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Original Research Article

A RANDOMIZED CONTROL TRIAL IN A TERTIARY CARE CENTRE ON SODIUM SUPPLEMENTATION AND GROWTH IN VERY LOW BIRTH WEIGHT INFANTS

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Abstract

Background: Sodium is highly essential for protein synthesis, bone mineralization, maintenance of extracellular space, and transport of glucose across the cell membranes. This study aims to assess the effects of early sodium supplementation on optimum weight gain in preterm infants who are fewer than 34 weeks old and have a birth weight of less than 1500 grams to those who are not. **Materials and Methods:** 30 infants were divided into intervention and placebo groups in this randomized study equally. The concentration of sodium used is the commercially available 3%sodium chloride with 0.5mEq per ml of the fluid. All the infants were monitored for birth weight, serum sodium levels, late-onset sepsis, patent ductus arteriosus and retinopathy of prematurity. **Result:** Sodium supplemented infants had significantly increased weight at day 35 of life when compared with the non-supplemented infants. Weight loss in the first week of life was less in the sodium supplemented infants compared to the non-supplemented infants. Weight gain between D7 & 14 and D14 & 35 was significantly high in sodium supplemented infants. No increased risk of comorbidities like late-onset sepsis, patent ductus arteriosus and retinopathy of prematurity was observed in the sodium supplemented group. **Conclusion:** In very low birth weight newborns, sodium supplementation has a significant impact on weight gain. There was no increased risk of comorbidities, which could be associated with sodium supplementation.

INTRODUCTION

In extremely low-birth-weight infants, nutrition strategies that provide enough protein and energy intake in the early days of life, combined with the provision of human milk feedings, improve weight gain, reduce prematurity-related morbidities, and improve neurodevelopmental outcomes.[1,2] A sufficient salt intake in the first month of life, in addition to macronutrients, has been recommended to aid somatic growth and later neurodevelopment, particularly in extremely preterm children.[3-5] For preterm newborns, the recommended sodium intake varies from 3 to 7 mEq/kg/d to maintain sodium balance and fulfil the increasing needs for the development of new tissues.[6,7] Preterm formulas and enriched human milk preparations supply about 3 mEq/kg/d on average.[8,9] The main aim in managing the growing preterm is to ensure that they maintain a growth rate similar to those in the third-trimester intrauterine period with respect to weight gain, length and brain growth.[10] Despite maximal calorie intake, sixty percent of very low birth weight infants still fail to thrive, suggesting that factors other than total calorie intake are important in ensuring consistent weight gain in the neonatal period. Several reports have indicated a positive sodium balance is critical in ensuring good weight gain in very low birth weight infants. Still, these infants are susceptible to low serum sodium concentrations. Sodium is highly essential for protein synthesis, bone mineralization, maintenance of extracellular space, and transport of glucose across the cell membranes.[11] Sodium can be considered a growth factor that stimulates protein synthesis and increase cell mass, and thus inadequate sodium intake can lead to chronic sodium depletion and thus growth failure.[12] Many studies in humans and animals have supported the growth-promoting effect of sodium in neonates. This study focuses on the early supplementation of sodium and its impact on optimal weight gain in preterm less than 34 weeks and less than 1500g of birth weight and compares with those not supplemented. These preterm low birth weight infants are already prone to sodium

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depletion due to impaired renal handling of sodium. Therefore, such infants are even more at increased risk of sodium depletion leading to poor weight gain.[13]

MATERIALS AND METHODS

This randomized control trial was conducted in the Government Thoothukudi medical college and hospital neonatal care unit. The study was conducted in preterm <34 weeks and very low birth weight infants with birth weight <1500g. The infants who were critically ill, on mechanical ventilation, with evidence of cardiorespiratory failure, signs of clinical edema, and major congenital malformations, were left and not included in the study.

The basic details of the baby, including birth weight, sex, gestational age (using the New Ballard score for gestational age assessment and as per LMP and EDD), Apgar score and basic details of the mother including age, obstetric code, Hemoglobin status and weight were documented. In addition, the sodium levels were taken as they enrolled in the study.

The infants were started on sodium supplementation from D4 of postnatal life orally or IV. The infants who reached enteral 100ml/kg of oral feeds were started on oral supplementation of sodium or distilled water. The concentration of sodium used is the commercially available 3%sodium chloride with 0.5mEq per ml of the fluid. The sodium content of the IV fluids, breast milk and human milk fortifiers was calculated and subtracted from the total sodium requirement. The placebo group is given the same volume calculated for sodium requirement as distilled water and breast milk or IV fluids.[14]

The infants were regularly monitored for signs of fluid overload. The weight at D7, D14, and D35 and the respective sodium levels were documented. The weights were plotted in the Fenton growth chart. In addition, common prematurity related morbidities such as NEC (according to Bell staging), PDA (by clinical examination and echocardiogram), late-onset sepsis (positive blood culture and >5 days of antimicrobial treatment), bronchopulmonary dysplasia, retinopathy of prematurity were monitored.

Continuous data were reported as mean ± standard deviation. An unadjusted comparison of continuous data was assessed using an independent t-test. Categorical data were compared using chi-square analysis.

RESULTS

Totally 134 infants were admitted to NICU who were less than 1500g and 34 weeks. The 30 randomized infants were almost similar with respect to mean birth weight, sex distribution, and gestational age. The mean gestational age in the placebo and interventional groups was 30.60 weeks and 30.53 weeks, respectively. Seventy-three percent of the infants in both groups belong to 32-34 weeks. The remaining infants were either <28 weeks or 32-34 weeks. The sex distribution of infants was almost equal in both groups. The mean age of mothers in both groups was 24 years. The number of AGA (Appropriate for Gestational Age) and SGA (Small for Gestational Age) infants was similar in the placebo and interventions group [Table 1].

Table 1: Demographic Data

Parameter	Placebo Group (n=15)	Intervention Group (n=15)	P value
Gestational Age (weeks)	30.60±2.13	30.53±1.88	0.928
Preterm Grade			
< 28 weeks	0	2	0.264
28-32 weeks	11	11	
32-34 weeks	4	2	
Sex Distribution			
Male	5	4	0.68
Female	10	11	
Age of Mother	24.80±4.00	24.00±4.47	0.610
Distribution of AGA and SGA			
AGA	10	9	0.705
SGA	5	6	

Table 2: Comparison of mean birth weight and sodium levels between placebo and intervention group

Parameter	Placebo Group (n=15)	Intervention Group (n=15)	P value
Comparison of weight			
Birth weight	1102.13 ± 196.53	1061.27 ± 213.82	0.590
Weight on D7	915.33 ± 155.74	932.20 ± 202.11	0.800
Weight on D14	962.67 ± 135.20	1014.67 ± 226.96	0.452
Weight on D35	1046.73 ± 339.67	1283.73 ± 318.91	0.059
Comparison of serum sodium levels			
Sodium level on D7	134.47 ± 4.61	138.73 ± 2.79	0.005
Sodium level on D14	136.07 ± 3.51	138.87 ± 1.19	0.007
Sodium level on D35	139.73 ± 2.58	139.67 ± 2.09	0.939

[Table 2] compares mean birth weight and serum sodium levels between placebo and intervention groups. The mean birth weight in the placebo group (1102.13g) was higher than that of the intervention group (1061.27g).

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However, they are statistically not significant (p=0.590). The intervention and placebo groups were started on their respective supplementation from D4, and the child's weight at D7 was monitored. The mean weight at D7 in the intervention group (932g) and the placebo group (915g). Though the mean weight at D7 was not statistically significant compared to the placebo group (p=0.800), the mean weight in the intervention group was higher than the placebo group. The mean weight at D14 in the intervention group was1014.67g, and that in the placebo group was 963.67g.

Similarly to D7, the mean weight at D14 was not statistically significant compared to the placebo group (p=0.452), the mean weight in the intervention group was higher than the placebo group. This persistent rise in the weight in the intervention group compared to the placebo group from the first week of life indicates a positive effect of sodium supplementation, though it could not be statistically proven at this stage of the postnatal period. The serum sodium levels were monitored simultaneously along with birth weight on D7, D14 and D35. In the study, the intervention and placebo were started on D4. The mean sodium levels were higher in the intervention group when compared to the intervention on D7 and D14, but on D35, the levels were almost equal. This trend indicates the renal maturity in sodium handling as age increases.

Table 3: Comparison of Late-onset sepsis, Patent ductus arteriosus and retinopathy of prematurity in placebo and intervention group

Parameter	Placebo Group (n=15)	Intervention Group (n=15)	P value
Late Onset Sepsis (LOS)			
Yes	5	1	0.068
No	10	14	
Patent Ductus Arteriosus (PDA)			
Yes	1	0	0.309
No	14	15	
Retinopathy of Prematurity (ROP)			
Yes	0	1	0.309
No	15	14	

Five infants in the placebo group developed late-onset sepsis, and one infant in the intervention group developed late-onset sepsis. Only one infant in the placebo group developed PDA. The baby was treated with IV paracetamol. Only one infant in the intervention group developed ROP on follow-up, which required laser intervention. [Table 3]

DISCUSSION

This is a randomized control trial single blinded where the parents of the infants were blinded about the type of intervention given to their babies. The infants in both groups were almost similar in gestational age, sex distribution of weight, age of mothers, their obstetric status. The infants who developed critical illness during illness were dropped from the study. The study included only clinically and hemodynamically stable infants. Isemann et al,[15] included extreme preterm < 27 weeks whereas other studies Al Dahhan et al,[16] included GA 31-34 weeks, Vanpee et al,[17] had 29-34 weeks. In this trial, all infants less than 34 weeks were included. The mean birth weight in the intervention group was lower when compared to the placebo group though it is not statistical significance (p=0.590).

The weight on day 7 in both groups was compared, which showed that the placebo group had more significant weight loss when compared to the intervention group. However, the weight loss is not statistically significant between both groups. Weight loss in the placebo group was around 17 % compared to the intervention group, which was 13 %. As the weight monitoring continued, the mean weight on day 14 was higher in the intervention group (1014g) than in the placebo group (962g). Among the 15 infants in the intervention group, two crossed their birth weight on day 14, and six were almost near their birth weight. Only two attained weight close to their birth weight in the placebo group. This indicates that though the mean weight when comparing both the groups was not significant, there was a considerable amount of weight gain in the intervention group. The babies were again followed up at 35 days. At 35 days, all the infants had gained weight. But when comparing the intervention and the placebo group, the intervention group had gained weight significantly more when compared to the placebo group (p=0.05). Thus on a direct comparison between mean weight in both the groups on days 7, 14 and 35, it was only on day 35 the mean weight was significantly raised in the intervention group compared to the placebo group. Vanpee et al,[17] followed only until 14 days, and Al Dahhan et al,[16] followed up the infants until 25 days Isemann et al,[15] followed up until 42 days of postnatal life.

The following parameter considered in our study was the serum sodium level. This was also measured in weight gain on day 7, days 14 and 35. The mean sodium levels on day 7 were higher in the intervention group when compared with the placebo group, and it was statistical significance with a p-value of less than 0.05. The mean serum sodium level on day 14 was higher in the intervention group when compared to the placebo group though the difference was not significant with a p-value of 0.07. On day 35, the serum sodium levels were almost equal, approximately 139 in both groups. In the intervention group, only one infant on D7 had serum sodium

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<135. Hyponatremia was not found on any other days (D14 and D35).

In contrast, in the placebo on D7, four infants and D14, five infants had serum sodium <135. On D35, no infants had hyponatremia in both groups. This pattern of serum sodium level in this study is proved to be on par with the other studies, which demonstrated the renal maturity in handling the sodium.[16,18] Most studies show that renal salt wasting and fractional urinary sodium excretion decrease as the gestational age progresses and postnatal age increases. The urinary sodium excretion is inversely related to gestational age. The non-supplemented group had almost equal sodium compared to the supplemental group as the age progressed. But when weight gain is considered, as mentioned by Haycock in a review article on the influence of sodium on growth in infancy, the effect of sodium on growth is critically age-dependent, having its maximum effect on growth during the early the rapid period of growth in the immediate personal period during which the appropriate Sodium supplementation and the normal sodium levels will increase the weight gain when compared the placebo group.[19] The study also monitored the development of other comorbidities in both groups. The commodities which were monitored were late-onset sepsis PDA ROP.

Regarding the late onset of sepsis, the infants in the placebo group developed late-onset sepsis compared to only one in the intervention group. Isemann et al,[15] in their study, observed that the incidence of LOS was reduced in sodium supplemented infants. One of the infants in the intervention group developed ROP but none in the placebo group.

The sample size of this prospective study is restricted. In addition, only 30 newborns remained in the hospital due to significant attrition due to transfer to a quaternary hospital and discharge. As a result, the ability to prove safety in terms of the incidence of common prematurity-related morbidities is restricted.

CONCLUSION

In very low birth weight newborns, sodium supplementation significantly impacts weight gain. However, there was no increased risk of comorbidities, which could be associated with sodium supplementation. Ultimately, this study demonstrates the advantages of establishing early sodium intake commensurate with current recommendations among most preterm newborns.

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