

## Comparison between Hypertonic Saline 3% and Mannitol, the Most Commonly Used Osmotic Agents, Regarding Effect on Blood Pressure, Electrolytes Level and Acid Base Balance

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### Abstract

**Background:** Increased ICP following neurological injury can decrease CBF and may also lead to brain herniation and death so it should be lowered. Mannitol and HTS are the most commonly used osmotic agents for management of intracranial hypertension to improve the outcome.

**Aim of Work:** The aim of this study was to assess complications of HTS and mannitol as they are commonly used for osmotherapy regarding effect on blood pressure, electrolytes level and acid base balance.

**Material and Methods:** 30 patients undergoing glaucoma surgery under general anesthesia were randomly allocated to 2 groups. One group received hypertonic saline 3% and the other group received mannitol. Mean arterial blood pressure was measured before infusion and then measured 5, 10, 20, 30, 60, 120min after end of infusion. Arterial blood gases (pH), and Na, K levels were measured at baseline (before infusion) and 60min after end of infusion.

**Results:** As regards MAP, both groups showed statistically significant increase in MAP initially followed by statistically significant decrease at 20min, 30min and 1h when collected data were compared to baseline.

Regarding Na level, there was statistically significant increase in Na level in HTS group in comparison to mannitol group despite being within normal range of Na level.

As to K level, both groups showed statistically significant decrease in K level. As regards PH, there was no statistically significant difference between both groups at baseline and after infusion.

**Conclusion:** Both HTS and mannitol had the same effect on MAP, K level and PH. Regarding Na level, it was increased slightly in HTS group while decreased in mannitol group.

**Key Words:** Hypertonic saline – Mannitol – Mean arterial blood pressure – Na – K – PH.

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### Introduction

**ANAESTHESIOLOGISTS** use Intravenous Hypertonic Saline (IVHTS) in amounts equivalent to 1-5mmol/kg sodium for management of hypovolemic shock and for decreasing intracranial pressure [1]. It increases systemic blood volume, elevates blood pressure and decreases intracranial pressure by pulling fluid osmotically from tissues to intravascular space [2]. There is no class 1 evidence to indicate that mannitol is more effective than hypertonic saline in lowering elevated intracranial pressure [3].

Elevated intracranial pressure following neurological injury is usually associated with poor outcomes [4]. Increased ICP reduces CBF and can lead to brain herniation and death. The Brain Trauma Foundation has recommended that therapy to reduce ICP should begin at pressures >20mm Hg. Hyperosmolar therapy is a commonly used treatment for intracranial hypertension. Currently, only 2 agents are used for this purpose: Mannitol and HTS. The Brain Trauma Foundation currently recommends mannitol as the mainstay in the management of intracranial hypertension, but HTS represents a potential alternative that is gaining favor [5]. The reported concentrations of HTS for clinical use range from 2% to 23.5% [6].

### Patients and Methods

Following the approval of the Ethical Committee of Kasr Al-Ainy Hospital of Cairo University from May 2015 to May 2016 and after obtaining informed permission from each patient, a total of 30 cases with glaucoma were randomly allocated in two groups, 15 each. GH received IV hypertonic saline 3% and GM received IV Mannitol 20%.

Subjects were randomly allocated to study groups by a computer-generated random list. Group assignment was sealed in sequentially numbered opaque envelopes that have been opened one hour before infusion to determine which treatment the subject would receive.

*These patients were randomly subdivided into 2 groups:*

- GH (n=15); received IV 3ml/kg hypertonic saline 3% over 30min.
- GM (n=15); received IV 0.5gm/kg Mannitol 20% over 30min.

*All the patients fulfilled the following inclusion and exclusion criteria:*

*Inclusion criteria:*

- Patients with glaucoma, with IOP 30mmHg or higher.
- Aging 35-60 years.
- ASA I-III.

*Exclusion criteria:*

- Patient refusal.
- Any active cardiac condition as congestive heart failure.
- Hypertension.
- Pregnancy and lactation.

*Once the patient had been chosen to be enrolled in this study, the patient was subjected to the following:*

- *Consent:* A written informed consent was taken from each patient. The patient was told that blood samples would be withdrawn twice from him. The importance of the study was explained to the patient.
- *History taking including:* Personal history, including name, age, occupation. Past history, to identify any systemic diseases as hypertension, heart failure.
- *General Examination:* Including appearance, weight. Arterial blood pressure was measured and Mean Arterial blood Pressure (MAP) was calculated.
- *Investigations:* Arterial blood gases, electrolytes level (Na<sup>+</sup>, K<sup>+</sup>).

An antecubital 18G venous cannula was inserted and connected to IV line for infusion of either 0.5gm/kg of 20% mannitol or 3ml/kg of 3% hypertonic saline over 30 minutes. MAP was measured

before injection and at 5min, 10min, 20min, 30min, 1h, and 2h after end of infusion.

Arterial blood gases (PH), Na and K levels were measured 60min after infusion.

*Primary outcome parameters:*

- 1- Mean arterial blood pressure.
- 2- Na, K level.
- 3- PH.

*Statistical analysis:*

Categorical variables will be assessed using chi-square or Fischer exact test where appropriate. Normally distributed data will be presented as mean (SD) and will be 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) will be presented as median (range) and were analyzed with Mann-Whitney U test or the Kruskal-Wallis test as appropriate. The software SPSS v15.0 for Windows (SPSS, Inc., Chicago, IL, United States) will be used for statistical analysis.

## Results

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

*GH:* Included 15 patients and received 3ml/kg HTS iv infusion over 30min.

*GM:* Included 15 patients and received 0.5mg/kg mannitol 20% iv infusion over 30min.

Both groups were compared as regards many variables including MAP, electrolytes level (Na<sup>+</sup>, K<sup>+</sup>) and PH.

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

Regarding mean arterial blood pressure, when comparing both groups together, there was statistically significant decrease in MAP in GH when compared with GM at 20min, 30min, 1h. (*p*=0.008, 0.03, 0.002 respectively).

As regards within same group comparison at different time intervals, regarding GH, there was statistically significant increase in MAP at 5min followed by statistically significant decrease at

20min, 30min and 1h when collected data were compared to baseline. Fig. (1) (Table 1).

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

Regarding Na level, there was statistically significant increase in Na level in GH in comparison to GM ( $p=0.002$ ). Fig. (2) (Table 2).

As regards within same group comparison, there was statistically significant increase in GH 60min after infusion when compared to baseline. ( $p=0.0001$ ) However, there was statistically significant decrease in GM 60min after infusion when compared to baseline. ( $p=0.0001$ ) Fig. (2) (Table 2).

Table (1): Comparison between both groups as regards MAP.

	G <sub>H</sub> (n=15)	G <sub>M</sub> (n=15)	p-value between both groups	p-value relative to baseline
Baseline	95±9	99.6±7.5	0.1	
5min	98±9†	102.6±7.5†	0.1	0.001
10min	96±4	98±7†	0.4	0.009
20min	91±4*†	96±6*†	0.008	0.04
30min	90±4*†	96±8*†	0.03	0.01
1 hour	90±4*†	97±7*†	0.002	0.001
2 hours	95±8	100±8	0.1	0.1

\*: Denotes significance relative to the other group.  $p<0.05$ .  
 †: Denotes significance relative to the baseline.  $p<0.05$ .  
 Numerical data were expressed as mean (standard deviation).  
 Categorical data were expressed as n (%).  
 $p<0.05$  was considered to be significant.

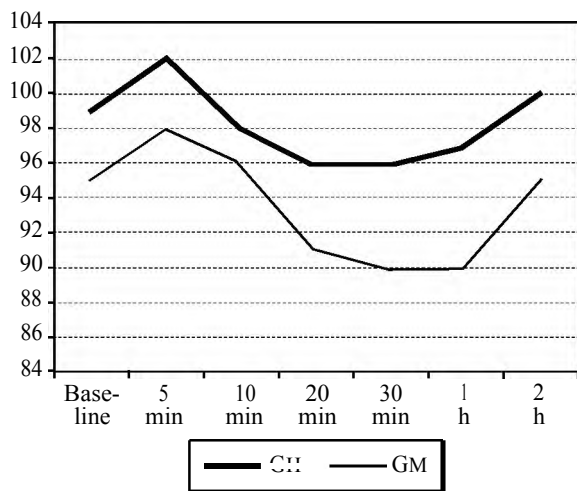


Fig. (1): Comparison between both groups as regards mean arterial pressure.

As to K level, when both groups were compared together, there was statistically significant decrease in baseline K level GH more than in GM. ( $p=0.014$ ) as regards within same group comparison, there was statistically significant decrease in GH 60min after infusion when compared to baseline. ( $p=0.025$ ).

Furthermore, there was statistically significant decrease in GM 60 min after infusion when compared to baseline. ( $p=0.04$ ) Fig. (3) (Table 2).

As regards PH, there was no statistically significant difference between both groups at baseline and after infusion.

Furthermore, the results collected 60min after infusions were comparable to those at baseline when within the same group comparison was done. Fig. (4) (Table 2).

Table (2): Comparison as regards electrolytes level (Na<sup>+</sup>, K<sup>+</sup>) and PH.

	G <sub>H</sub> (n=15)	G <sub>M</sub> (n=15)	p-value
<i>Na (meq/L):</i>			
Baseline	140 (138-142)	141 (139-142)	0.8
After	142 (140-145)*†	137 (135-140)†	0.002
<i>K (meq/L):</i>			
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
<i>PH:</i>			
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

\*: Denotes significance relative to the other group.  $p<0.05$ .  
 †: Denotes significance relative to the baseline.  $p<0.05$ .  
 Numerical data were expressed as median (range).  
 Categorical data were expressed as n (%).  
 $p<0.05$  was considered to be significant.

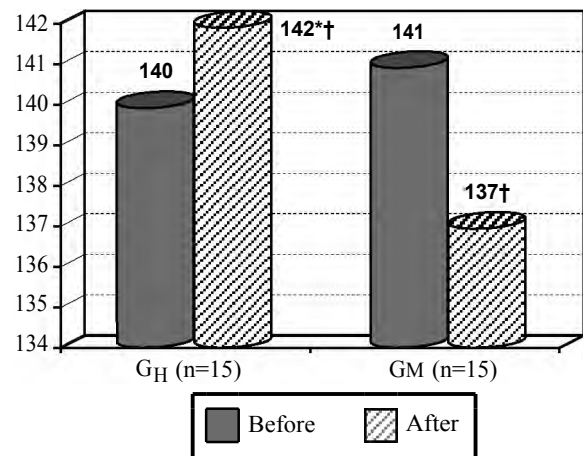


Fig. (2): Comparison between both groups as regards Na level.

\*: Denotes significance relative to the other group.  $p<0.05$ .  
 †: Denotes significance relative to the baseline.  $p<0.05$ .

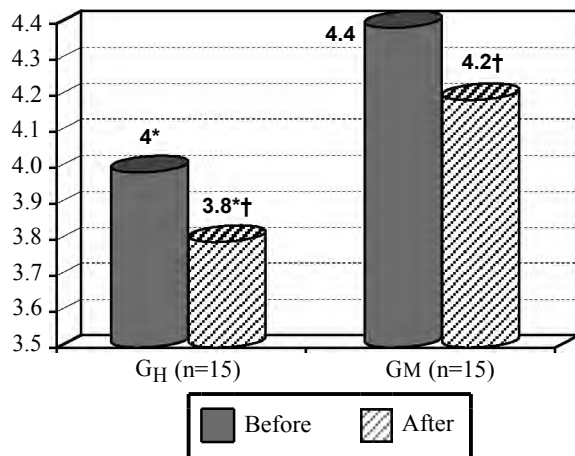


Fig. (3): Comparison between both groups as regards K level.

\*: Denotes significance relative to the other group.  $p < 0.05$ .

†: Denotes significance relative to the baseline.  $p < 0.05$ .

### Discussion

Regarding role of hypertonic saline for reducing intracranial pressure, Kamel H et al., [8] compared hypertonic saline with mannitol for the treatment of elevated intracranial pressure through meta-analysis of randomized clinical trials. This study included 5 trials comprising 112 patients and concluded that hypertonic saline was more effective than mannitol for the treatment of elevated intracranial pressure.

Furthermore, Peterson B et al., [9] included sixty-eight children with closed head injury and reported that Hypertonic saline administration to children with closed head injury appeared to be a promising therapy for control of cerebral edema.

Mannitol is primarily excreted in the urine as an unchanged drug; therefore, adverse effects are most likely to be found in patients with impaired renal function or after repeated administration of high doses. Nephrotoxicity can be prevented by avoiding the use of mannitol in patients with pre-existing renal disease or sepsis and by avoiding the use of other nephrotoxic drugs [10].

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

As to MAP, in the present study, there was a decrease in MAP in both groups, GH and GM, after a transient elevation. As regards GH, MAP started to increase at 5min and found to decrease at 20min to 1h. Regarding GM, MAP started to increase at 5min and began to decrease at 10min to 1h. Although these changes were statistically significant in both groups, none of the patients needed IV

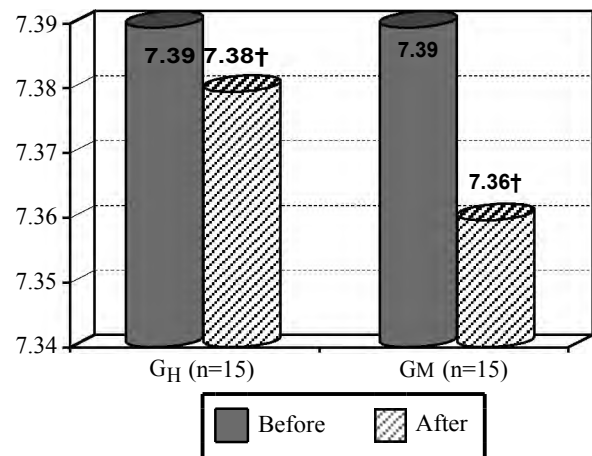


Fig. (2): Comparison between both groups as regards PH.

\*: Denotes significance relative to the other group.  $p < 0.05$ .

†: Denotes significance relative to the baseline.  $p < 0.05$ .

intervention. This decrease might be secondary to their diuretic effect.

In contrast to results of this study, Harju et al., [1] showed increase in BP 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 [11]. Similarly, fluid was also pulled from the vitreous with subsequent reduction in IOP.

Furthermore, Mortazavi et al., [12] concluded that multiple studies showed superior effectiveness of HTS compared with mannitol in decreasing ICP. However, there was not a clear benefit when HTS was used compared with mannitol as regards to neurological outcome, even though there was a minor positive trend for HTS. Also, HTS did not cause the hypotension seen when mannitol was used.

Regarding sodium level, in this study, HTS caused Na level to be increased from 140meq/L to 142meq/L however in GM, there was decrease in Na level from 141meq/L to 137meq/L. Although these changes were of statistical significance in both groups but were of no clinical importance. Although slightly elevated sodium level was found in GH, several studies showed neither very rapid increases in blood sodium levels nor Osmotic Demyelination Syndrome (ODS) have been reported after HTS infusion to correct hypovolaemic shock or to lower intracranial pressure [11,13,14].

Tyagi R [11] reported that even with elevated serum  $\text{Na}^+$  concentration after continuous infusion of 3% HTS, no ODS was visible on Magnetic Resonance Imaging (MRI). Bolus infusions of HTS

in humans documented elevated serum  $\text{Na}^+$ , but did not cause neurologic deficits [11].

In addition, Khanna et al., [13] studied the effect of continuous infusion of 3% saline on a sliding scale used to achieve a target serum sodium level that would maintain ICP <20mm and concluded that an increase in serum sodium concentration significantly decreases ICP and increases CPP. Hypertonic saline was an effective agent to increase serum sodium concentrations. Sustained hypernatremia and hyperosmolarity were safely tolerated in pediatric patients with traumatic brain injury [13].

As to Potassium level, it decreased in both groups from 4meq/L to 3.8meq/L. in GH and from 4.4meq/L to 4.2meq/L in GM. There was statistically significant decrease in Potassium level 30 min after infusion when compared to baseline data in both groups. This was consistent with study of Seo et al., [14]. They noticed that hypokalemia was observed after mannitol infusion. This study was undertaken to evaluate whether significant alterations in serum osmolality, ( $\text{Na}^+$ ), and ( $\text{K}^+$ ) occur after the repeated dosing of mannitol and whether these imbalances increased accordingly with the progress of mannitol application. This study was conducted by performing a retrospective medical record review of brain injury patients who were admitted to the neurological intensive care units of a university hospital located in Incheon, South Korea.

Hypertonic saline infusions may also cause electrolyte abnormalities in form of hypernatremia and hypokalemia [15].

Hess et al., [16] concluded that infusion of 4ml/kg of 7.5% saline over 10min caused only minor changes in electrolyte concentrations, however, and the 3ml/kg dose of 3% saline used in this study was much lower. Hess et al., [16] studied the combination solution of 7.5% NaCl/6% dextran 70 (HSD) administered IV for hemodynamic improvement in the treatment of hemorrhagic hypotension.

As regards PH, there was 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 administration of 10min infusion of 4ml/kg 7.5% NaCl in 14 fasting women before hysterectomy.

In contrast to the results of this study, Kang et al., [17] found that intravenous infusion of mannitol could induce metabolic alkalosis and hypokalemia, regardless of its dose. The mannitol induced alkalosis may be caused by increased renal  $\text{HCO}_3^-$  production. The study subjects were divided into 3 groups: For Group A, an amount of 300-900mL 15% mannitol was intravenously infused over the period of 60 to 90 minutes; for Group B, 1,200-2,600mL over 12 to 24 hours; and for Group C, 3,200-4,900mL over more than 24 hours.

In our study we concluded that HTS and mannitol, being widely used as osmotic agents, had the same effects on MAP, K level and PH. Regarding Na level, while it was increased slightly in HTS group and decreased in mannitol group, all recorded data were within normal range of plasma Na level.

## References

- 1- MIKA HARJU, TERO KIVELÄ, NINA LINDBOHM, RIKU KOIVUSALO and MARKKU PALOHEIMO: Intravenous hypertonic saline to reduce intraocular pressure. *Acta Ophthalmologica*, 1755-3768, 2012.
- 2- BATTISTELLA F.D. and WISNER H.: Combined hemorrhagic shock and head injury: Effect of hypertonic saline 7.5% resuscitation. *J. Trauma*, 31 (2): 182-8, 1991.
- 3- MATTHEW E. FINK: *Neurology*, 18 (3): 640-54, 2012.
- 4- FORSYTH L.L., LIU-DERYKE X., PARKER D.J.R. and RHONEY D.H.: Role of hypertonic saline for the management of intracranial hypertension after stroke and traumatic brain injury. *Pharmacotherapy*, 28: 469-84, 2008.
- 5- VOLOPICH S., MOSING M., AUER U. and NELL B.: Comparison of the effect of hypertonic hydroxyethyl starch and mannitol on the intraocular pressure in healthy normotensive dogs and the effect of hypertonic hydroxyethyl starch on the intraocular pressure in dogs with primary glaucoma. *Veterinary Ophthalmology*, 9: 4, 239-44, 2006.
- 6- Brain Trauma Foundation: American Association of Neurological Surgeons, Congress of Neurological Surgeons, Joint Section on Neurotrauma and Critical Care, AANS/CNS: Guidelines for the management of severe traumatic brain injury, ed 3. *J. Neurotrauma*, 24 (Suppl 1): S1-S106, 2007.
- 7- MAUGER T.F.1, NYE C.N. and BOYLE K.J.: Intraocular pressure, anterior chamber depth and axial length following intravenous mannitol. *Ocul. Pharmacol. Ther.* Dec., 16 (6): 591-4, 2000.
- 8- KAMEL H., et al.: Hypertonic saline versus mannitol for the treatment of elevated intracranial pressure: A meta-analysis of randomized clinical trials. *Crit. Care. Med.*, 39: 554-9, 2011.
- 9- PETERSON B., KHANNA S., FISHER B. and MARSHALL L.: Prolonged hypernatremia controls elevated intracranial pressure in head injured pediatric patients. *Crit. Care. Med.*, 28: 1136-1143, 2000.

- 10- GONDIM F.A., AIYAGARI V. and SHACKLEFORD A.: Osmolality not predictive of mannitol-induced acute renal insufficiency. *J. Neurosurg.*, 103: 444-7, 2005.
- 11- TYAGI R., DONALDSON K., LOFTUS C.M. and JALLO J.: Hypertonic saline: A clinical review. *Neurosurg. Rev.*, 30: 277-90, 2007.
- 12- M.M. MORTAZAVI, et al.: Hypertonic saline for treating raised intracranial pressure: Literature review with meta-analysis. *J. Neurosurg. Jan.*, 116 (1): 210-21, 2012.
- 13- KHANNA S., DAVIS D., PETERSON B., FISHER B., TUNG H., O'QUIGLEY J. and DEUTSCH R.: Use of hypertonic saline in the treatment of severe refractory posttraumatic intracranial hypertension in pediatric traumatic brain injury. *Crit. Care Med.*, 28: 1144-51, 2000.
- 14- SEO W. and OH H.: Alterations in serum osmolality, sodium, and potassium levels after repeated mannitol administration. *J. Neurosci. Nurs.* Aug., 42 (4): 201-7, 2010.
- 15- KOLSEN-PETERSEN J.A., NIELSEN J.O. and TONNESEN E.K.: Acid base and electrolyte changes after hypertonic saline (7.5%) infusion: A randomized controlled clinical trial. *Scand. J. Clin. Lab. Invest.*, 65: 13-22, 2005.
- 16- HESS J.R., DUBICK M.A., SUMMARY J.J., BANGAL N.R. and WADE C.E.: The effects of 7.5% NaCl/6% dextran 70 on coagulation and platelet aggregation in humans. *J. Trauma.*, 32: 40-4, 1992.
- 17- KANG K.P., LEE S., LEE K.H. and KANG S.K.: Mannitol-induced Metabolic Alkalosis. *Electrolyte & Blood Pressure*, 4 (2): 61-5, 2006.

## مقارنة بين محلول الملح 3% والمانيتول كأكثر الأدوية الشائع إستخدامها لزيادة الخاصية الأسمولية للدم بخصوص التأثير على ضغط الدم ونسبة الصوديوم والبوتاسيوم وحموضة الدم

يعد محلول الملح المركز والمانيتول من أكثر الأدوية التي تستخدم لزيادة الخاصية الأسمولية بالدم وقد قام أطباء التخدير بإستخدام محلول الملح المركز عن طريق الوريد لتقليل الضغط داخل المخ وعلى مدار الخمسة والعشرون سنة السابقة قد أصبح محلول الملح المركز أكثر شيوعا كبديل للمانيتول.

إن هدف هذه الدراسة هو مقارنة بين محلول الملح 3% والمانيتول بخصوص التأثير على ضغط الدم ونسبة الصوديوم والبوتاسيوم بالدم وأيضا حموضة الدم.

وقد كشفت نتائجنا ما يلي:

إنخفاض ضغط الدم في مجموعة محلول الملح المركز ومجموعة المانيتول بصورة ذات دلالة إحصائية بعد إرتفاعه في البداية.

فروق ذات دلالة إحصائية بين المجموعتين بخصوص نسبة الصوديوم بالدم بعد التنقيط الوريدي حيث إنها إرتفعت في مجموعة محلول الملح المركز وإنخفضت في مجموعة المانيتول.

إنخفاض نسبة البوتاسيوم بالدم في المجموعتين بعد التنقيط الوريدي بصورة ذات دلالة إحصائية.

إنخفاض حموضة الدم في المجموعتين بعد التنقيط الوريدي بصورة ذات دلالة إحصائية.