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Alaa A. Ibrham
Memoral Institute of Ophthalmology

Ashraf A. H. Mhmoud
National Heart Institute, ashraf_soliman76@yahoo.com

Mohmed H. Mohamed
National Heart Institute

Wael A. E. Elhakeem
National Heart Institute

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Original Article

Efficacy and safety of intravenous 3% hypertonic saline compared to mannitol 20% for lowering intraocular pressure in patients with glaucoma: a prospective randomized double-blind study

Ashraf A.H. Mhmoud[a], Alaa A. Ibrham[b], Mohmed H. Mohamed[a], Wael A.E. Elhakeem[a]

[a]Ansethesia Departmaent, National Heart Institute, [b]Ophthalmology Department, Memoral Institute of Ophthalmology, Giza, Egypt

Abstract

Objective

The purpose of this study was to assess the efficacy and safety of intravenous 3% hypertonic saline (HTS) compared with mannitol 20% for lowering intraocular pressure (IOP) in patients with glaucoma.

Patients and methods

A total of 30 patients between age 35 and 60 years with American Society of Anesthesiologist status I–III with glaucoma (IOP=30 mmHg) were enrolled in a double-blind comparative study. Patients were randomized to one of two groups: group GH (n=15), where patients received HTS, and group GM (n=15), where patients received mannitol 20%.

Results

Regarding demographic data, no statistically significant difference was observed between the two groups. There was a statistically significant decrease in mean arterial pressure in GH when compared with GM. There was a statistically significant increase in Na level in GH in comparison with GM. There was statistically significant decrease in K level in GH more than in GH. Regarding pH, there was no statistically significant between the two groups.

Conclusion

Intravenous infusion of HTS 3% is effective in decrease IOP in patients with glaucoma. It is considered a good alternative to mannitol for this purpose.

Keywords: Glaucoma, hypertonic saline, mannitol

Introduction

Hyperosmolar therapy is a commonly used treatment for intracranial hypertension. Currently, the only two agents used for this purpose are mannitol and hypertonic saline (HTS). The Brain Tauma Foundation currently recommends mannitol as the mainstay in the management of intracranial hypertension, but HTS represents a potential alternative that is gaining a favorable response. So, when planning this study, it was hypothesized that it might offer a way to manage patients with glaucoma by lowering their intraocular pressure (IOP). Mannitol is naturally occurring sugar alcohol. For clinical use, it is supplied as a sterile solution of 10 and 20% in a 500-ml bag of water containing 50 and 100 g of mannitol, respectively. Its chemical formula is $C_6H_{14}O_6$. It is found in marine algae, fresh mushrooms, and exudates from trees. It is an isomer of sorbitol, which is usually synthesized by the hydrogenation of specialty glucose syrup [1]. Mannitol solutions are acidic, crystallized at room temperature but can be made soluble again by warming the solution, and it has a low molecular weight [2]. The osmolarity of mannitol

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Correspondence to: Ashraf A.H. Mhmoud, MD, Department of Anesthesia, National Heart Institute Tel: +20 100 375 9851. E-mail: ashraf_soliman76@yahoo.com

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20% is 1098 mosm/l [3]. Adverse effects of mannitol including brain edema, osmotic demyelination syndrome, nephrotoxicity, initial volume expansion, hypovolemia, and anaphylaxis [4–6]. HTS might offer a way to manage patients with glaucoma by lowering their IOP. HTS is an osmotic solution with a NaCl concentration greater than that found in normal physiology [7]. Intravenous (i.v.) HTS could provide the clinician with one more option to lower IOP rapidly (Table 1).

The adverse effects of HTS include central pontine myelinolysis, hypernatremia, brain edema, hyperchloremic acidosis, hypokalemia coagulopathy, and complication of rapid blood volume expansion [9–11].

Well-known systemic medications to reduce IOP rapidly include acetazolamide either oral or i.v., oral glycerol, and i.v. mannitol. Because of their contraindication profiles and dangerous adverse effects, they are not always applicable to all patients. I.v. HTS could provide the clinician with one more option to lower IOP rapidly.

Aim

The aim of this study was to evaluate efficacy and safety of i.v. infusion of HTS 3% compared with mannitol 20% for lowering IOP in patients with glaucoma and studying possible complications that might happen from both infusions.

Patients and methods

Ethical Committee approval was taken. This study was held in the period of time from May 2017 to February 2019. It included 30 glaucoma eyes. Following obtaining informed consent from patients, a total of 30 cases with glaucoma were randomly allocated in two groups, with 15 patients each.

(1) GH (n = 15) received i.v. 3 ml/kg HTS 3% over 30 min.
(2) GM (n = 15) received i.v. 3 ml/kg mannitol 20% over 30 min.

Inclusion criteria

Patients with glaucoma, with IOP 30 mmHg or higher, aged 35–60 years, with American Society of Anesthesiologist status I–III were included.

Exclusion criteria

Patients' refusal, any active cardiac condition such as congestive heart failure, pregnancy, and lactation were the exclusion criteria.

Once the patient had been chosen to be enrolled in this study, the patients were subjected to the following: written informed consent; history taking to identify any systemic disease like hypertension and heart failure; general examination to calculate arterial blood pressure; IOP measurement with the Goldmann applanation tonometer; and investigations for arterial blood gases and the electrolyte levels (Na and K). An antecubital 18 G venous cannula was inserted and connected to an i.v. line for infusion of either 0.5 g/kg of 20% mannitol or 3 ml/kg of 3% HTS over 30 min. IOP and mean arterial pressure (MAP) were measured before the injection and at 5, 10, 20, 30 min, 1, and 2 h after the end of infusion. Arterial blood gases (pH) and Na and K levels were measured 60 min after infusion.

Table 1: Composition of hypertonic saline according to concentration[8]

Concentration	Osmolarity (mosm/l)	Sodium content (mEq/l)	Chloride content (mEq/l)
3%	1027	513	513
5%	1712	856	856
7.2%	2464	1232	1232
23.4%	8008	4004	4004

Sample size

Based on the assumption that a 25% difference in the mean IOP is considered a clinically significant difference between the two groups and a common treatment standard deviation of 2.3 mmHg and taking power 0.9 and error 0.05, a minimum sample size of 15 patients is calculated for each group.

Statistical analysis

Categorical variables were assessed using χ^2 or Fisher exact test where appropriate. Normally distributed data were presented as mean (SD) and were analyzed using Student's t test and two-way analyses of variance with repeated measures and post-hoc Dunnett test as appropriate. Data not normally distributed (tested by Kolmogorov–Smirnov test) were presented as median (range) and were analyzed with the Mann–Whitney U test or the Kruskal–Wallis test as appropriate. The software SPSS, v15.0 for Windows (SPSS Inc., Chicago, Illinois, USA) was used for statistical analysis.

Results

In this study, 30 patients with glaucomatous eyes, who fulfilled the inclusion and exclusion criteria for the study were chosen and arranged into two equal groups:

(1) GH: it included 15 patients and received 3 ml/kg HTS i.v. infusion over 30 min.
(2) GM: it included 15 patients and received 0.5 mg/kg mannitol 20% i.v. infusion over 30 min.

Both groups were compared regarding many variables including demographic data, IOP, MAP, electrolytes level (Na^+, K^+), and pH.

IOP and MAP were recorded at baseline, 5, 10, 20, 30 min, 1, and 2 h after infusion. Blood samples were collected twice, before infusion and 60 min after infusion, and then Na, K, and pH level were measured.

Regarding demographic characteristics, statistical studies between both groups showed no significant differences (Table 2).

Regarding IOP, when comparing both groups together, there was a statistically significant increase in GH more than GM regarding baseline. There was a statistically significant

decrease in the IOP in GM more than in GH at 1- and 2-h recorded data ($P = 0.02$ and 0.03, respectively) (Table 3).

In addition, within the same group comparison at different time intervals, regarding GH, there was a statistically significant decrease in IOP at 5 min when compared with baseline up to 2 h. However, in GM, there was a statistically significant decrease in IOP at 10 min when compared with baseline for up to 2 h (Table 3)

Regarding MAP, when comparing both groups together, there was a statistically significant decrease in MAP in GH when compared with GM at 20, 30 min, and 1 h ($P = 0.008$, 0.03, and 0.002, respectively)

Regarding within the same group comparison at different time intervals, regarding GH, there was a statistically significant increase in MAP at 5 min followed by a statistically significant decrease at 20, 30 min, and 1 h when collected data were compared with the baseline (Table 4).

In GM, there was a statistically significant increase in MAP at 5 and 10 min followed by a statistically significant decrease at 20, 30 min, and 1 h when collected data were compared with baseline (Table 4).

Regarding Na level, there was a statistically significant increase in Na level in GH in comparison with GM ($P = 0.002$) (Table 5). Regarding within same group comparison, there was a statistically significant increase in GH 60 min after infusion when compared with baseline ($P = 0.0001$). However, there was a statistically significant decrease in GM at 60 min after infusion when compared with baseline ($P = 0.0001$) [Table 5].

Regarding the K level, when both groups were compared together, there was a statistically significant decrease in baseline K level GH more than in GM ($P = 0.014$). Regarding within same group comparison, there was a statistically significant decrease in GH 60 min after infusion when compared with baseline ($P = 0.025$).

Furthermore, there was a statistically significant decrease in GM 60 min after infusion when compared with baseline ($P = 0.04$) (Table 5).

Regarding pH, there was no statistically significant difference between both groups at baseline and after infusion. Furthermore, the results collected 60 min after infusions were comparable to those at baseline when within the same group comparison was done (Table 5).

Table 2: Comparison between both groups regarding demographic characteristics

Demographic characteristics	GH	GM
Age (years)	52 (47-58)	46 (38-53)
Sex (male :female)	7 : 8	8 : 7
Glaucoma type		
Primary open-angle	9 (60)	8 (53.3)
Angle-closure	5 (33.3)	6 (40)
Congenital glaucoma	1 (6.6)	1 (6.6)

Numerical data were expressed as median (range). Categorical data were expressed as *n* (%).

Table 3: Comparison regarding intraocular pressure (mmHg)

IOP (mmHg)	GH ($n=15$)	GM ($n=15$)	*P* between both groups	*P* relative to baseline
Baseline	40±8.7	34±3	0.017	
5 min	34±7.8†	33.8±3	0.9	<0.001
10 min	27.6±11†	30.6±4†	0.3	<0.001
20 min	27.2±11.3†	26.6±4.6†	0.8	<0.001
30 min	28±12.6†	21.8±3.6†	0.07	<0.001
1 h	28.4±12.6†*	20.2±4.4†*	0.02	<0.001
2 h	28.4±12.6†*	21.4±4†*	0.03	<0.001

Numerical data were expressed as mean±SD. IOP, intraocular pressure. *Significance relative to the other group ($P<0.05$). †Significance relative to the baseline ($P<0.05$).

Table 4: Comparison between both groups regarding mean arterial pressure

	GH ($n=15$)	GM ($n=15$)	*P* between both groups	*P* relative to baseline
Baseline	95±9	99.6±7.5	0.1	
5 min	98±9†	102.6±7.5†	0.1	0.001
10 min	96±4	98±7†	0.4	0.009
20 min	91±4*†	96±6*†	0.008	0.04
30 min	90±4*†	96±8*†	0.03	0.01
1 h	90±4*†	97±7*†	0.002	0.001
2 h	95±8	100±8	0.1	0.1

Numerical data were expressed as mean±SD. *Significance relative to the other group ($P<0.05$). †Significance relative to the baseline ($P<0.05$). *P* value less than 0.05 was considered to be significant.

Discussion

In this study, 30 patients were included and were divided into two equal groups (GH and GM), with 15 patients each

Regarding IOP, it was found that IOP started to decrease earlier in GH at 5 min after the end of HTS infusion and reached maximal decrease at 10–20 min after infusion. However, in GM, the IOP started to decrease at 10 min and reached a maximal decrease at 1 h after infusion.

Inconsistency with these results, Harju *et al.*[12] studied the effect of HTS on nineteen patients and found that the IOP lowering effect of the small dose HTS is large enough to be of clinical relevance when IOP is moderately elevated and a fast reduction is desired. I.v. HTS reduced elevated IOP in glaucoma eyes a median of 7 mmHg within 5 min irrespective of baseline IOP. Injection of 0.5 mmol Na/kg was as effective as the double dose. They concluded that the IOP can be lowered safely by HTS preoperatively. The effect lasted for at least 2 h, enough to complete most surgeries.

They concluded that HTS seems to be an effective and rapid method to reduce IOP. This reduction seems to be

Table 5: Comparison regarding electrolytes level ($Na^+$and K^+) and pH

	GH (n=15)	GM (n=15)	P
Na (mEq/l)			
Baseline	140 (138-142)	141 (139-142)	0.8
After	142 (140-145)*†	137 (135-140)†	0.002
K (mEq/l)			
Baseline	4 (3.6-4.1)*	4.4 (4.0-4.5)	0.014
After	3.8 (3.4-3.9)*†	4.2 (3.6-4.4)†	0.034
pH			
Baseline	7.39 (7.37-7.4)	7.39 (7.37-7.42)	0.6
After	7.38 (7.36-7.39)†	7.36 (7.34-7.38)†	0.3

Numerical data were expressed as median (range). *Significance relative to the other group (P<0.05). †Significance relative to the baseline (P<0.05).P value less than 0.05 was considered to be significant.

independent of topical medication or glaucoma subgroup. HTS could be a practical method to reduce IOP before or during eye surgery.

Regarding MAP, in the present study, there was a decrease in MAP in both groups, GH and GM, after a transient elevation. Regarding GH, MAP started to increase at 5 min and found to decrease at 20 min to 1 h. Regarding GM, MAP started to increase at 5 min and began to decrease at 10 min to 1 h. Although these changes were statistically significant in both groups, none of the patients needed i.v. intervention. This decrease might be secondary to their diuretic effect.

In contrast to the results of this study, Harju *et al.*[12] showed an increase in blood pressure after HTS which was explained by the increase in the osmotic gradient between tissues and the blood, pulling fluid from interstitial spaces to the intravascular space [13]. Similarly, fluid was also pulled from the vitreous with the subsequent reduction in IOP.

Regarding Na level, in this study, HTS caused Na level to be increased from 140 to 142 mEq/l; however in GM, there was a decrease in Na level from141 to 137 mEq/l. Although these changes were of statistical significance in both groups, they were of no clinical importance.

Although slightly elevated Na level was found in GH, several studies showed neither very rapid increases in blood Na levels nor osmotic demyelination syndrome has been reported after HTS infusion to correct hypovolemic shock or to lower intracranial pressure [2,13].

Tyagi *et al*.[13] reported that even with elevated serum Na^+ concentration after continuous infusion of 3% HTS, no osmotic demyelination syndrome was visible on MRI. Bolus infusions of HTS in humans documented elevated serum Na^+ but did not cause neurologic deficits [13].

Regarding the potassium level, it decreased in both groups from 4 to 3.8 mEq/l. in GH and from 4.4 to 4.2 mEq/l in GM. There was a statistically significant decrease in potassium level 30 min after infusion when compared with baseline data in both groups. This was consistent with the study of Seo and Oh [2]. They noticed hypokalemia was observed after mannitol infusion.

Hess *et al.*[14] concluded that infusion of 4 ml/kg of 7.5% saline over 10 min caused only minor changes in electrolyte concentrations, however, and the 3 ml/kg dose of 3% saline used in this study was much lower.

Regarding pH, there was a decrease in pH level in both groups; in GH the values decreased from 7.39 to 7.38, and from 7.39 to 7.36 in GM. These findings were consistent with those of Kolsen-Petersen *et al.*[15] who concluded that a decrease in pH of 0.05 (range, 0.02–0.07) was found after the administration of a 10-min infusion of 4 ml/kg 7.5% NaCl in 14 fasting women before hysterectomy.

In contrast to the results of this study, Kang *et al.*[16] found that i.v. infusion of mannitol could induce metabolic alkalosis and hypokalemia, regardless of its dose. The mannitol-induced alkalosis may be caused by increased renal HCO_3^- production.

Conclusion

In this study, we concluded that i.v. infusion of HTS 3% is effective in decreasing IOP in patients with glaucoma. It is considered a good alternative to mannitol for this purpose.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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