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# Maintenance intravenous fluid therapy in infants with sepsis and hyponatremia: a clinical trial

Hani Milani[1], Saleheh Tajalli[2], Kamran Behrouzi[1], Nakisa Homan[3], Fateme Zamaniashtiani[2], Ali Vafaee[4], Zahra Vahedi[3] and Nasrin Khalesi[3*]

## Abstract

**Background** This study aimed to compare the effect of two methods of maintenance intravenous fluid therapy on hyponatremia in hospitalized infants with sepsis.

**Methods** In a double-blinded randomized clinical trial, 60 term infants with sepsis were enrolled. Blood samples were taken to determine sodium, potassium, Creatinine, and BUN levels before the initiation of treatment. Urine samples were taken to assess specific gravity and urinary output. Infants in the intervention group received half saline in 10% dextrose and infants in the control group were assigned to receive the conventional solution as maintenance. The above indicators were re-evaluated 24 and 48 h after the initiation of treatment. Two groups were compared concerning the incidence of hyponatremia, and other criteria such as urinary output and urinary specific gravity, blood urea nitrogen (BUN), and creatinine levels.

**Results** Hyponatremia was more common in the control group. Sodium levels were significantly higher in half saline recipients 24 h (137.83 ± 2.86 vs. 134.37 ± 1.91 mmol/L), and 48 h (138.10 ± 2.41 vs. 133.66 ± 1.98 mmol/L) after treatment ($P < 0.001$). Although BUN in the intervention group was significantly higher in comparison to the control group, the difference in urinary output, urine specific gravity, potassium, and Creatinine levels were not significant in the two groups.

**Conclusions** The use of a half-saline solution as maintenance fluid reduces the risk of hyponatremia after 48 h when compared to 0.18%NaCl.

**Trial registration** This has been registered at Iranian Registry of Clinical Trials (Retrospectively registered, Registration date: 2017-10-12, identifier: IRCT2017053034223N1, https://irct.behdasht.gov.ir/trial/26204).

**Keywords** Neonate, Maintenance fluid, Hyponatremia, Sodium, Newborn

*Correspondence:
Nasrin Khalesi
nasrinkhalessi@yahoo.com
[1]Department of Neonatology, Kamali Hospital, Alborz University of Medical Sciences, Alborz, Iran
[2]School of Nursing and Midwifery, Tehran University of Medical Sciences, Tehran, Iran
[3]Department of Pediatrics, Iran University of Medical Sciences, Tehran, Iran
[4]Department of Nursing, Faculty of Nursing and Midwifery, Tehran Medical Sciences, Islamic Azad University, Tehran, Iran

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## Background

Neonates have greater body surface area to weight compared to older children and adults, which along with higher metabolic and respiratory rates leads to more insensible water loss and higher calorie-fluid needs. In the first few days of life, the consequence of renal immaturity, extra-renal water, electrolyte losses, and tubular immaturity, lead to difficult fluid and electrolyte management [1].

It should be noted that in the first 2–3 days of life, the interstitium provides a large fluid reserve. The neonate with this interstitial fluid reserve can adapt to fluid challenges, however, critically ill neonates with inappropriately administered fluid are exposed to volume and electrolyte imbalance. In complicated ill neonates, providing appropriate fluid and electrolytes is the cornerstone of intravenous fluid therapy. Inappropriate intravenous (IV) fluid therapy may result in hypovolemia, volume overload, hyperosmolarity, and metabolic abnormalities resulting in renal or pulmonary dysfunction [2, 3]. Term and Preterm neonates are prone to hyponatremia as a result of inadequate salt intake and excessive salt loss due to immature renal function [4]. Previous studies reported that about 14.0% of preterm infants with gestational age less than 32 weeks, had hyponatremia [5, 6]. Hao found that 29.4% of the preterm infants born before 36 weeks of gestation suffered from hyponatremia [7]. Bamehrez reported that 27% of preterm infants born at King Abdulaziz University Hospital experience hyponatremia [8]. Hyponatremia either because of the illness itself or iatrogenic is considered a cause of morbidities such as lethargy, seizure, and other severe neurological complications as well as mortality [9, 10]. Symptoms and signs are related to duration and degree of hyponatremia. Clinical signs of hyponatremia are decreased weight, weak poor skin turgor, tachycardia, hyperthermia, rising BUN, and metabolic acidosis. The newborn may develop decreased urine output, decreased urine SG, if renal function is mature [11, 12].

Neonates with sepsis are vulnerable to hyponatremia due to ECF volume excess [13]. Previously association between sepsis and hyponatremia has been vastly described [14]. Hannon and Boston found that hyponatremia associated with sepsis can increase morbidity and mortality by unknown etiology. Also they mentioned that this phenomenon may be related to the dilution of the extracellular space with retained exogenous fluid [15].

Hyponatremia occurring within the first week of life is associated with increased mortality [16]. In fact hyponatremia within the first postnatal week was associated with an increased risk of mortality in neonates without acute kidney injury (AKI) [17, 18]. There have been some recent studies investigating the safety and efficacy of different methods of maintenance fluid therapy in children and infants [19–23].

Postnatal diuresis as a urine output > 80% of volume input can begin as soon as 12–48 h after birth. This may result early hyponatremia. So conventional fluid therapy may also result in exacerbation of hyponatremia [24].

Previous studies suggested that isotonic replace hypotonic fluids as the standard maintenance IV fluid to avoid the hyponatremia [9, 25]. However, isotonic fluids may result in hypernatremia due to fluid overload [26, 27]. Wang et al., found isotonic fluids have more risk of developing hyponatremia versus hypotonic fluids in hospitalized children requiring maintenance IV fluid therapy [28].

Despite some evidence in pediatrics, on wide review literature, the authors could not find any evidence in the term infant with sepsis population. The current trial could be conducted because in the authors' setup still, the routine standard of care is to prescribe 3–4 mEq/kg of sodium saline solution in all infants. As there is a lack of studies done on the different types of intravenous maintenance fluid therapy to prove its positive effects on hyponatremia, we intend to study the effects of two methods of maintenance intravenous fluid therapy (7.7 and 3 mEq/kg of sodium) on the occurrence of hyponatremia in hospitalized infants with sepsis, through a clinical trial.

## Methods

### Design and patients

A double-blinded randomized controlled trial study was conducted at the NICU of Aliasghar Hospital; a tertiary referral center and also one of the teaching hospitals affiliated with Iran University of Medical Sciences (Tehran-Iran) from November 2020 to August 2022. The study population was 60 term infants hospitalized in NICU (level II and III) due to sepsis requiring intravenous maintenance fluid for at least 48 h. Based on an investigation by McNab et al., study, with isotonic and hypotonic fluid therapy, 17 and 34% of infants were at risk of hyponatremi [29]. By using the formula, the proposed sample size of 30 for each group, the study had a power of 80% and an alpha error of 0.05.

Two hundred-one-term infants were assessed for eligibility. The inclusion criteria were infants of 3 days old and more with a gestational age of 38–42 weeks, normonatremic, and NICU (level II and III) admission by the presumed diagnosis (basis on positive blood culture) of sepsis. Sixty infants have eligible criteria and were divided randomly using random blocks into two groups of 30. Due to renal electrolyte excretion in patients with some conditions, we excluded infants if they had congenital heart diseases (heart failure, ventricular septal defect, and patent ductus arteriosus), phototherapy requirement,

hypertension, severe dehydration, renal dysfunction and pseuohyponatremia due to hyperglaicemia and hyperlipidemia and small for gestational age infants. (In total, 60 patients were finally selected after exclusion criteria (each group=30) (Fig. 1). This study adheres to CONSORT guidelines.

#### Randomization and blinding

The blocked randomization with block sizes of 4 with an equal probability was used to enroll the eligible infants. We assign the infants to half saline (group B) and standard maintenance fluid (group A). We have six possible combinations of group assignments regarding the size of block 4. All possible combinations were AABB, ABAB, BAAB, BABA, BBAA, and ABBA. At the first, we select one of these arrangements at random and the four eligible admitted infants were assigned accordingly in each block. We repeated this process many times to include the eligible infants. This study was conducted double-blinded: the infants (patients) and the neonatologist (evaluator) were not aware of the course of the intervention. Bottles containg liquides were similar in both control and intervention groups. The clinicians (researchers) were informed of the allocation of the intervention and control groups. All participants' parents gave written consent and accepted the interventions. At admission time five milliliters of venous blood were collected from all participants.

#### Intervention

The intervention group received 7.7 mEq/kg of sodium (half saline) in a 10% dextrose solution, whereas the control group received 3 mEq/kg of sodium in a 10% dextrose solution. Both groups received the same amount of potassium (2 mEq/kg), as potassium chloride (KCl) was 15%. The glucose Infusion Rate (GIR) for both groups was 5–6 mg/kg/min and the osmolarity of fluids was calculated before the initiation of IV fluid therapy by online osmolarity calculator(http://rxkinetics.com). The osmolarity of the infusion fluids was calculated for all patients. IV fluid osmolarity in the intervention and control groups were in ranges of 650–670 mosmol/L and 580–600 mosmol/L, respectively. Serum electrolytes were rechecked after 24 and 48 h after initiation of intravenous fluid therapy. All of them were NPO during three day of intervention. The duration of treatment for hospitalized infants was between 3 and 14 days, and the amount of fluid administered on different days was as follows, based on references for term infants on day one of life 80 cc/kg, 90 cc/kg on the second day, 100 cc/kg on the third day, 110 cc/kg on the fourth day and 120 cc/kg thereafter.

All interventions were monitored for potential side effects e.g. convulsion or any other complication such as altered alertness, significant alterations in blood pressure, or the occurrence of electrolyte disturbance. In the occurrence of such complications, intervention should be immediately stopped, the subject should be excluded from the study, and be controlled with routine treatment.

#### Outcomes and measurements

All recorded data related to total IV fluids administered, type of fluid, and electrolyte concentrations at the time of IV fluid administration, after 24 and 48 h were analyzed and compared in the 2 groups. Specific laboratory kits were used to evaluate blood and urine parameters. Sodium and POTASSIUMsamples were analyzed using Electrolyte Analyzer Caretium XI-921 Series, and BUN and Cr samples were analyzed by Biolis 24i Premium Auto-analyzer.

The primary outcome was a comparison of plasma sodium between the 2 groups. Comparison of other plasma electrolytes concentrations including Potassium, BUN, Creatinine weight gain and death between two groups was considered as the secondary outcome. Hyponatremia considered a serum sodium level of less than 135 mmol/L and hypernatremia is a serum sodium level greater than 145 mmol/L [30].

#### Data collection methods

The data were collected by clinical observation, and laboratory findings; all were gathered by researcher-designed checklists and then recorded in the data bank.

#### Data analysis

The data were entered into the statistical analysis software, SPSS, version 16, and then statistically analyzed. Kolmogorov-Smirnov was used to assess the normality of data distribution. All descriptive data had a normal distribution. Therefore, the results for the quantitative and ordinal qualitative variables were reported in mean±SD format and frequency and percentages respectively. Repeated measures analysis of variance (ANOVA), independent samples t-test and Chi-square test were used to analyze the correlations between variables (Mean±SD). A p-value<0.05 was considered significant.

## Results

The mean postnatal ages of infants in the intervention and control groups were 7.76±5.63 and 8.90±6.84 days, respectively. There were no significant differences between the two groups for infants' age ($p$=0.48) and sex ($p$=0.43). Moreover, there were no significant differences in serum electrolytes concentrations between the two groups such as Sodium ($P$=0.67), Potassium $P$=0.84), creatinine ($P$=0.13), urine-specific gravidity ($P$=0.17), and urine output ($P$=0.51) (Table 1).

Administration of a half-saline solution (7.7 mEq/kg) as maintenance fluid reduces the risk of hyponatremia after

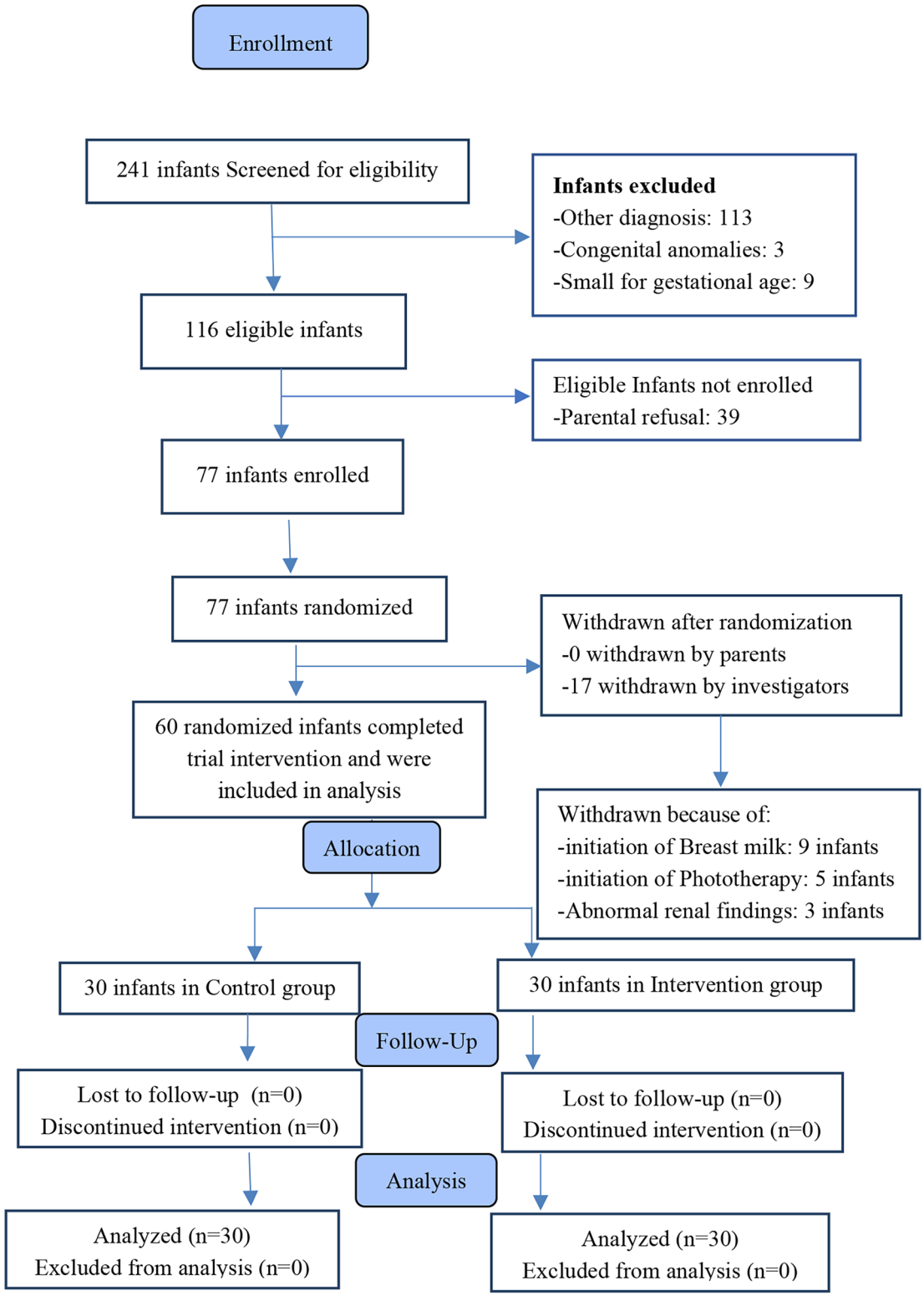


**Fig. 1** Follow-up Diagram of Patients (According to Consort Statement)

**Table 1** Baseline characteristics of intervention amd control study groups

| Variables | Intervention | Control | *P* value [a] |
|---|---|---|---|
| | N(%) | N(%) | |
| Gender | | | 0.43 |
| Male | 17 (56.6%) | 16 (53.3%) | |
| Female | 13 (43.3%) | 14 (46.6%) | |
| | Mean ± SD | Mean ± SD | |
| Age (days) | 7.76 ± 5.63 | 8.90 ± 6.84 | 0.48 |
| Sodium (mmol/L) | 133.88 ± 3.89 | 134.26 ± 3.15 | 0.67 |
| Potassium (mmol/L) | 4.25 ± 0.56 | 4.28 ± 0.58 | 0.84 |
| BUN | 11.36 ± 5.4 | 12.13 ± 4.2 | 0.54 |
| Creatinine | 0.73 ± 0.19 | 0.65 ± 0.23 | 0.13 |
| Urine specific gravity | 1.010 ± 0.006 | 1.012 ± 0.005 | 0.17 |
| Urine output (ml/Kg/hour) | 1.19 ± 0.32 | 1.14 ± 0.25 | 0.51 |

SD: standard deviation

**Table 2** Serum electrolytes concentrations between 2 groups at admission, 24 and 48 h

| Variables | At admission Mean ± SD | 24 h later Mean ± SD | 48 h later Mean ± SD | *P* value [a] |
|---|---|---|---|---|
| **Sodium** | | | | |
| Intervention | 133.88 ± 3.89 | 137.83 ± 2.86 | 138.10 ± 2.41 | < 0.001 |
| Control | 134.26 ± 3.15 | 134.37 ± 1.91 | 133.66 ± 1.98 | |
| P value [b] | $p = 0.679$ | < 0.001 | < 0.001 | |
| **Potassium** | | | | |
| Intervention | 4.25 ± 0.56 | 4.33 ± 0.56 | 4.2733 ± 0.50 | 0.57 |
| Control | 4.28 ± 0.58 | 4.27 ± 0.43 | 4.48 ± 0.36 | |
| P value | $p = 0.84$ | $p = 0.64$ | $p = 0.68$ | |
| **BUN** | | | | |
| Intervention | 11.36 ± 5.4 | 10.20 ± 3.89 | 7.66 ± 2.66 | < 0.001 |
| Control | 12.13 ± 4.2 | 6.579 ± 3.11 | 5.20 ± 2.32 | |
| P value | 0.54 | < 0.001 | < 0.001 | |
| **Creatinine** | | | | |
| Intervention | 0.738 ± 0.193 | 0.66 ± 0.15 | 0.60 ± 0.11 | 0.48 |
| Control | 0.65 ± 0.23 | 0.63 ± 0.15 | 0.61 ± 0.14 | |
| P value | $P = 0.13$ | $P = 0.47$ | $P = 0.72$ | |
| **Urine output** | | | | |
| Intervention | 1.19 ± 0.32 | 1.54 ± 0.33 | 1.64 ± 0.36 | 0.44 |
| Control | 1.14 ± 0.25 | 1.65 ± 0.25 | 1.82 ± 0.18 | |
| P value | $P = 0.59$ | $P = 0.14$ | $P = 0.18$ | |
| **Urine specific gravity** | | | | |
| Intervention | 1.01 ± 0.00 | 1.01 ± 0.01 | 1.00 ± 0.00 | 0.62 |
| Control | 1.01 ± 0.00 | 1.01 ± 0.00 | 1.00 ± 0.00 | |
| P value | $P = 0.17$ | $P = 0.79$ | $P = 0.61$ | |

[a.] P value for repeated measures ANOVA.

[b.] P value for Independent samples T–test

SD: standard deviation

48 h when compared to a standard 0.19 saline solution. The results of the independent samples t-test indicated although there was no significant difference between the groups for serum Sodium concentration at admission time ($p = 0.679$), after 24- and 48 h serum sodium was higher in the intervention group compared to the control group ($p < 0.001$). Plus, serum BUN concentration was higher in the intervention group compared to the control group ($P < 0.001$). Also, there were no observed differences between groups in serum potassium concentration, serum creatinine, urinary output, and specific gravity over 24 ($p = 0.64$, $p = 0.47$, $p = 0.14$, and, $p = 0.79$, respectively) and 48 h after admission ($p = 0.68$, $p = 0.72$, $p = 0.18$, and, $p = 0.61$, respectively). There were no cases of death and weight gain in both control and intervention groups(Table 2).

In repeated measures analysis of variance, the group-time interaction was not significant for Potassium($p = 0.57$), creatinine ($p = 0.48$), urine output ($p = 0.44$), and urine specific gravity ($p = 0.62$). However, the group-time interaction was significant for Sodium, i.e., over time, the trend of mean Sodium was different between standard 0.19 saline and half-saline solution. Furthermore, the repeated measure ANOVA showed significant differences in Sodium and BUN between the standard 0.19 saline and half-saline group ($p < 0.001$) (Table 2). No complication occurred in any of the study groups.

## Discussion

The standard maintenance solution for intravenous fluid therapy in infants is 0.19 saline (0.18% NaCl or 30.8 mEq/L of sodium) used as a hypotonic solution, however, acute hyponatremia has been reported more frequently in children [31]. Although several studies have assessed the influence of different types of intravenous maintenance fluid on plasma electrolyte concentrations in children [19–22], but very few investigations have focused on this subject among neonates. In the present study, we evaluated the influence of 2 different methods of intravenous maintenance fluid therapy including half saline and standard fluid composed of 3 mEq/kg NaCl on biochemical serum elements concentration. Our results showed that the use of a Half-Saline solution (7.7 mEq/kg) as maintenance fluid did not increase the risk of hypernatremia after 24 and 48 h when compared to 0.19 Saline solutions, which is by now the conventional maintenance. We found that 24 and 48 h after initiation of half saline IV therapy, serum Sodium concentration increased significantly. On the other hand, neonates in the other group (receiving 3 mEq/kg of sodium in 10% dextrose) showed hyponatremia. This finding can show the protective effect of half-saline administration on neonatal hyponatremia. Moreover, in consistency with our results, Choong et al., 2006 revealed that the infusion of hypotonic solution could increase the risk of hyponatremia up to 17.2 times [32].

A systematic review and meta-analysis of randomized controlled trials was done by Hasim et al. They reported

isotonic solution is protective against hyponatremia while hypotonic solution increases the risk of this for intravenous maintenance fluids in hospitalized children [33]. Shukla et al. found administration of hypotonic fluids is associated with acute hospital-acquired hyponatremia [34]. In another study by MCnab et al., also demonstrated that of 1104 infants, 449 of them were infused with isotonic and 521 received hypotonic solution as well as hypotonic solution significantly increased the risk of hyponatremia compared to infusion of isotonic solution (34% vs. 17%) [21]. This finding was confirmed by Wang et al.,2014 [35], their study showed that the administration of hypotonic solution could rise the incidence of hyponatremia 2.2 times and the risk of severe hyponatremia up to 5.2 times in comparison with isotonic solution, as well. On the other hand, there were no significant differences between the two groups due to the risk of hypernatremia [36]. In agreement with our data, Valadão et al.,2014 reported that in the post-operative children, infusion of hypotonic solution (3 mEq/kg, 0.18%) did not increase the risk of hyponatremia when compared to isotonic saline [30]. Dathan, K., and Sundaram recently found isotonic fluid isn't superior to hypotonic fluid in reducing the development of hyponatremia after 24 h of intravenous fluid therapy in neonates [37]. Tuzun et al., concluded hypotonic fluids can lead to unsafe plasma sodium decreases in term newborns. While isotonic fluids are protective against hyponatremia after the first few days of life [38]. a prolonged period of nothing by mouth (NPO) can pose risks due to the potential for bacterial overgrowth in the intestines. This overgrowth can disrupt the balance of gut flora and increase the likelihood of sepsis, a severe systemic infection. The absence of bowel movements for an extended period can indicate gastrointestinal issues, such as obstruction or dysfunction, which may lead to complications if not addressed promptly. Therefore, monitoring and addressing any concerns regarding a newborn's bowel movements are crucial to prevent potential health risks associated with NPO status [39].

Although the infusion of half saline solution could significantly increase the level of BUN in the intervention group, this alteration of BUN was not in a dangerous range. Moreover, infusion of half saline solution did not have any influence on serum potassium and Creatinine concentration as well as urine output or specific gravity in these different periods of time.

### Limitation

The selection of infants with sepsis may have some bias in studying hyponatremia in infants. It may cause abnormalities in water and electrolyte balance in infants with severe sepsis cases even with a normal sodium level at the beginning of the study. Also, we did not follow up for long-term outcomes and complications. Further studies on this topic, with larger sample sizes and longer, follow-up periods would be more informative and beneficial.

## Conclusion

In the neonatal population, Maintenance fluid therapy with 7.7 mEq/kg of sodium in a 10% dextrose solution could be beneficial to prevent hyponatremia after 48 h when compared to 3 mEq/kg of sodium in a 10% dextrose. Our results suggest that the replacement of fluid and electrolytes in hospitalized term infants needs to be monitored closely.

## Suggestion

However, now conventional maintenance fluid therapy is common in the neonatal population. Nevertheless, further carefully designed studies with a more prolonged intervention period are necessary to confirm both the safety and long-term outcomes of this therapeutic modality.

## Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12887-024-04901-0.

Supplementary Material 1

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### Author contributions

HM: Conceptualization, Supervision, Investigation, Methodology, Writing - review & editing, Funding acquisition. ST: Project administration, Data curation, Investigation, Methodology, editing draft. FZ: Writing original draft, review & editing. NH: Project administration, Conceptualization, Supervision, Investigation, Methodology, review & editing. KB: Investigation, Methodology, Validation, Writing review & editing, Resources. AV: Writing original draft, review & editing. ZV: Writing -review & editing. NKh: Conceptualization, Supervision, Writing -review & editing, Resources. All authors contributed to the article and approved the submitted version.

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### Data availability

The original contributions presented in the study are included in the article. Request access to other supplementary material can be directed to the first or corresponding author.

## Declarations

### Ethics approval

In all steps carried out in this study, the principles of the Declaration of Helsinki. The intervention substances were administered with informed consent from the newborns' parents before blinding. The infant's caretaker was properly informed about enrolling in the study and their informed consent was taken. They were free to withdraw from the study in any step of

the study and for any reason or for no reason at all. All patients' information was held confidential, was not made accessible to any person or organization and was reported only in aggregate. Ethics approval for the study was obtained from the institutional review board of Iran University of Medical Sciences according to Helsinki declaration (ID; IR. IUMS. REC 1395.9411403002) and has been registered at Iranian Registry of Clinical Trials (Registration date: 2017-10-12, identifier: IRCT2017053034223N1, https://irct.behdasht.gov.ir/trial/26204).

**Consent for publication**
Not applicable.

**Competing interests**
The authors declare no competing interests.

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