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Original Article

Comparison of Parenteral Maintenance Isotonic and Hypotonic Fluid Therapies administered to Hospitalized Children In Terms of Hyponatremia Risk

Hastenede Yatan Çocuklarda Parenteral İdame İzotonik ve Hipotonik Sıvıların Hiponatremi Riski Açısından Karşılaştırılması

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ABSTRACT

Objective: Isotonic fluids are recommended for parenteral maintenance fluid therapy because they reduce morbidity and mortality due to iatrogenic hyponatremia in children. However, there is still an ongoing debate regarding the ideal fluid therapy to be used in children. This study aims to provide insight into the development of hyponatremia in patients using hypotonic and isotonic fluids for maintenance and the comparative effects of these fluid regimens.

Method: The study included hospitalized patients aged 1 to 83 months between January 2021 and June 2022, with normal serum sodium levels and given maintenance fluid therapy. Patients were categorized into three maintenance fluid groups: 0.3% saline (0.3% saline in 3.3% dextrose), 0.45% saline (0.45% saline in 5% dextrose), and normal saline (0.9% saline in 5% dextrose). The groups were further stratified based on control sodium level measurement times (8-16 hours, 17-32 hours, and 33-48 hours), and data were compared with baseline sodium levels.

Results: The study involved 215 patients aged 1-83 months. There was no significant difference between the groups in terms of initial serum sodium levels. However, comparing control sodium levels revealed significant distinctions between each group (respectively, 0.3% saline and 0.45% saline groups (p=0.009), 0.45% saline and normal saline (p=0.003), 0.3% saline and normal saline groups (p<0,001). Significantly, the difference between baseline and control sodium values varied across fluid groups (p<0.001). Treatment duration did not impact the sodium level change.

Conclusion: Using hypotonic fluids in pediatric maintenance fluid therapy elevates the risk of hospital-acquired hyponatremia. Opting for isotonic fluids in parenteral maintenance therapy is safer.

Keywords: Child, hyponatremia, maintenance fluid, isotonic, hypotonic

ÖZ

Amaç: Çocuklarda izotonik sıvıların daha yaygın kullanımının iyatrojenik hiponatremiye bağlı morbidite ve mortaliteyi azaltacağı düşünülmektedir. Ancak çocuklarda kullanılacak ideal sıvı tedavisine ilişkin tartışmalar halen devam etmektedir. Bu çalışmada idame tedavide kullanılan hipotonik ve izotonik sıvıların hiponatremi riski açısından karşılaştırılması amaçlanmıştır.

Yöntem: Çalışmaya Ocak 2021 ve Haziran 2022 tarihleri arasında hastanede yatırılarak izlenen ve yatışı sırasında serum Sodyum düzeyi normal saptanan, 1 ay-83 ay arası hastalar dahil edildi. Hastalar idame sıvı içeriğine göre, %0,3 salin (%3,3 dekstrozda %0,3 salin), %0,45 salin (%5 dekstrozda %0,45 salin) ve normal salin (%5 dekstrozda %0,9 salin) olmak üzere üç gruba ayrıldı. Gruplar, kontrol sodyum seviyesi ölçüm sürelerine göre (8-16 saat, 17-32 saat ve 33-48 saat) gruplandırıldı ve veriler başlangıçtaki sodyum seviyeleriyle karşılaştırıldı.

Bulgular: Çalışmaya 1-83 ay arası 215 hasta dahil edildi. Hastalar aldıkları mayilere göre başlangıç sodyum düzeyi açısından karşılaştırılmış ve gruplar arasında anlamlı fark saptanmamıştır. Ancak kontrol sodyum düzeyleri karşılaştırıldığında her grup arasında anlamlı fark saptanmıştır. Sırasıyla; %0,3 salin ve %0,45 salin grupları (p=0,009), %0,45 salin ve normal salin grupları (p=0,003), %0,3 salin ve normal salin grupları (p<0,001). Hastalar, aldıkları mayilere göre başlangıç ve kontrol sodyum değerleri arasındaki fark açısından karşılaştırıldığında üç grup arasında anlamlı fark olduğu görülmüştür (p<0,001). Kontrol sodyum alınma saatinin sodyum düzeyindeki değişimi etkilemediği görülmüştür.

Sonuç: Çocuk hastalarda idame sıvı tedavisinde hipotonik sıvılar kullanıldığında hastane kaynaklı hiponatremi riski artmaktadır. Parenteral idame sıvı tedavisinde izotonik sıvıların kullanımı hiponatremi riski açısından daha güvenlidir.

Anahtar kelimeler: Çocuk, hiponatremi, idame sıvı, izotonik, hipotonik

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INTRODUCTION

Children's daily dietary, hydration, and electrolyte requirements change. Due to increased fluid loss and decreased nutrition and fluid intake, infants are more susceptible to developing dehydration quickly. However, because of age-related increases in the efficiency of compensatory systems such as water and electrolyte absorption and excretion, signs of fluid loss in older children may become manifest 12-18 hours after onset of severe dehydration[1]. Parenteral replacement of fluids and electrolytes becomes a crucial component of treatment when infections, surgical complications, or risks associated with oral intake prevent enteral feeding[2]. The most frequent electrolyte imbalance among these individuals is hyponatremia[3-5]. Hyponatremia may develop due to increased water retention with antidiuretic hormone (ADH) release, which may also be triggered by conditions such as pain and stress. It is recommended to avoid hypotonic solutions to prevent development of neurologic complications that may occur in these patient groups who should be especially careful in terms of the risk of hyponatremia[6,7]. Until recently, hypotonic fluids such as 0.3% and 0.45% saline solutions were frequently used as maintenance fluids in children. In recent years, many studies have been published showing that the use of hypotonic solutions as maintenance fluids in children increases the risk of hyponatremia, which decreases with the use of isotonic fluids. In 2018, the American Academy of Pediatrics (AAP) published a guideline with evidence-based recommendations for the treatment of pediatric patients who need maintenance fluid therapy[2]. Isotonic fluids containing 5% dextrose and 0.9% sodium chloride are recommended as daily maintenance fluid therapy in children between 28 days and 18 years of age, except for patients with congenital or acquired heart disease, renal disease, liver disease, central nervous system disease, diabetes insipidus, cancer, and severe burns[1,2]. Increased usage of isotonic fluids for maintenance is advised by recent studies. However, few clinical studies in our country have examined the effects of maintenance fluid therapies on blood sodium (Na) levels, which may be associated with the continued use of hypotonic solutions in many centers. This study aims to evaluate the impact of maintenance fluid therapies using hypotonic and isotonic solutions on the incidence of hyponatremia in hospitalized children.

MATERIALS and METHODS

This prospective, single-blind, randomized, controlled clinical study, which included 215 patients aged 1 to 83 months hospitalized in pediatric inpatient wards between January 2021 and June 2022, was conducted in our tertiary referral center after obtaining approval from the Clinical Research Ethics Committee of University of Health Sciences Turkey, Ankara Dr. Sami Ulus Maternity, Child Health and Diseases Training and Research Hospital (approval number: 2020-021, dated: 02.12.2020). Patients with symptoms such as diarrhea and vomiting that may affect fluid-electrolyte balance, patients with serum Na levels outside the normal limits during hospitalization, patients requiring deficit fluid therapy due to dehydration, and patients with chronic diseases that may progress to Na and water balance disorders were excluded from the study. A wide range of patients including those with drug intoxication, lower respiratory tract infection, abdominal pain, urinary tract infection, aphthous stomatitis, gastrointestinal bleeding, immune thrombocytopenic purpura, and anemia were enrolled in the study. Daily parenteral maintenance fluid requirements were calculated according to the Holliday Segar formula[1]. A total of 215 patients included in the study were divided into three groups according to maintenance fluid therapy they received as follows: 0.3% saline (0.3% saline in 3.3% dextrose) (n=69); 0.45% saline (0.45% saline in 5% dextrose) (n=72) and normal saline (0.9% saline in 5% dextrose) (n=74) (Table 1). The majority of the patients were those who were unable to consume sufficient oral nutrition during the first days of hospitalization or had their oral intake restricted due to potential complications. Serum Na levels <135 mmol/L and >145 mmol/L were accepted as criteria for hypo-and hypernatremia, respectively[5]. Based on serum Na levels, hyponatremia was defined as mild (135-130 mEq/L), moderate (130-125 mEq/L), and

Table 1. Distribution of fluid treatment contents by age groups

Age groups (months)	0.3% saline (n)	0.45% saline (n)	Normal saline (n)	Total (n)
1-24	**44**	25	38	107
25-60	20	40	34	94
61-83	5	7	2	14
Total	**69**	**72**	**74**	215

severe (<125 mEq/L) hyponatremia[5]. Serum Na levels of the patients were checked at 8-16, 17-32, and 33-48 hours after administration of different concentrations of maintenance fluids to evaluate their effects on serum Na levels. In the study the first control serum Na level of each patient measured after the initiation of maintenance fluid therapy was compared with the baseline Na level. The patients were divided into three age groups as follows: 1-24 months (n=107), 25-60 months (n=94), and 61-83 months (n=14). Table 1 shows the fluid contents received by the patients in these three age groups. In each patient group, initial and control serum Na levels were compared. Informed consent forms were obtained from the parents of the patients, and principles of confidentiality were maintained by the investigators. Age, gender, clinical findings, and serum Na levels of the patients were recorded. Serum Na levels were quantified by the ion-selective analyzer method using a Beckman Coulter brand AU5800 model biochemistry autoanalyzer and Beckman Coulter brand kits after blood samples were centrifuged at 4000 rpm for 10 minutes.

Statistical Analysis

The research data were evaluated using the SPSS, version 22.0. Descriptive statistics were expressed as standard deviation, numbers, percentages, ratios, median, and mean values. Mean ± standard deviation and median (minimum-maximum) values were used for quantitative variables, and numbers (percentages) for qualitative variables. Whether there was a statistically significant difference between the categories of the qualitative variable with two categories for the quantitative variable was examined using the Student's t-test, independent sample t-test, and dependent sample t-test if the assumptions of normal distribution were met. For the quantitative variables, if the assumptions of normal distribution were met, the One-Way ANOVA test was used to determine whether there was a statistically significant difference between the categories of the qualitative variable with more than two categories. A post-hoc test was used to check whether there was a significant difference between the two categories. The chi-square test was used to examine the relationship between two qualitative variables. The statistical significance level of the p-value was considered to be below 0.05.

RESULTS

The study included a total of 215 patients aged between 1 and 83 months (median age:25 months), and 58.1% of them were male. Patients were divided into 0.3% saline (n=69:32.1%), 0.45% saline (n=72:33.5%), and normal saline (n=74:34.4%) according to the concentration of Na they received for their fluid therapies The incidence of hyponatremia among patients receiving three fluid therapies with 0.3% saline, 0.45% saline, or normal saline was 37%, 16%, and 1%, respectively. In the study, two of the 42 patients with hyponatremia had moderate, and 40 cases had mild hyponatremia. No patient had severe hyponatremia. The data obtained by comparing the baseline and control Na values of all patients according to the fluid therapies they received are shown in Table 2. No significant difference was found between the groups when patients were compared in terms of the baseline Na levels. While control Na levels were significantly different between groups in the (0.3% saline vs 0.45% saline groups (p=0.009), 0.45% saline vs normal saline (p=0.003), 0.3% saline vs normal saline groups (p<0,001) (Figure 1, Table 3). The timing of measurements of control Na levels varied due to several factors, including the fact that all control blood samples were collected by our team, the clinical condition of the patient influencing the timing of sample collection, patient density in the clinic, and early termination of fluid replacement therapies before 24 hours. The serum Na level was measured at an average of 21 hours after admission. The median time for control blood collection was 22.4 hours, ranging from a minimum of 8 hours to a maximum of 48 hours after patient's referral. Control Na levels were measured between 8-16 (n=73:33%), 17-32 [n=124: (57%) 33-48 (n=17:7%] hours after their admission to the clinic. It was observed that the timing of control Na sampling did not significantly affect changes in Na levels. The patients

Table 2. Baseline and control Na^{++} values of the patients according to the fluid they received

Fluid contents	Mean baseline Na^{++} level (meq/L)*	p-value**	Mean control Na^{++} level (meq/L)*	p-value**
0.3% saline (n=69)	137.38±2.08	0.769	135.36±2.42	**0.03001**
0.45% saline (n=72)	137.21±1.92		136.5±2.27	
Normal saline (n=74)	137.1±1.50		137.74±2.13	

*: Mean ± standard deviation, **: ANOVA, Na: Sodium

were divided into three groups according to age: 1-24 months (n=107), 25-60 months (n=94), and 61-83 months (n=14). Since the majority of cases in the study were in the 1-24 month age group, the data for this group were analyzed in greater detail. No significant difference was found between hospitalization and control serum Na levels according to age groups. When the patient group aged 1-24 months was compared in terms of baseline and control Na levels, no difference was found between the groups receiving 0.3% saline and 0.45% saline treatments (p=0.422), and the control Na level of the group receiving normal saline was significantly higher than the other two groups (p=0.018, p<0.001, respectively). Patients aged between 1 and 24 months were also compared by dividing them into 2 groups as patients who did and did not receive normal saline concentration. There was no significant difference between the baseline Na values of both groups. The control Na values of the group that did not receive normal saline concentration were found to be significantly lower than the group that did (p<0.001). In the comparison of the difference between the baseline and control Na values of the patients aged 1-24 months according to the fluid therapy groups, a significant difference was observed between these three groups (p<0.001). In the post hoc analysis, it was observed that the difference between the baseline and control Na values of the group receiving 0.3% saline solution was higher than those of the groups receiving 0.45% saline or normal saline (p=0.007, p<0.001, respectively) (Table 4). Patients between the ages of 25 and 60 months were divided into normal saline, 0.45% saline and 0.3% saline groups. Baseline Na concentrations of the groups' were similar. Albeit the presence of a borderline intergroup significance (p=0.052) mean control Na levels did not differ significantly between groups of patients receiving 0.45% saline vs isotonic fluid therapy. Also

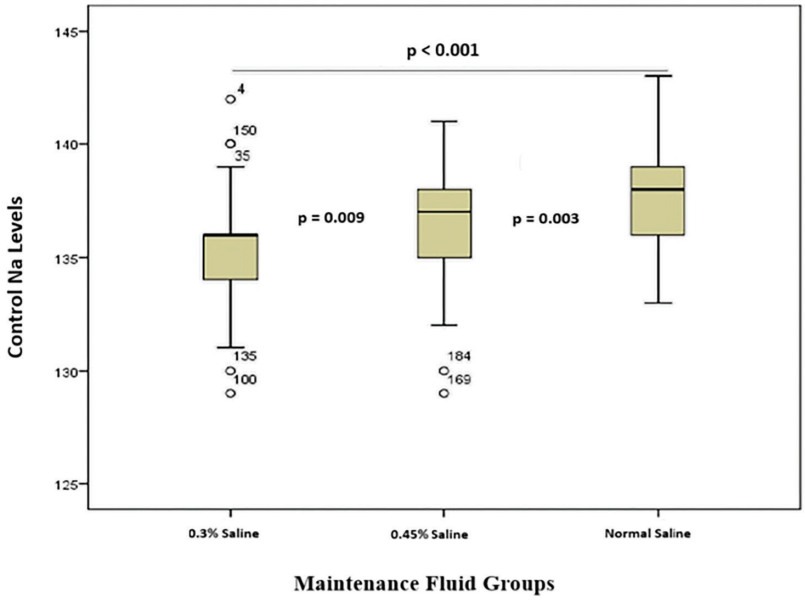

Figure 1. Comparison of baseline and control sodium levels according to fluid contents

Table 3. Comparison of baseline and control sodium values according to fluid therapies used

Fluid contents	Mean baseline Na level (meq/L)*		p-value**	Mean control Na level (meq/L)*		p-value**
0.3% saline-0.45% saline	137.38±2.08	137.21±1.92	0.851	135.36±2.4	136.5±2.27	**0.009**
0.45% saline-normal saline	137.21±1.92	137.1±1.50	0.988	136.5±2.27	137.74±2.13	**0.003**
0.3% saline-normal saline	137.1±1.50	137.38±2.08	0.768	137.74±2.13	135.36±2.42	**<0.001**

*: Mean ± standard deviation, **: ANOVA post-hoc analysis, Na: Sodium

Table 4. Comparison of control sodium levels in patients aged 1 to 24 months according to fluid therapy groups				
Fluid contents	**Baseline Na[44] level* (mg/dL)**	**Control Na level* (mg/dL)**	**Difference between baseline and control Na values**	**p-value**
0.3% saline (n=44)	137.66±2.3	135.55±2.5	-2.1136	**<0.001**
0.45% saline (n=25	136.4±1.0	136.24±1.6	-0.1600	
Normal saline (n=38)	137.05±1.5	137.82±2.0	-0.7632	
*: Mean ± standard deviation, **: Post-hoc analysis, Na: Sodium				

no discernible difference was noted in baseline serum Na concentrations of patients receiving 0.3% vs 0.45% saline solutions. Significantly lower control Na values were noted in other groups compared to the isotonic group (p=0.000).

DISCUSSION

In the literature the incidence of hospital-acquired hyponatremia varies between 15% and 42%[2,9,11]. Numerous factors, such as pulmonary system pathologies, central nervous system infections, and surgical procedures trigger non-osmotic ADH release in pediatric patients, resulting in increased water retention and hyponatremia. Due to the relatively larger brain tissue occupied in the cranial cavity of the children compared to adults, the risk of symptomatic hyponatremia and the neurological complications like seizures and cerebral edema is elevated. Thus, the authors recommend using isotonic fluids as a crucial measure to prevent hospital-acquired hyponatremia[13]. Holiday and Segar noted that hypotonic fluid treatments, used for acutely ill children, could cause hyponatremia, particularly with potential risk of overhydration, and suggested use of protocols involving isotonic fluids. However, they also acknowledged that isotonic fluids might raise the risk of hypernatremia[14].

Many recent studies have shown that hypotonic fluids administered as daily maintenance fluid therapy may cause iatrogenic hyponatremia and the use of isotonic fluids is effective in preventing the development of mild or moderate hyponatremia[5,8,9-12] in their study conducted in 2003, Moritz and Ayus[13] examined more than 50 cases of hospital-acquired hyponatremia resulting in morbidity and mortality, especially related to the neurological system.

The present study has clearly shown that the patients in the 1/3 saline group had noticeably lower control Na levels than the normal saline group. The study has also demonstrated that the incidence of hyponatremia considerably increased when three fluid therapies with lower Na concentrations were used Choong et al.[9] followed up their patients postoperatively after their discharge from intensive care unit, and detected the incidence rate of 42%, for the hospital-acquired hyponatremia while Carandang et al.[11] reported its incidence as 34.7%. In our study, the frequency of hyponatremia was determined to be 19%. The group that received 1/3 saline treatment had the highest frequency of hyponatremia (37%), whereas the group receiving normal saline with 5% dextrose had a significantly lower rate of hyponatremia (1%). We have observed that as the Na content of the three fluids used decreases, the incidence of hyponatremia significantly increases. A Finland study conducted in 2021 assessed severe cases f hospital-acquired hyponatremia in children. They evaluated 46.518 children under 15 years of age who presented to the emergency departments over a decade. Findings revealed that 7 out of 6.984 patients receiving maintenance fluid therapy developed severe hyponatremia, with two of them displaying neurological symptoms, suggesting that the severe hyponatremia was present in approximately one in every 998 acute pediatric patients receiving moderately hypotonic fluid therapy. Excluding high-risk patient groups in the study may have lowered the complication rates, and larger patient groups could pose a higher risk of complications and severe hyponatremia[15]. When reviewing relevant studies in the literature, it was observed that the sample size, the number of control groups, the characteristics of the patient population, and the duration of treatment vary among studies. In our study, a significant portion of the patient population consisted of those admitted to the general pediatric service with conditions such as pneumonia, bronchiolitis, seizures, and suspected drug ingestion. The study excluded children with congenital or acquired heart diseases, malnutrition, malabsorption,

diarrhea, vomiting, chronic kidney or liver disease, diabetes mellitus, diabetes insipidus, and diuretic users. Consequently, the frequency of hyponatremia may be lower in our study compared to other publications. The baseline serum Na levels in the three fluid therapy groups were similar, with an approximate mean value of 137 mEq/L. However, the post-fluid treatment control Na levels were notably different, with 135.36 mEq/L in the 1/3 saline, 136.5 mEq/L in the 1/2 saline, and 137.74 mEq/L in the normal saline groups with statistically significant differences among groups ($p<0.001$). The timing of control sample collection did not significantly affect fluctuations in serum Na levels. Although the difference in post-treatment serum Na levels among three groups was statistically but not clinically significant, The mean Na levels in all groups remained within their normal physiological ranges, and patients did not exhibit symptoms of hyponatremia or hypernatremia. Therefore, while the results support the preference for isotonic fluids in preventing hyponatremia, the clinical impact of these differences on serum Na levels remains minimal. However, it should be noted that the difference in sodium levels may be more pronounced and clinically significant in patients who require parenteral fluid therapy for longer durations. Carandanget al.[11] conducted the longest serum Na monitoring study in the literature, extending to 7 days, and reported a 34.7% incidence for hospital-acquired hyponatremia. In a Mexican study comparing fluid therapies in patients aged 3 months to 15 years, control serum Na levels were measured at the postprocedural 8th hour. Results showed that patients receiving hypotonic fluids had lower serum Na levels, with values of 134.65 mEq/L in the 1/3 saline and 134.90 mEq/L in the 1/2 saline groups, while those in the isotonic saline group had serum Na levels of 137.98 mEq/L[16]. In a study published in The Lancet in 2015 by McNab et al.[17], similar to our study, the use of isotonic saline was found to reduce the risk of hyponatremia. According to a study conducted by Bagri et al.[18] in India in 2019, 75 patients who received 1/2 normal saline were compared with 75 patients who received isotonic saline solutions. The 24-hour control Na levels in the isotonic saline group were significantly higher than those in the hypotonic saline group (mean values: 135.1 mEq/L, vs. 138.3 mEq/L)[18]. In a 2019 study conducted by Torres et al.[19] in Argentina, 294 patients aged 29 days to 15 years were divided into two groups as those receiving 1/2 normal saline vs. isotonic saline treatment. After 24 hours, the isotonic saline group had significantly higher serum Na levels (139.3±3.1 mEq/L) compared to the hypotonic saline group (134.4±5.6 mEq/L). This research highlighted the fact that children under one year of age receiving hypotonic fluid therapy are at higher risk for hyponatremia due to various factors such as body surface area-to-weight ratio and fluid requirements[19]. Therefore, our study separately assessed patients under two years regarding hyponatremia, and comparable data were obtained when our study group was compared with the other study groups in terms of risk of hypothermia. In a study comparing hypotonic and isotonic solutions used for fluid therapy in patients with gastroenteritis, Neville et al.[20] reported that hyponatremia was more prevalent in the hypotonic saline group after a four-hour follow-up. In another study by the same researchers, dehydration, vomiting, and stress were identified as major stimulants of ADH release. It was also reported that patients receiving hypotonic saline for four hours or longer had 29% higher plasma ADH levels. All of these factors can contribute to dilutional hyponatremia[21]. More comprehensive research is needed on this subject. In a study led by Kumar et al.[22], 168 patients aged 3 months to 5 years admitted to the general pediatric service were equally distributed into two groups as those receiving 1/2 normal or isotonic saline), and their serum Na levels were monitored at 12 and 24 hours. After 12 hours, no significant difference was found between the fluid therapy groups. Regarding incidence of hyponatremia. However, at 24 hours, patients in the isotonic saline group had significantly higher serum Na levels. The study noted a lack of data on simultaneous oral fluid intake and excessive hydration in patients[22]. It should be noted that factors like these can lead to different results in studies. In our study, hypernatremia was examined as a secondary variable,and levels above 145 mg/dL were considered evidence of hypernatremia. One of the concerns in the use of isotonic parenteral maintenance fluid therapy in children is the possibility of developing hypernatremia. In another study, patients who received 0.45% saline and normal saline were compared based on their serum Na values measured at 24 and 48 hours[23]. In this study, no patients experienced hypernatremia[13]. In the current study, remarkably, none of the patients developed hypernatremia, including the group with serum Na controls at 33-48 hours after receiving fluid therapy. It's essential to acknowledge that longer- term or larger-scale studies may yield different findings regarding hypernatremia. To obtain reliable information on how many days after maintenance fluid therapy there is a risk of developing hypernatremia, serum Na levels should be examined in a larger number of patients that require maintenance fluid therapy for a longer time

period. Although the recommendations in the current literature and AAP recommendations are very clear, pediatricians may not always prefer isotonic fluids. In a survey study in 2020, it was reported that the rate of using isotonic fluid increased as the age of the patient increased[24]. According to a study conducted in the United States, after the training given to clinicians in line with the recommendations of the AAP, the rate of isotonic fluid use increased from 63% to 95% within 9 months[25]. This highlights the importance of training in raising awareness among pediatricians.

Study Limitations

Among the limitations of our study is the lack of data on patients' serum ADH levels, urine osmolality, body weights before, and after fluid therapy. Although these data could have been useful in excluding overhydration, these risks could be observed equally in all groups. Due to the principles of the minimally invasive approach in pediatric patients, unnecessary tests are avoided, and detailed analysis cannot always be conducted. In addition, our study was conducted in a single center. Serum Na levels were mostly measured within the first 24 hours after initiation of fluid therapy. However the incidence of hyponatremia when hypotonic fluids were used was statistically, but not clinically significant. A more comprehensive risk assessment for hyponatremia can be conducted in multicenter studies with larger sample sizes and with patients receiving long-term maintenance fluid therapy.

CONCLUSION

In our country, there are not enough clinical studies on the effect of maintenance fluid content on serum Na levels, and hypotonic fluids continue to be used in many centers. This study highlights any potential risks connected to using hypotonic fluids. It promotes a switch to isotonic solutions to reduce the risk of hyponatremia, emphasizing the need for additional research and physician education.

Ethics

Ethics Committee Approval: This prospective study was conducted in our tertiary referral center after obtaining approval from the Clinical Research Ethics Committee of University of Health Sciences Turkey Ankara Dr. Sami Ulus Maternity, Child Health and Diseases Training and Research Hospital (approval number: 2020-021, date: 02.12.2020).

Informed Consent: Informed consent forms were obtained from the parents of the patients, and principles of confidentiality were maintained by the investigators.

Footnotes

Author Contributions

Surgical and Medical Practices: N.Ç., E.A.A., F.Z.Ö.Ç., M.M.O., Concept: N.Ç., E.A.A., Design: N.Ç., E.A.A., Data Collection or Processing: N.Ç., E.A.A., F.Z.Ö.Ç., M.M.O., Analysis or Interpretation: N.Ç., E.A.A., F.Z.Ö.Ç., M.M.O, Literature Search: N.Ç, E.A.A., Writing: N.Ç., E.A.A.

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