136±4·3	45·3±1·3	7·28±0·02
Mannitol, 60	35·1±1·7	138·1±0·5	3·9±0·1	134±3·5	41·7±1·7	7·35±0·01
Mannitol, 90	34·9±1·4	146·1±0·7	3·7±0·2	133±6·8	39·5±1·2	7·34±0·03

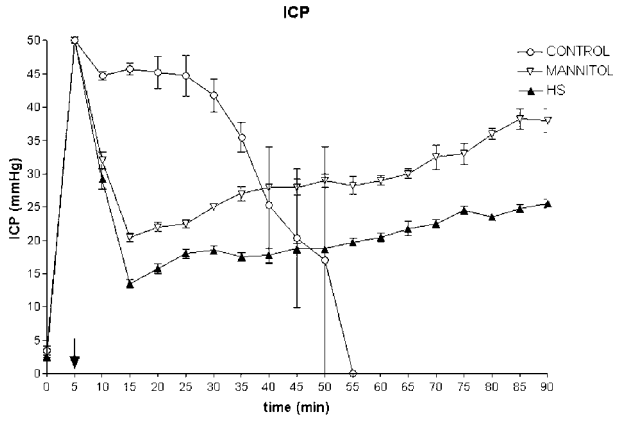

Figure 2 Intracranial pressure (mmHg) evolution during observation period. ↓ = drug infusion

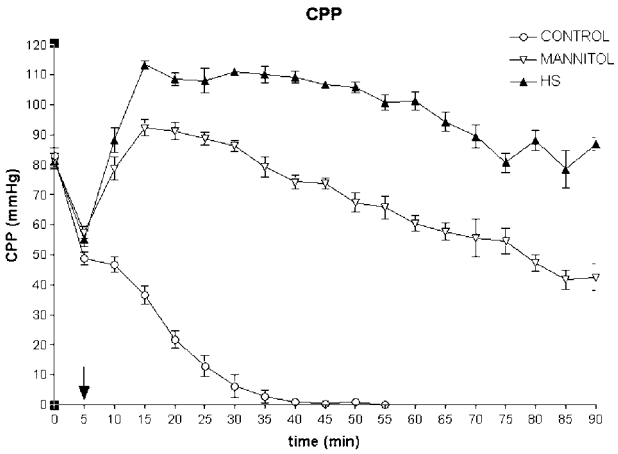

Figure 3 Cerebral perfusion pressure (mmHg) evolution during observation period. ↓ = drug infusion

glucose, hypertonic magnesium sulfate sodium arabinate and the later discovery that hypertonic urea was clinically useful[42,43].

The ideal osmotic agent establishes a strong transendothelial osmotic gradient by remaining largely in the intravascular compartment. It is inert, nontoxic and has minimal systemic side effects. Various substances, including urea, glycerol, sorbitol, mannitol and, more recently, HS formulations, have been investigated. Although effective, urea is associated with numerous side effects, including nausea, vomiting, diarrhea, hemoglobinuria, coagulopathies and rebound IH, and is no longer used. Glycerol and sorbitol are only moderately successful at decreasing ICP and are associated with significant hyperglycemia[4,10,13,44] Mannitol is effective and safe and is recommended by both the Brain Trauma Foundation and the European Brain Injury Consortium as the osmotic drug of choice[45,46].

Nowadays, reports about HS superiority to conventional mannitol, even in refractory cases, should not be considered the advent of a new therapy. Instead, the evolving role of HS would be comprehended as the consolidation of a safe and efficacious osmotic agent potentially more adequate in specific etiologies of IH[10,24,47].

Curiously, there are only a few experimental or clinical comparisons of these agents (summarized in *Tables 2–4*). The majority of these works lacks in scope and uniformity of protocol. Because mechanisms of ICP elevation differ according to the underlying etiology, accurate animal models would be developed and specific clinical scenarios must be tested[10,24].

The present experiment findings demonstrate a higher efficacy of HS treatment in this comparison with mannitol. The experimental acute IH model used was developed to simulate a life-threatening herniation syndrome.

Reversal of transtentorial herniation syndrome in human treated with HS was recently reported. Consecutive 68 patients with clinically defined herniation syndrome treated with 23·4% saline were included in a retrospective cohort. Treatment was associated with rapid reversal of transtentorial herniation, reduced ICP and few adverse effects. Recovery from herniation symptoms was predicted by a ⩾5 mmol/l rise in serum sodium concentration or absolute serum sodium of ⩾145 mmol/l after HS infusion[48].

Although cumulative knowledge regarding HS supports its clinical use as an alternative to mannitol,

Table 2 Animal experiments using HS for IH

Author, year(REF)	*Lesion, animal*	*[NaCl]*	*Control Fluid*	*Shock*	*Results*
Gunnar, 1988(11)	Epidural, dob	3%	0·9% NaCl, Dextran	Yes	↓ ICP and herniation
Zornow, 1989(55)	Criogenic, rabbit	1·8%	RL	No	↓ Cerebral water content
Wisner, 1990(53)	Criogenic, rat	6·5%	RL	Yes	↓ Cerebral water content
Battistella, 1991(3)	Criogenic, sheep	7·5%	RL	Yes	↓ ICP, ↑ CPP
Walsh, 1991(49)	Criogenic, pig	7·5%	RL	Yes	↓ ICP, ↑ CPP
Sheikh, 1996(43)	Criogenic, sheep	7·5%	RL	Yes	↓ Cerebral water content
Anderson, 1997(1)	Criogenic, sheep	7·5%	RL	Yes	↓ reanimation volume
Shackford, 1997(40)	Criogenic, pig	7·5%	RL	Yes	↓ ICP, ↑ CPP
Bacher, 1998(2)	Criogenic, rabbit	7·5%	0·9% NaCl	Yes	↓ edema
Prough, 1999(30)	Subdural, dog	7·2%	0·9% NaCl	Yes	↓ ICP

Table 3 Animals studies comparing HS and Mannitol

Author, year(REF)	*Lesion, animal*	*[NaCl]*	*Shock*	*Results*
Freshman, 1993(8)	Epidural, sheep	7·5%	No	No difference
Berger, 1994(4)	Criogenic/epidural, rabbit	7·2%	No	↓ ICP
Qureshi, 1999(34)	Intracerebral hemorrhage,dog	3/23·4%	Yes	↓ ICP

Table 4 Clinical studies using HS for IH

Author, year(REF)	*Type*	*Etiology*	*n*	*Treatment*	*Results*
Qureshi, 1998(32)	Retrospective	Multiple	27	3% NaCl	↓ ICP
Schwarz, 1998(39)	Prospective	Stroke	9	7·5% NaCl/20% Mannitol	↓ IH refractory episodes
Simma, 1998(44)	prospective, randomized	Pediatric head trauma	32	2% NaCl continuously	↓ Mortality, ↓ IH refractory episodes
Qureshi, 1999(33)	Retrospective	Head trauma	82	2–3% NaCl continuously	↑ Mortality
Suarez, 1999(46)	Retrospective	SAH	29	NaCl-acetate	No difference
Schwarz, 2002(38)	Prospective	Stroke	9	10% NaCl/20% Mannitol	↓ IH refractory episodes
Vialet, 2003(48)	prospective, randomized	Head trauma	20	7·5% NaCl/20% Mannitol	↓ IH refractory episodes
Tseng, 2003(47)	Retrospective	SAH	17	23·4% NaCl	↑ perfusion defects in Xenon-CT
Murphy, 2004(26)	Prospective	Hepatic failure	30	30% NaCl	↓ IH refractory episodes
Larive, 2004(19)	Prospective	Multiple	19	3% NaCl/Mannitol	No difference
Harutjunyan, 2006(15)	prospective, randomized	Multiple	40	7·2% NaCl/15% Mannitol	↓ ICP, ↑ MAP and CPP

further efforts should be directed toward the development of clinical studies using iso-osmotic doses of mannitol and HS in specific IH etiologies.

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