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COMPARISON OF THE EFFECTS OF MANNITOL AND HYPERTONIC SALINE 5% ON ELECTROLYTE BALANCES DURING BRAIN TUMOR SURGERY

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ABSTRACT

Introduction: This study attempts to compare the effect of mannitol and hypertonic saline 5% on electrolyte balance of patients undergoing brain tumor surgery. **Methods:** In this study, 34 patients were placed in two groups mannitol 20% and hypertonic saline 5% as a randomized double blind prospective clinical trial. Primary end points included: The amount of electrolytes (sodium, potassium, chloride and bicarbonate) before anesthesia, during induction, 120 minutes after the start of treatment and also at the end of surgery. The secondary end point were amount of bleeding, urinary output, heart rate and systolic and diastolic blood pressure of patients at the start of anesthesia, at 30, 60, 90 and 120 minutes after onset of anesthesia. **Results:** There was a significant difference between the two groups in amount of sodium and chloride during the surgery ($p<0.05$). There was no significant difference between groups in concentrations of potassium and bicarbonate ($p>0.05$). Hemodynamic variables of patients showed that there was a significant difference between groups at 120 minutes ($p<0.05$). Urine output was higher with mannitol than hypertonic saline in the 90 ($p = 0.035$) and 120 minutes ($p = 0.041$) respectively. Also there was no significant difference between the two groups in amount of bleeding at none of

the times (p>0.05). **Conclusion:** It can be concluded hypertonic saline increases the concentration of electrolytes and provides a more appropriate hemodynamic status than the mannitol. Hypertonic saline was associated with less diuretic effect; therefore generally the hypertonic saline can be used as a substitute for mannitol.

KEYWORDS: Mannitol, Hypertonic Saline, Brain Tumor.

INTRODUCTION

One of the main goals of anesthesia in brain tumors surgery is to prevent of increasing or decreasing the ICP. When the skull is opened, the surgical access will be easier due to loosening the intracranial contents; but if ICP is high, brain herniation may occur in craniotomy area.[1-3] To reduce it, physician should reduce the intracranial volume in coping with the increase of ICP. Diuretics are widely used in brain surgical operations to reduce the fluid inside and outside the cells. It seems that the extracellular fluid will be more affected by these drugs, because glia and neurons have a fast and efficient regulatory mechanisms.[2,4] Both loop diuretics and osmotic diuretics are used to this purpose; although data obtained suggests that the loop diuretics are also effective, the osmotic diuretics especially mannitol are most used in clinical cases due to high speed and efficiency.[4]

The use of mannitol, as a therapeutic osmolarity in health care, is used by neuro-anesthesiologists. The side effects of using the mannitol can refer to its effects on kidney and lung system, electrolyte imbalance, decrease in blood pressure, severe decrease of blood volume and reintegration of increased ICP.[5,6] Considering the numerous side effects during the use of mannitol in craniotomy surgeries, the use of a viable alternative to mannitol is useful which can be used in brain surgeries with proper functioning and less complications. Some of these drugs which can be pointed out are hypertonic saline that has the concentration of osmotic like the mannitol.[7] Compared with mannitol, Hypertonic saline have additional beneficial effects like improvement of cardiac output, mean arterial pressure and decrease of extra vascular lung volume, leading to enhanced gas exchange and better partial pressure of oxygen in the blood. In addition, it is cheaper than the mannitol in terms of cost and causes to faster revive with smaller volume, reducing the environmental resistance and lowering the intracranial pressure than the mannitol.[8-11]

Given the need to reduce the intracranial pressure during brain tumors surgery and improve the results of these surgeries for reducing the side effects of drugs use, hence this study was

designed to compare of the effects of mannitol and hypertonic Saline 5% on electrolyte balances during brain tumor surgery.

METHODS

After approval by the Ethics Committee of Ahvaz Jundishapur of Medical Sciences and written informed consent of the patients this study was conducted as a randomized prospective clinical trial, on 34 patients, aged18 to 60 years with ASA I- II undergoing brain tumor surgery from Golestan Hospital, Ahvaz, Iran. patients randomly divided into two groups: mannitol and hypertonic salin groups (mannitol 20% to a rate of 5 ml/kg) and (hypertonic saline 5% to a rate of 2.5 ml/kg) respectively.

Inclusion criteria

Age 18 to 60 years, ASA class 1 or 2 (American Society of Anesthesiologists), Glasgow coma scale (GCS) >13 and patients candidate for brain tumor surgery.

Exclusion criteria

The lack of consent to participate in the study, electrolyte imbalance, metabolic disorders, and patients with heart, lung, kidney and hepatic problems, getting diuretic or osmotic drugs before surgery, a history of chronic alcohol abuse and brain herniation.

Study procedure

Patients were randomly allocated into two groups – mannitol (M group) and HS (HS group) by a computer-generated randomization chart. (17 patients in each group). In the operation room, peripheral intravenous line was secured and 0.9% normal saline was given for fluid management. The standard monitors including electrocardiogram (ECG), invasive blood pressure (IBP) and pulse oximeter were attached and baseline heart rate (HR), IBP and SPO2 readings were recorded. At the beginning of anesthesia, all patients were pre-oxygenated with 100% O2 for 3 min and then, all patients were equally placed under general anesthesia with fentanyl 2 µg/kg, thiopental 5 mg/kg, atracurium 0.5 mg/kg. Maintenance of anesthesia was conducted with isoflurane 0.5-1% and N2O and oxygen to the ratio of 50%. During the surgery, the anesthesiologist prescribed a sufficient volume of crystalloid to patients based on calculating the required fluid.

A written informed consent was obtained from the patients before surgery and patients were placed in order of entering the operating room in a list that was previously in a randomized

blocking method. The list was included the patient's name and surname and file number, and code A and B was the alternative for type of medication used by the patients. Age, gender, height and weight of patients were recorded on hospitalized file.

Primary end points included

The amount of electrolytes (sodium, potassium, chloride and bicarbonate) before anesthesia, during induction, 120 minutes after the start of treatment and also at the end of surgery.

The secondary end point included

amount of bleeding, urinary output, heart rate and systolic and diastolic blood pressure of patients at the start of anesthesia, at 30, 60, 90 and 120 minutes after onset of anesthesia. An expert who was unaware of the type of drugs prescribed completed the relevant form.

Statistics

Statistical methods of Independent-Samples T-test, Chi-square and Repeated-measures Analysis were used for statistical analysis of the results. Data analysis was performed by using the SPSS V 20 software. $P<0.05$ was considered significant. The descriptive statistics including indexes of central tendency and dispersion (mean and standard deviation) and frequency distribution was used to describe the specifications of research units in both groups.

RESULTS

This clinical study comprised 34 patients who underwent brain tumor surgery and Were divided into two groups: 17 patients in the mannitol 20% group and 17 patients in the hypertonic salin 5%.

The average age in the group treated with hypertonic saline was 47.88(±8.83) and in the group treated with mannitol was 48.29(±10.10) (p=0.15). Gender distribution of patients in the group treated with hypertonic saline was 35.29% men and 64.71% women and in the group treated with mannitol were 58.82% men and 41.18% women. Patients had no also significant difference in terms of weight, heights and operation time.

In results of this study, there was a significant difference between the two groups in amount of sodium and chloride electrolytes at 120 minutes after the start of surgery and at the end of surgery and Independent-Samples t-test showed the significant difference of these electrolytes between groups less than 0.05 in both times, but there was not observed a

significant difference between groups in the concentrations of potassium and bicarbonate in none of the study times ($p>0.05$).

Hemodynamic status of patients showed that there was a significant difference between groups in systolic and diastolic blood pressure and heart rate of patients only at 120 minutes after administration of the solutions by using the Independent-Samples T-test ($p<0.05$) and the hemodynamic status of patients was similar for both groups in other times investigated of the study.

The amount of diuresis during the surgery of patients was similar for two groups to 60 minutes after the start of study, but the amount of diuresis was significantly higher in patients receiving mannitol than the hypertonic saline at 90 and 120 minutes after the start of solutions injection and the amount of diuresis in the minutes 90 and 120 was (1082.35 ml versus 823.64 ml, $p = 0.035$) and (1382.35 ml versus 1051.05 ml, $p = 0.041$) respectively. As well as, the amount of bleeding during the surgery was measured in both groups up two hours after the start of drug administration and investigated at minutes of 30, 60, 90 and 120 which there was no significant difference between the groups in terms of bleeding at none of the times ($p>0.05$).

DISCUSSION

This study has been designed with the aim to investigate the effect and safety of using the hypertonic sodium solution compared to mannitol in patients undergoing brain surgery. Our results of this study showed that the use of hypertonic saline instead of mannitol caused a significant increase in sodium and chlorine concentration, but there was not observed change in blood potassium and bicarbonate concentration at all times of the study. In this study, the hemodynamic status of patients showed that patients in hypertonic saline group experienced higher systolic and diastolic blood pressure and heart rate than the mannitol group, but the difference between groups was significant only at 120 minutes after the surgery. The amount of diuresis was similar in both groups up to 60 minutes after the start of surgery, but amount of diuresis was higher in mannitol group at 90 and 120 minutes after the surgery; and also patients in mannitol group had lower bleeding at all times in terms of bleeding, but the difference between groups was only significant only at 30 minutes after the start of surgery. The physical effects of using the hypertonic saline and mannitol on brains of patients with normal intracranial pressure have been investigated in several studies. Gemma et al and De Vivo et al in their study have reported that the use of mannitol and hypertonic saline drugs

causes to satisfying provide of mental relaxation in patients candidate for elective craniotomy surgery.[12,13] But the patients' candidate for brain tumor surgery have been studied in our study and there is a risk for rising the intracranial pressure in these patients and the selection of more effective drugs to prevent the development of this complication is critical.

The use of hypertonic saline or mannitol in studies on animals and humans has shown that it increases the concentration of sodium or osmolarity and decreases the intracranial pressure and reduces the overall content of water in different brain areas.[14-21] The main mechanism involved in creating this effect of water shift from brain tissue to intravascular space with the hyperosmolar effect of hypertonic saline and mannitol is due to permeability of blood-brain barrier to sodium and mannitol. Effectiveness of hyperosmolar solutions depends on Reflection Coefficient (RC) which is defined as relative permeability of blood-brain barrier to a solution. RC equal to 1 means the absolute impermeability of that solution and RC equal to 0 indicates the absolute permeability of solution. Hypertonic saline solution may be more theoretically useful than the mannitol solution due to more osmotic effects of sodium compared to mannitol. The less leaking of liquid may be due to more osmolarity effect of sodium and this higher osmotic gradient of trans-endothelial in vascular space may cause getting out the water from brain and more transfer the fluids to intravascular space. In addition, the lower RC is associated with the fewer incidences of return phenomena of cerebral edema. Accordingly, our results showed that the effectiveness of hypertonic saline versus the mannitol is consistent with improving the clinical status of patients and in line with the theory of hyper osmotic therapy.[22]

Results of the present study showed that patients in hypertonic saline group had significantly higher concentrations of sodium and chloride during the study and the results obtained in present study were similar to study results of Wu et al and Rozet et al which the use of hypertonic saline also caused to increase the sodium concentration in their studies.[22,23] In a study, Ichai and colleagues also examined the results of using the solution with the same osmolarity (hypertonic lactate saline and mannitol 20%) in patients with traumatic brain injury and observed that the amount of sodium concentration after administration of these solutions was more in hypertonic lactate saline group, but there was no difference between groups in the chlorine concentration.[24] Perhaps the reason for lack of change in chlorine concentration is that unlike the present study, the lactate used in their study has been quickly metabolized after administration and created an imbalance in positive and negative charge of

the cells which cause to create a positive charge on the outside of cells and the body is forced to compensate for the extracellular positive charge that gets out the chloride ion with negative charge from the cell to compensate as one of the main intracellular inorganic ions that are involved in intracellular tonicity, but the solution containing lactate was not used in the present study and concentration of sodium and chloride similarly increased in patients within the hypertonic saline group.

In this study, the concentration of potassium increased to the baseline state in both groups over the time, but the difference between groups was not significant. A number of studies have obtained conflicting results compared to our study and announced that hypokalemia happens through using the mannitol or hypertonic saline and pointed out to the effects of these drugs on hemodilution and also more excreted of potassium ion by kidney in justifying their results, but they did not mention a definite and precise mechanism for the occurrence of this change in potassium concentration.[25-28] In another study, Rozet and colleagues mannitol 20% compared with the hypertonic saline on the balance of electrolytes; the use of hypertonic saline produced transient hypokalemia based on their results and the hyperkalemia occurred during the study period by using the mannitol. The reason of hypokalemia produced is considered by them due to compensatory effect of body to maintain a neutral electric position of cells in the face with hyperchloraemic acidosis created by hypertonic.[23] On the other hand, Villas Boas et al.[29] in their study reported a significant increase in the blood concentration of potassium by using the hypertonic saline and mannitol and it seems that increasing the concentration of potassium in the present study and the study of Vilas Boas is due to the mechanisms involved in removing the potassium along with water in hyperosmolar status, diluted acidosis caused by inflation of intracellular fluid or lower the concentration of bicarbonate.

Another case examined in this study is amount of bicarbonate concentration which decreased in both groups during the study, but the difference between groups was not significant at none of times. Like our study, Vilas Boas et al stated that there is no difference in the bicarbonate concentration of groups receiving the mannitol 20% and hypertonic saline, but the amount of bicarbonate in that study significantly decreased in each of the groups after 120 minutes compared to the initial time of the study and they consider the reason of this change resulting from diluted hyperchloraemic acidosis that this result was not found in our study.[29]

For comparison of normal saline solutions, hypertonic saline lactate and hypertonic sodium bicarbonate, Duburcq et al in their study reported that bicarbonate concentration decreases to 5 hours after administration by using the normal saline solutions, but there is no significant change; while bicarbonate concentration significantly increases from approximately 29mmol/L to 55mmol/L in patients receiving hypertonic saline lactate and hypertonic sodium bicarbonate. It seems that this sharp increase in the bicarbonate concentration is due to presence of lactate and bicarbonate in these groups, but none of them were used in our study and there was not observed a significant change in bicarbonate concentration.[30]

The other results obtained in this study can be the higher amount of diuresis in mannitol group at 90 and 120 minutes after the start of surgery that the similar results on more diuresis of mannitol than the hypertonic saline have been also obtained in previous studies such as Vilas Boas et al and Battison et al.[29,31] In the present study, patients' diuresis was evaluated up two hours after administration of solutions. The use of mannitol compared with hypertonic saline has increased the urinary output of patients during two hours after the start of drug administration in results obtained from study of Francony et al.[32] In another similar study conducted by Rozet and colleagues[23], amount of patients' diuresis in group receiving mannitol was more than the patients in hypertonic saline group up to 6 hours after starting treatment, but diuresis of patients in both groups had significantly difference in 3 first hours ($p = 0.001$). In addition to the diuretic effect of mannitol, it seems that the other reasons for lesser of urinary output in hypertonic saline group is because of increasing the sodium concentration that this increase can stimulate the release of antidiuretic hormones and this caused more water reabsorption from the kidneys and may thus cause the less urinary output in patients receiving the hypertonic saline compared with the mannitol.[22,23,33]

The amount of bleeding in patients of both groups was measured up two hours after the start of solutions administration during the study and although the amount of bleeding in the group receiving hypertonic saline was greater at all times of the study, there was not observed a significant difference in amount of bleeding at none of the studied times. Rozet et al also reported that there is no difference in amount of bleeding of patients in both groups after drug administration up to 6 hours through the use of mannitol 20% and hypertonic saline 3%.[23]

In this study, the hemodynamic status of patients was compared in the two groups and the systolic and diastolic blood pressure in group of patients receiving the hypertonic saline was significantly higher than the patients in mannitol group during the study, but difference of the

groups was significant only at 120 minutes after the start of study. Harutjunyan et al in their study announced that hypertonic saline is more effective than the mannitol in the treatment of increasing the intracranial pressure and this is due to the effect of hypertonic saline in increasing the blood pressure of patients and subsequently increasing the cerebral perfusion pressure.[34] In other study on pigs, Duburcq et al compared the solution of hypertonic saline lactate with the solution of sodium bicarbonate and normal saline, and the difference of mean arterial blood pressure in patients with hypertonic saline lactate group was significantly higher than the other groups after two hours and cardiac index also was better like our study.[30] In comparison of mannitol 20% and hypertonic saline lactate 0.5M, Ahmad et al also showed that the mean arterial pressure significantly increases in patients receiving hypertonic saline lactate after 45 minutes of starting the administration of solutions; and since the amount of diuresis in group receiving mannitol was more in their study like our ones, the higher the blood pressure of patients in both studies maybe because of more excretion of fluid from the body by mannitol and reducing the preload of patients that this change in amount of body fluids reduces the cardiac output and subsequently reduces the blood pressure of patients.[35] But the same result was not observed in hemodynamic changes of patients in Rozet et al study; they used of hypertonic saline 3% and mannitol 20% in their study and the hemodynamic fluctuations between patients in both groups were similar during their study. They have known this result obtained from their study due to the effect of anesthetic drugs that cause the effect of using these solutions on blood pressure of patients is not well observed, but it seems that the difference between their study and the present study is that they used of hypertonic saline 3%, but the hypertonic saline 5% was used in our study and better result was obtained.[23]

CONCLUSION

It can be concluded hypertonic saline increases the concentration of electrolytes and provides a more appropriate hemodynamic status than the mannitol. Hypertonic saline was associated with less diuretic effect; therefore generally the hypertonic saline can be used as a substitute for mannitol.

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