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Alterationss Serum Sodium Levels on Intravena Administrations of 20% Manitol and Hypertonic Sodium Lactate in Male Wistar Rats

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ABSTRACT

Background: Prolonged use of hyperosmolar solution in elevated ICP (Intracranial Pressure) increases the sodium concentration which associated with mortality and ICU (Intensive Care Unit) length of stay. Hypertonic sodium lactate as a new sodium-based solution does not yet have an evidence base that states that long-term use is safe in increasing ICP.

Objective: Knowing the effect of hypertonic sodium lactate on alterations sodium level in male wistar rats compared to mannitol.

Methods: This research is an experimental laboratory study using a simple random sampling design. 38 male wistar rats were obtained with age and body weight 14.22±0.43 weeks and 301.56±25.10gr in the mannitol group and 14.17±0.38 weeks and 277.61±18.85gr in the sodium lactate hypertonic group. Both groups were given hypertonic sodium lactate or mannitol for 5 days and assessed on changes sodium level after administration.

Results: The highest alterations sodium levels in the hypertonic sodium lactate group compared to mannitol occurred on the first day compared to sodium levels before treatment (5.06±4.25 vs 5.67±2.96 mEq / L) (p = 0.222) and the lowest changes were obtained at the third day compared to the second day (0.22±3.51 vs 0.22±2.29 mEq / L) (p = 0.568). The highest mean in the hypertonic sodium lactate group compared to mannitol was 147.83±3.35 vs 147.83±3.35 mEq / L and the lowest mean was 145.83±2.07 vs 146.06±2.92.

Conclusion: In this study, administration of hypertonic sodium lactate and mannitol significantly increase sodium levels compared before administration, but not followed by significant changes on the first day to the fifth day. There was no significant difference between hypertonic sodium lactate and mannitol to changes in sodium levels over 5 days.

Keywords: Hypernatremia; Hypertonic; Lactate; Manitol

Abbreviations: ICP: Intracranial Pressure; ICU: Intensive Care Unit; TBI: Traumatic Brain Injury; TRPV1: Transient Receptor Potential Vanilloid Type 1; SID: Strong Ion Difference

Introduction

Mannitol, hypertonic saline and hypertonic sodium lactate has been in clinical for intracranial hypertension. Hyperosmoler therapy has been use in neurosurgical patients to maintain circulation, prevent hypovolemia, hypervolemia, hypoosmoler condition, and hyperglycemia. Maintain the systemic pressure is very important in traumatic brain injury patients [1]. Mannitol is the most an osmotic diuretic recommendation as a first-line agent to reduce intracranial pressure for decades [2]. However, side effects of mannitol are electrolyte imbalances induced by slow elimination and accumulation of mannitol in serum [3]. Repeated administration of mannitol induced water loss through osmotic diuresis is associated with an increase in sodium levels. The retrospective study on 2006, the use of mannitol

as a therapy for intracranial hypertension affected the incidence of hypernatremia (24.3%) [4]. The other study in 2010, using mannitol for patients with intracranial hypertension induced hypernatremia in 10% of the total patients on the first day and 10-21% on mannitol administration up to the seventh day [5].

In traumatic brain injury (TBI), hypernatremia is associated with length of Intensive Care Unit (ICU) stay and an increased risk of death. The previous study in 2008, mortality in TBI with hypernatremia reached 65% [6]. The higher level of sodium in patients with traumatic brain injury significantly affected in mortality [7]. The incidence of hypernatremia mostly showed in the first week after trauma and is associated with the use of hyperosmoleric fluids. as management of increasing ICP [8]. Lactate is known as a key intercellular or interorgan metabolite between glycolysis and oxidative phosphorylation that can be produced and used by the brain as an energy source under pathological conditions [9]. An experimental data on rat hippocampus shows that lactate is a better substrate of glucose and is able to significantly improve cognitive function deficits compared to 3% NaCl at 24 hours and 30 days after surgery on orientation, registration, attention, remembering and language values. High sodium content stimulate vagal respon to secreting Atrial Natriuretic Peptide (ANP) and affected to increase natriuresis to maintain blood pressure and decrease sodium or water levels [10,11]. In a study in mice in 2007, the use high concentrations sodium solution is associated with the activation of Transient Receptor Potential Vanilloid type 1 (TRPV1) which results in an increase in the process of natriuresis and diuresis [12].

The use of hypertonic sodium lactateassosiated with increase the Strong Ion Difference (SID) or pH (alkalosis) and prevent acidosis hyperchloremia condition [13]. Based on the high incidence intracranial hypertension, increase in sodium levels is associated with high mortality and morbidity because using mannitol and hypertonic sodium lactate appears as a new alternative therapy to reduce ICP. Lack of this solution is the absence of long-term studies to evaluate the alterations in sodium levels. Therefore, researchers try to compare alterations in sodium levels between mannitol and hypertonic sodium lactate in experimental animals as a first step. The experimental animals used in this study were male iistar rats.

Methods

Animal Groups and Protocols

This study was an experimental laboratory study with a simple randomized design. All experiments were approved by the Institutional Animal Care and Use Committee of Gajah Mada University (KE/FK/0958/EC/2019). 36 male Wistar rats weighing above 250g, were housed in the animal facility for 1 week before used in the experiments. During the adaptation period the mice are in adequate cages suitable for food, bedding, and equipment related to maintenance. Air exchange, temperature, humidity, noise, light intensity and the light cycle are maintained within limits according to the health and welfare of animals. Feeding uses the manufacturer's standard feed (AD II) which meets the nutritional requirements of rat maintenance both macro and micronutrients.

Experimental Procedure

On the day of treatment the rats were divided into 2 groups (group A as treatment using mannitol, group B with hypertonic sodium lactate treatment). Rats were anesthetized with intraperitoneally ketamine 1mg/100grBB before IV line insertion with abocath number 27G in the rat tail vein then fixed with silkam 2.0. A rat given mannitol through intravenous infusion through the caudal vein as much as 0.5 mL/100gr. Rat B was given hypertonic sodium lactate as much as 0.15ml/100gr. Rats left back to the cage after the protocol. During the trial period, rats feeding was adjusted to the nutritional requirements of mouse rearing. There was no limit on intake volume in mice during the study. After 6 hours of fluid administration, blood drawn using venous blood through the sinus orbital in the eye as much as 0.5cc. Total blood sampling in rats was 2.5cc during the trial period. This is adjusted to the maximum blood loss limit of rats with a weight of 250gr is 15% of the total blood volume of the rat.

Measurement

Blood is sent to the UGM Clinical Pathology Laboratory for examination of sodium levels. This research was conducted on all mice for 5 days.

Statistical Analysis

Statistical processing and analysis was performed by comparing alterations sodium levels in the two groups. Normality test with Shapiro-Wilk for numerical scale data. Independent T-test is used to analyze data with normal distribution and Mann Whitney if not normally distributed. Researchers used General linear models (GLM) to assess the effect of giving both hyperosmolar solution in sodium levels alterations from day to day conducted for 5 days.

Results

There were no significant differences in the age of the rats and variations in sodium levels between the two groups with respect to the age of the experimental animals (Table 1). There were significant differences between the two groups on body weight before the study ($p < 0.05$), but after analysis (Table 2) there was no significant effect of weight differences between the two groups in sodium levels alterations ($p = 0.486$). After administration of hyperosmolar solution in both groups, serum sodium levels variation in the mannitol group from the first day to the fifth day is 141-152 mEq/L, whereas in the hypertonic sodium lactate group is 139-156 mEq/L. Sodium levels alterations (Δ) between days can be seen in Figure 1. The highest sodium levels alterations in the mannitol group occurred on the first day, where the level of serum sodium increase to 5.67±2.96 mEq/L. This

situation was similar in the sodium lactate group (5.06±4.25 mEq/L). In this analysis (Table 2) also no significant difference was found between administration of hypertonic sodium lactate to sodium levels alterations compared with administration of mannitol (p> 0.05).

Table 1: Demographic data.

	Groups		
	Mannitol ± SD	Hypertonic sodium lactate ± SD	p
Age (week)	14,22±0,43	14,17±0,38	0.673
Weights (gram)	301,56±25,10	277,61±18,85	0,003*
Sodium serum (mEq/L)	142,5±2,247	142,5±2,247	0,8812

Note: *p<0,05 (Significant)

Table 2: Analysis of the relationship between the use of hyperosmoleric fluids (mannitol and hypertonic sodium lactate) and body weight on alterations in sodium levels.

No.	Variable Relationship	p
1.	Δ sodium and weight	0,486
2.	Δ sodium and mannitol and hypertonic sodium lactate	0,189

Note: GLM test by Wilks' Lambda value, where

1. There is no significant difference between body weight and alterations in sodium levels;
2. There was no significant difference between the mannitol and hypertonic sodium lactate groups on alterations in sodium levels from day to day; Δ = alterations sodium levels

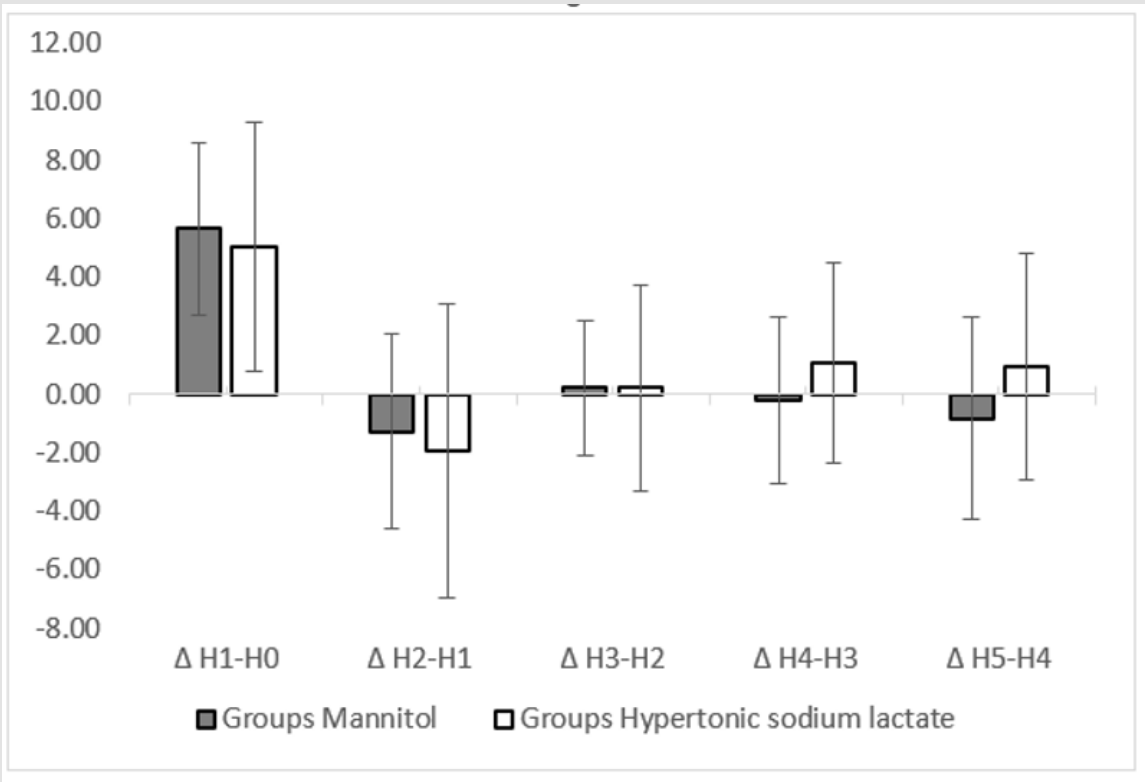

Figure 1: Alterations in sodium levels.

The highest serum sodium level in mannitol was highest on the first day (148.17 ± 2.96), whereas hypertonic sodium lactate occurred on the fifth day (147.83 ± 3.35). The difference in mean serum sodium between mannitol and hypertonic sodium lactate varies considerably from the first day to the fifth day (Figure 2). Serum sodium levels in the hypertonic sodium lactate group were lower in the first 3 days, whereas mannitol was lower on the fifth day. From the statistical analysis using the GLM (Table 3) it was stated that the treatment (hyperosmolar solutions) in both groups would significantly increase the sodium level when compared with before giving (p <0.05). The significance only occurred when compared to before administration, but in an analysis there was no significant difference between the use of mannitol and hypertonic sodium lactate after treatment (first day to fifth day) (p> 0.05). In this analysis also found no significant difference between administration of hypertonic sodium lactate on sodium level compared with administration of mannitol (p>0.05).

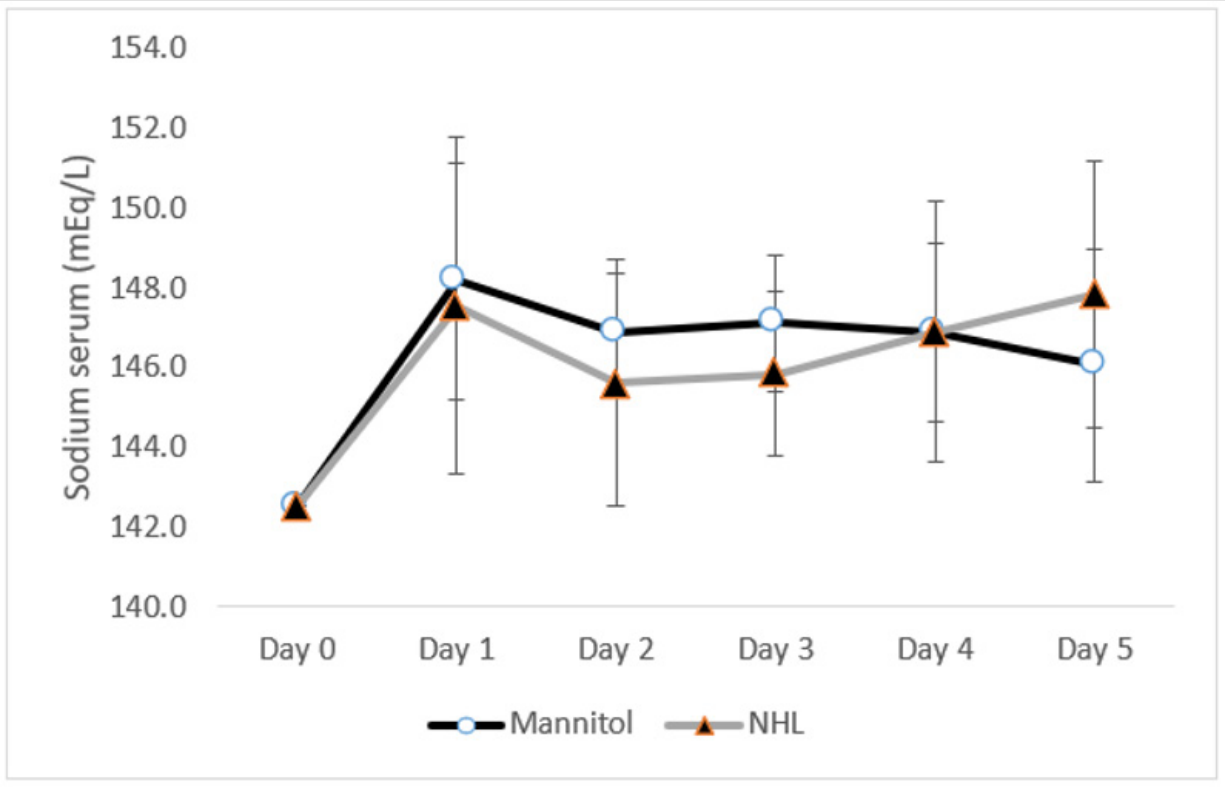

Figure 2: Alterations sodium level.

Table 3: Analysis of the relationship between time and use of hyperosmolar solutions (mannitol and hypertonic- sodium lactate) on average sodium levels.

No	Variable Relationship	p
1.	Relation between time and mannitol – hypertonic sodium lactate	0,118
2.	Relation between time and alterationss sodium level	0,000*

Note: GLM test by Wilks' Lambda value, where

1. There was no significant difference between the mannitol and hypertonic sodium lactate groups on alterationss in sodium levels from day to day;
2. There is a significant difference between the days before and after administration of both hyperosmolar solutions (mannitol and hypertonic sodium lactate); *p<0,05 (significant)

Discussion

The results of this study found a significant difference between body weight in mannitol mice and hypertonic sodium lactate mice (p <0.05). This condition cannot be controlled by researchers because there is no difference in treatment between the two groups of mice. The administration of fluid doses in both groups was adjusted to the body weight of mice in grams. In the analysis using GLM significant weight differences in the two groups did not affect the results of the study. No significant difference was found between the effect of body weight on alterationss in serum sodium levels in the two study groups (p = 0.486), as a whole or when viewed from changes in sodium levels from day to day until the fifth day (p> 0.05). Evaluation of sodium levels in both groups before administration of hyperosmolar fluid showed the same mean sodium level. Both groups had a mean initial sodium level of 142.5 mEq / L. Looking at the data from this study (gender, age, and average sodium level), no significant differences in the characteristics of the sample between the mannitol and hypertonic sodium lactate groups. no significant effect of weight difference was found on alterationss in sodium levels after statistical analysis. From these characteristics it can be concluded that this study is worth comparing. The primary outcome in this study was the alterationss in sodium levels in the administration of hypertonic mannitol and sodium lactate in male wistar rats. From this study, there is no difference between administration of hypertonic sodium lactate and mannitol to changes in sodium levels for 5 days. At the beginning of administration of the two hyperosmolar solutions, both of them will cause an increase in sodium levels, but after that the sodium levels in both groups are relatively fixed. In this study the hypothesis of hypertonic sodium lactate administration has a lower effect on increasing sodium levels in wistar male rats compared with mannitol administration was not proven.

Be observed from the average serum sodium levels, the use of hypertonic sodium lactate and mannitol both increased the mean sodium in rats when compared to before the study. The results of this study showed a significant effect on mannitol administration (142.5±2.25 vs 148.17±2.96) on the first day and hypertonic sodium lactate administration (142.5±2.25 vs 147.56±4.25) compared to the day before treatment ($p < 0.05$). This is consistent with the previous theory, where an increase in sodium levels is one of them influenced by the administration of hyperosmolar solutions (mannitol and hypertonic sodium lactate). From the first day to the fifth day, sodium levels varied in both groups (> 145mEq/L). hypertonic sodium lactate on the first day to the third day had a lower mean sodium concentration than mannitol, while on the fifth day the mannitol group was lower. This variation was considered not significant in statistical analysis. There was no difference between administration of hypertonic sodium lactate and mannitol to changes in mean sodium from the first day to the fifth day ($p > 0.05$). The other factors that influence the discrepancy of research results and hypotheses are factors that cannot be controlled and are not assessed by researchers so that this becomes a limitation in this study. Increased serum sodium levels in the hypertonic sodium lactate group can be caused by ANP secretion, regulation of osmolarity changes and stimulation of TRPV1.

ANP Secretion

In this study, there may be a disorder that inhibits ANP secretion so that it affects natriuresis and diuresis. In this study no volume status measurement was carried out. Measurement of volume status can be seen by assessing fluid intake and urine output. The situation was not assessed because of the difficulty of measuring the intake of volume and shape of the cage that was inadequate to maintain the condition of the urine does not evaporate. The effect of hemodynamic changes that can affect ANP secretion cannot also be assessed in this study due to the limitations of measuring devices for measuring hemodynamics in laboratory animals.

Osmolarity

Increased osmolarity will cause increased thirst response, ADH secretion and ANP secretion by carotid baroreceptors. Not achieving osmolarity in the use of hypertonic sodium lactate will cause no increased thirst response in mice and reduced ADH secretion so that water retention does not occur. The loss of water can cause disruption of sodium regulation. In future studies, consideration should be given to the assessment of changes in osmolarity.

Activation of TRPV1

Activation of TRPV1 is influenced by the use of sodium-based liquids with high concentrations, pathological conditions such as decreased pH, body temperature, and increased metabolic lipid concentrations. In this study these factors have not been excluded because they cannot be included in the study variables. If you view the results, both hypertonic sodium lactate and mannitol will significantly increase sodium levels compared before administration. Manifestations that can arise in elevated levels of sodium are restlessness, lethargic, hyperflexia and can lead to seizures, coma to death. Manifestations in hypernatremia did not appear in this study. So it can be stated that it is safe to be given to experimental animals for 5 days.

Conclusion and Suggestion

Conclusion

In this study, administration of hypertonic sodium lactate and mannitol significantly increase sodium levels compared before administration, but not followed by significant changes on the first day to the fifth day. There was no significant difference between hypertonic sodium lactate and mannitol to alterations in sodium levels over 5 days.

Suggestion

In this study, we have a significant weight difference between the mannitol group and hypertonic sodium lactate as a confounding factor in the study, therefore in subsequent studies an effort was needed to maintain homogeneity before the study was conducted. In the next research, it is necessary to evaluate other variables that affect the research, such as hemodynamics, nutrient intake and nutritional status, urine output and volume status, sampling place, rat weight evaluation after treatment or before treatment the next day to minimize confounding factors in the study. This research is quite safe when given to experimental animals, so it is recommended to continue the research on humans for more than 48 hours. This is because there is no significant difference between the use of hypertonic sodium lactate and mannitol to changes in sodium levels for 5 days in experimental animals.

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