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Provision of early and high amounts of parenteral amino acids to preterm neonates: A prospective matched controlled trial.

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Abstract

Background: Several studies have demonstrated that Administration of Amino Acids (AAs) in the first days of life decreases protein losses and maintains a positive nitrogen balance. This study aimed to determine whether high and early doses of intravenous AAs would improve postnatal weight gain and metabolic control in preterm neonates.

Method: A prospective matched control trial was conducted in Neonatal Intensive Care Unit (NICU) at Nasser Medical Complex (NMC) in which 68 preterm neonates were matched for birth weight, gestational age and gender and allocated into two groups. The intervention group consisting of 34 neonates received high and early doses of AAs and the control group consisting of 34 neonates received standard dose of AAs. Data were collected at admission to NICU, at day 3 and at day 7.

Results: The result reported that within the control group, the mean weight decreased by 94.40 g between admission and 3rd day, decreased by 78.00 g between admission and 7th day, and increased by 16.40 g between 3rd day and 7th day. For the intervention group, the mean weight decreased by 128.79 g between admission and 3rd day, decreased by 83.90 g between admission and 7th day, and increased by 44.88 g between 3rd day and 7th day. The results also showed that neonates from the intervention group had significantly higher levels of total protein, but there were no significant differences in serum albumin.

Conclusion: The study concluded that administering of early and high protein to premature neonates could improve protein balance, increase protein accretion and can reduce the duration of hospitalization.

Keywords: Neonates, Premature, Parental, Amino acid, Gaza.

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Introduction

Despite advances in healthcare, Preterm Birth (PTB) remains a major global health problem [1]. Postnatal Growth (PNG) failure is common in the Very Low Birth Weight (VLBW) (<1,500 g) and Extremely Low Birth Weight Infant (ELBW) (≤ 1,000 g), and that Growth Failure (GF) is associated with an increased risk of poor neurodevelopment outcome [2]. Furthermore, inadequate postnatal nutrition is an important factor contributing to GF, as most ELBW infants experience major protein and energy deficits during the Neonatal Intensive Care Unit (NICU) hospitalization [2].

Although modern neonatal care including surfactant replacement therapy, Mechanical Ventilation (MV), and neonatal transfer; however, has resulted in significantly increased survival rates for ELBW infants the PNG of ELBW infants remains poor and does not come close to approximating rates of in utero growth [3]. Most preterm infants fail to grow after birth for days, often weeks (infants <1,000 g birth weight take a mean of 14–17 days to regain birth weight), and once they start to grow, they do not keep up with normal rates of intrauterine growth [4]. There is good evidence that early deficiencies in protein is and an important contributor to the poor growth outcomes. Protein losses are inversely related to gestational age, and ELBW infants lose 1% to 2% of their total endogenous body protein stores each day that they receive glucose alone [5]. Given that LBW neonates usually lose 10%–20% of their body weight during the first 7-10 days of life is a big challenge [6]. Provision of approximately 1.00 g/kg/day of AAs will result in a protein balance close to zero, whereas delivery of a higher amount of protein will accomplish protein accretion [5]. Moreover, AAs infusion after birth with a rate of 2.5-3.0 g/kg/day for a VLBW infant has been found to provide temporary safety to the infant, proved by randomized controlled trials [7]. No strong and permanent evidence is available so far to support this aspect. The study was conducted to determine whether provision of high and early doses of intravenous AAs would improve postnatal weight gain and metabolic control in preterm infants in comparison to standard dose of AAs.

Methods

Subjects

This matched controlled trial enrolled inborn babies PTB neonates (1000 to 2499 g) from NICU at NMC in Khanyounis, Gaza Strip, Palestine between January 2016 and August 2017. A third inclusion criterion of Gestational Age (GA) >24 to >37

weeks was added by the Helsinki ethics committee because of the high mortality rate of infants <24 weeks gestation. Babies having obvious congenital anomalies and inborn error of metabolism, neonates with confirmed diagnosed of major illness such as renal disease, significant cardiovascular disease, significant respiratory problems, neonates who receive enteral, breast and or bottle feeding and neonates with APGAR score 7 and less were excluded from the study.

Enrollment and treatment

Sixty-six prematurely born infants with a birth weight (1000 to 2499 g) were matched and allocated into two groups within first 24 hours of life to receive 2 different doses of parenteral AAs preparation. The Parenteral Nutrition (PN) administered to the infant in both groups was composed of Dextrose 10%, AAs, sodium and potassium. The PN was administered through peripheral intravenous line. The recruited infants were matched according to birth weight (1000 to 2499 g), gestational age (from >24 to less than 37 weeks) and gender. The neonates were allocated to either a control group or an intervention groups. The control group consisted of 32 neonates who received 1 g/kg/d of parenteral AAs on day 2 and increased by 0.5 g/kg every day till maximum of 2 g/ kg/d with standardization of other nutrients and fluids according to weight formulas. The amino acid intervention continued until the seventh Day of Life (DOL). The amino acid administration was given according to ministry of health protocol. The intervention group consisted of 34 neonates who received 2 g/kg/d of parenteral AAs from day 1 of life with increases of 0.5 g/kg every 24 hours until a maximum of 3.5 g/kg/day with standardization of other nutrient and fluids according to weight formulas. The high dose of amino acid started as soon as possible (1 to 2 hours) after birth and lasted for seven days as shown in Table 1.

Days	Control group	Intervention group
Day 1	0	2
Day 2	1	2.5
Day 3	1.5	3
Day 4	2	3.5
Day 5	2	3.5
Day 6	2	3.5
Day 7	2	3.5
Total amount of protein/Kg	10.5	21.5

Table 1. The amount of protein/Kg of neonate's weight given to the neonates during the study period.

Both groups were received Dextrose 10% according to body weight "80 ml/kg/day", while fluid given according to other material formula. Mineral doses were standardized for both groups according to body weight. The kind of AAs used in NICU is (Aminoplasmal B. Braun 10% E) product of Braun Melsungen AG, Germany. Each 1000 ml of solution contains the following gradients in Table 2.

Gradient	Amount/1000 ml	Gradient	Amount/1000 ml
Amino acids			
Isoleucine	5.00 g	Leucine	8.90 g
Lysine	6.85 g	Methionine	4.40 g
Phenylalanine	4.70 g	Threonine	4.20 g
Tryptophan	1.60 g	Valine	6.20 g
Arginine	11.50 g	Histidine	3.00 g
Alanine	10.50 g	Glycine	12.00 g
Aspartic acid	5.60 g	Glutamic acid	7.20 g
Proline	5.50 g	Serine	2.30 g
Tyrosine	0.40 g		
Electrolytes			
Sodium acetate	2.859 g	Sodium hydroxide	0.360 g
Potassium acetate	2.453 g	Magnesium chloride	0.508 g
Disodium phosphate	3.581 g		
Others			
Total amino acids	100 g	Total nitrogen	15.8 g
Calories	400 Kcal	Osmolarity	1021 mosm

Table 2. Gradients of aminoplasmal B. Braun 10% E/1000 ml solution.

After the study period, all infants were maintained on PN with AA dosage at 3.5 g/kg/day until sufficient enteral feedings were accomplished and then weaned as PN volume decreased. All neonates in the NICU routinely have laboratory studies on days 1,2,3,5, and 7. The study investigators monitored laboratory values throughout the hospital course on enrolled infants. The study protocol allowed the attending neonatologist to stop the AAs administered if 1) metabolic acidosis on at least 2 arterial blood gases (HCO3<18 mmol/L), 2) the plasma ammonia level was >91 mmol/L by DOL 1 or >79 mmol/L by DOL 3 and 3) serum blood urea nitrogen (BUN) was >60 mg/d.

Anthropometric measurement and biochemical analysis

Trained research nurses measured weight (to the nearest 10 g; Seca scales; seca), Length was measured using an Infantometer with fixed headpiece and moveable foot piece (to the nearest 0.1 cm, Seca Infantometer and Head Circumference (HC) was taken to the nearest 0.1 cm by using fiberglass tapes. Venous blood samples were taken from all recruited neonates, the measured biochemical were Complete Blood Count (CBC),

serum iron, serum ferritin, Iron binding capacity, Albumin/total protein and blood glucose. All the anthropometric measurements and biochemical tests were measured thrice and averaged immediately after birth and subsequently on day 3 and on day 7.

Statistical analysis

Data analyses were conducted by using SPSS 24.0 for Windows. The results were presented in tables, in the form of percentage and of means with standard deviations. The anthropometric measures and biochemical variables of the neonates in the two groups were compared on admission to NICU, after three days of intervention, and at the seventh day to evaluate the efficacy of the intervention by using one-way repeated measure ANOVA. The level of significance was set at 0.05.

Results

A total of 68 infants were matched and allocated into either a control group (n=34) or an interventional group (n=34). Two parents from the control group were withdrew their consent on the third day of the study, and also they removed from the results. There were no study withdrawals (apart from deaths).

The basic demographic and nutritional data are summarized in Table 3. For the 66 PTB infants in this study, 31 cases were females; the mean birth weight was 1747.38 g and 1732.26 g in the control group and interventional group respectively. There were no clinically important differences in respect to gestational age, birth weight and anthropometric measurements between the groups at the base line level, hence, no adjustment needed to be done while performing the analysis of variance.

Variables	Control Group (N=32)		Intervention Group (N=34)	t-stat/x2	P-Value	
	N (%)	Mean (SD)	N (%)	Mean(SD)		
Gender					0.03	0.671¶
Male	17(53.1)		18(52.9)			
Female	15(46.9)		16(47.1)			
Gestational age (weeks)		32.25 (2.64)		32.35(1.96)	1.75	0.857*
Type of delivery					3	0.083¶
Normal	12(37.5)		20(58.8)			
C/S	20(62.5)		14(41.2)			
Weight (g)		1747.38(457.23)		1732.26(404.80)	0.142	0.887*
VLBW	11(50.0)		11(50.0)		0.03	0.862¶
LBW	21(47.7)		23(52.3)			
Length (cm)		39.72(3.91)		39.81(2.48)	-0.11	0.914*
Head Circumference(cm)		29.22(2.60)		29.74(2.05)	-0.89	0.376*
Length of stay in hospital (Days)		15.09(8.75)		12.74(5.59)	1.31	0.194*

Table 3. Comparison between control group and intervention group at baseline level+.*: Independent T-test; : Pearson chi-square.

Changes in the anthropometric measurements

Figure 1 illustrates the changes in the weight of the neonates at the three different points, as both groups reported significant reduction in the weight, 94.50 g for the control group *vs.* 128.80 g for the intervention group in the first three days of the intervention. Neonates in both the groups started to catch up weight at day 3 onward.

Despite the dramatic reduction of weight in the intervention group at pre-post1 interval, the neonates of this group gained a considerable weight (44.90 g) compared to the weight gained in the control group (16.50 g) at the post1-post2 intervals. Though the improvement in the weight of neonates of the intervention was better than that of the control group, none of these were improvement were significant.

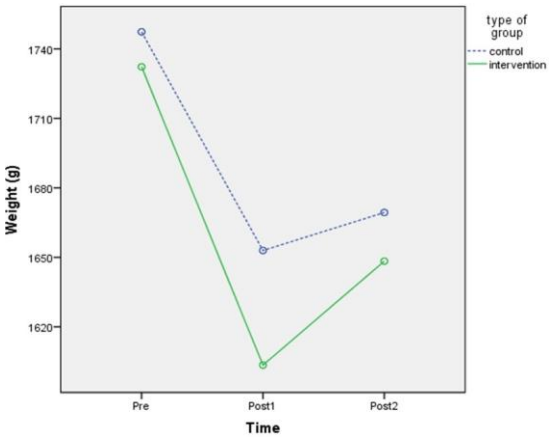

Figure 1. Comparison of weight measures within groups.

The results indicated that there were no significant differences in length of neonates or their HC during the 7 days' course of the study. Concerning head circumference (Figure 2), for the control group, there was no change in the mean HC between admission and on 3rd day, and between admission and 7th day increased by 0.025 cm, and between 3rd day and 7th day increased by 0.025 cm.

For the intervention group , the mean HC between admission and on 3rd day increased by 0.006 cm, and between admission and 7th day increased by 0.074 cm, and between 3rd day and 7th day increased by 0.068 cm. The differences in HC were statistically significant and indicated that HC of neonates who received high and early dose of AAs increased more than neonates who received standard dose of AAs.

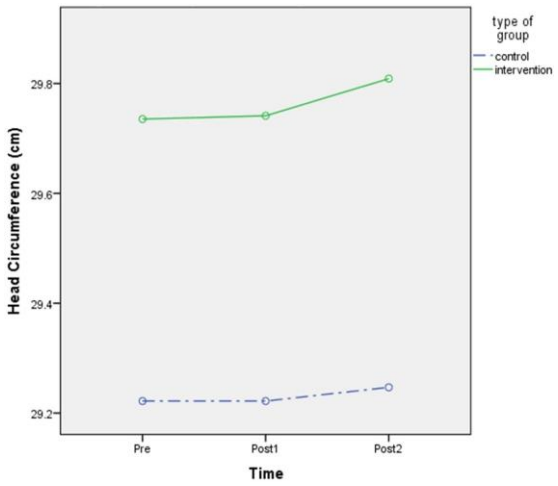

Figure 2. Comparison of head circumferences within groups.

Length of stay in hospital

Figure 3 illustrates the length of stay of neonates in hospital for both groups. The length of stay in NICU for neonates in the control group was 15.09 days while the length of stay for neonates in the intervention group was 12.74 days, which revealed that neonates who received high and early dose of AAs (2 g/k/day) within first 24 hours of life had shorter stay in NICU compared to neonates who received 1 g/kg/d of parenteral AAs on day 2. Though there was a difference in the length of stay in hospital, these differences were not significant.

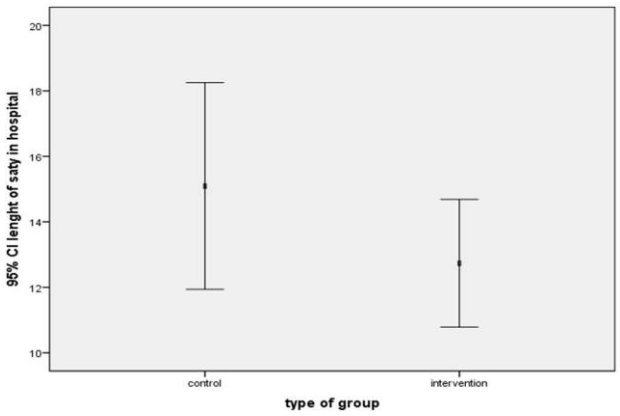

Figure 3. Comparison on the length of stay in hospital between the two groups.

Biochemical changes

Table 3 shows the biochemical differences between the two groups. In the control group, the mean serum ferritin increased by 18.4, 23.9 and 42.34 at pre-post1, post1-post2 and pre-post2 receptively. For the intervention group, the mean serum ferritin between admission and on 3rd day increased by 13.0, and between admission and 7th day increased by 19.8, and between 3rd day and 7th day increased by 6.85. A repeated measure of ANOVA of variances.

Measurement level	Control group (N=32)		Intervention group (N=34)	
	MD (95% C.I.)	p-value	MD (95% C.I.)	p-value A
Albumin				
Pre-post1	-0.22(-0.38,-0.06)	0.004	-0.25(-0.36,-0.14)	<0.001
Post1-post2	-0.35(-0.52,-0.18)	<0.001	-0.21(-0.31,-0.12)	<0.001
Pre-post2	-0.57(-0.81,-0.34)	<0.001	-0.46(-0.58,-0.34)	<0.001
Total protein				<0.001
Pre-post1	-0.04 (-0.21, 0.13)	1	-0.34 (-0.41, -0.27)	<0.001
Post1-post2	-0.19 (-0.35, -0.04)	0.011	-0.29 (-0.36, -0.23)	<0.001
Pre-post2	-0.24 (-0.42, -0.06)	0.006	-0.64 (-0.71, -0.56)	<0.001
Ferritin				
Pre-post1	-18.4 (-34.2, 2.63)	0.018	-13.0 (-24.1,-1.99)	0.016
Post1-post2	-23.9 (-37.8, -10.0)	<0.001	-6.85 (-15.3, 1.63)	0.149
Pre-post2	-42.34 (-64.6,-20.1)	<0.001	-19.8 (-36.3,-3.44)	0.013
Random Blood Sugar		<0.001		
Pre-post1	-9.31 (-14.5, -4.15)	<0.001	-19.2 (-22.6, -15.8)	<0.001
Post1-post2	-15.9 (-20.8, -11.2)	<0.001	-18.7 (-22.1, -15.4)	<0.001
Pre-post2	-25.3 (-31.2, -19.3)	<0.001	-37.9 (-42.2, -33.7)	<0.001
Calcium				<0.001
Pre-post1	-0.31 (-0.54, -0.07)	0.006	-0.55 (-0.73, -0.37)	<0.001
Post1-post2	-0.39 (-0.56, -0.24)	<0.001	-0.48 (-0.57, -0.41)	<0.001
Pre-post2	-0.70 (-1.02, -0.39)	<0.001	-1.04 (-1.27, -0.80)	<0.001

Table 3. Biochemical differences between the two groups.

There were changes in neonates' serum albumin during the intervention in NICU. For the control group, the mean albumin between admission and on 3rd day increased significantly by 0.22 mg/dl, and between admission and 7th day increased by 0.57 mg/dL, and between 3rd day and 7th day increased by 0.35 mg/dL.

For the intervention group, the mean serum albumin between admission and on 3rd day increased significantly by 0.25 mg/dL ($p<0.001$), and between admission and 7th day increased by 0.46 mg/dL ($p<0.001$), and between 3rd day and 7th day increased by 0.21 mg/dL ($p<0.001$).

Also, there were changes in neonates' total protein during the intervention in NICU. For the control group, the mean total protein between admission and on 3rd day increased by 0.04 mg/dL, and between admission and 7th day increased by 0.24 mg/dL, and between 3rd day and 7th day increased by 0.19 mg/dL. For the intervention group, the mean total protein between admission and on 3rd day increased by 0.34 mg/dL, and between admission and 7th day increased by 0.64 mg/dL, and between 3rd day and 7th day increased by 0.29 mg/dL. This result indicates that neonates who received high dose of AAs had higher levels of total proteins compared to neonates who received standard dose of AAs.

In addition, there were changes in neonates' Random Blood Sugar (RBS) during the intervention in NICU. For the control group, the mean RBS between admission and on 3rd day increased by 9.31 mg/dL, and between admission and 7th day increased by 25.30 mg/dL, and between 3rd day and 7th day increased by 15.90 mg/dL. For the intervention group, the mean RBS between admission and on 3rd day increased by 19.20, and between admission and 7th day increased by 37.90 mg/dL, and between 3rd day and 7th day increased by 18.70 mg/dL, which implies that neonates who received high dose of AAs had higher levels of blood glucose compared to neonates who received standard dose of AAs.

Also, there were changes in neonates' serum calcium during the intervention in NICU. For the control group, the mean serum calcium between admission and on 3rd day increased by 0.31, and between admission and 7th day increased by 0.70, and between 3rd day and 7th day increased by 0.39. For the intervention group, the mean serum calcium between admission and on 3rd day increased by 0.55, and between admission and 7th day increased significantly by 1.04, and between 3rd day and 7th day increased by 0.48, which suggests that neonates who received high dose of AAs had higher levels of serum calcium compared to neonates who received standard dose of AAs.

Discussion

Feeding issues in preterm infants are a growing concern for neonatologists because of their contribution to outcome and the fact that attainment of independent oral feeding is one of the prerequisites for hospital discharge following their management. Weight gain, length and occipitofrontal circumference are routine parameters measured during the follow up management of preterm infants [8].

The results of our study indicated that there was statistically significant improvement in weight of neonates in the intervention group, demonstrating that to ensure better protein accretion for these neonates, energy requirements especially from carbohydrates must be adequate. In this situation, glucose was provided at 8 mg/min/kg as soon after birth as possible and adjusted according to frequent measurements of plasma glucose to achieve and maintain concentrations >45 mg/dl but <120 mg/dl to avoid the frequent problems of hyperglycemia and hypoglycemia. Our findings were in line with previous trials where aggressive early AAs administration plus enteral feeding during the first few days of life for preterm infants was associated with improved weight gain. The length of neonates remained statistically unchanged and these findings could be explained by different reasons. Firstly, longer trial duration enables meaningful changes in length to be observed. Second; protein loss in very preterm infants is approximately two folds greater than that in full-term newborn infants [5]. Moreover, the small sample size, which might have resulted in type II error, and finally; the absence of Intra-lipid in the PN infusion.

Lipid is required to provide at least 0.5 g/kg/day to prevent essential fatty acid deficiency. However, the high rate of carbohydrate and lipid supply that preterm infants often get based on the assumption that this is necessary to promote protein growth [9].

Some of the literature argue and attribute the increase in weight to the influence of sodium on fluid balance rather than tissue growth [10], but this postulation was not true in our case as the current study reported significant improvement not only in weight but also in HC.

It is worth saying that the goal for nutrition of the preterm neonate should be to achieve a postnatal growth rate approximating that of the normal fetus of the same gestational age. Unfortunately, most preterm neonates, especially those born very preterm with ELBW, are not receiving sufficient amounts of nutrients to produce normal fetal rates of growth and, as a result, end up growth-restricted during their hospital period after birth. A review study carried out by Lee, in Korea reported that most randomized controlled trials showed that early and high AA dose (3.5 to 4.9 g/kg/day) do not improve long-term growth, and that high-dose AA supplementation may lead to early metabolic disturbances and excessive or disproportionate plasma AA levels, particularly in infants of very low gestational age [11].

On the other hand, different trials were inconsistent with our findings. A double-blinded controlled trial conducted in India found that the gain in weight, length, and head circumference were significantly lower in the high AA group (3 g/kg/d) compared to low AA group (1 g/kg/d) [12]. Moreover, Heimler and his co-workers concluded that there was no significant effect on body weight and redistribution of body fluid compartments in infants receiving AA early during the first week of life, and serum urea concentrations were significantly higher in infants receiving early AA [13]. A very recent trial indicated that immediate recommended daily intake of parenteral AA does not benefit body composition or growth to term and may be harmful [14]. Our results are in line with the main metabolic role of protein intake in promoting nitrogen retention and increasing protein synthesis [15]. Early amino acid administration could also increase insulin secretion and contribute to greater protein deposition [16]. Several reports have described relations between a low albumin concentration and morbidity and mortality rates in premature neonates [17,18] and in the fasting state, albumin concentrations drop 2-3 g/L in the first 24 h after birth [19].

Our results reflected that neonates who received high dose of AAs had higher serum total protein but not albumin compared

to neonates who received standard dose of AAs. Our data are not consistent with the assumption that parenteral AA administration in premature neonates stimulates albumin synthesis. A rise in albumin synthesis does not automatically coincide with a parallel rise in concentration. Albumin is a negative acute-phase protein, which means that its level will decrease during inflammation. Cytokines might be responsible for this paradoxical increase [20,21]. Its relatively long half-life (14 to 20 days) and large body pool (4 to 5 g/kg of body weight) cause serum albumin levels to respond very slowly to nutritional change. Alterations in the concentration of protein can exert a major influence on the measured total serum calcium concentrations. The total calcium concentration increases significantly with addition of protein due to the increase of the bonding to plasma protein and calcium retention [22].

Serum ferritin concentration has been used as a standard measurement of iron stores in infants, children and adults [23,24]. In spite of the wide availability of serum ferritin as a screening test, normative data at birth, as a function of specific gestational ages from 23 to 41 weeks, are limited. Elevated ferritin concentrations in the newborn can be a consequence of neonatal hemochromatosis, excessive iron administration or RBC transfusions. Serum ferritin concentrations are also elevated during periods of infection, inflammation and neoplasia. Under these conditions, serum ferritin behaves as an acute-phase reactant that can mask the diagnosis of iron deficiency [25].

Conclusion

This study aimed to examine the impact of two different doses of parenteral AAs (2 g/kg/d *vs.* 1 g/Kg/d) on weight among preterm neonates. This study was a real challenge to the researcher because of the sensitivity and fragility of the target participants. It was difficult to obtain approval to conduct the study and introduce a high dose of AAs for the purpose of experiment because the introduction of early high dose of AAs is still controversial globally.

The study results proved that early administration of high dose of AAs to preterm LBW neonates improved weight gain and head circumference better than standard dose. Also, the results revealed that neonates included in the study tolerated the high dose of AAs without clinical complications. Furthermore, neonates who received high dose of AAs had a shorter stay in NICU compared to neonates who received standard dose of AAs, suggesting reduction of costs and lowering of expenses, and can be linked to cost effectiveness.

Declarations

Ethics approval and consent to participate

A written informed consent was obtained from the parents before enrolment. The Helsinki ethics committee in Gaza Strip approved the study. Also, approval letter to conduct the study was obtained from the Palestinian Ministry of Health.

Consent for publication

Written informed consent for the publication was obtained from the participants.

Availability of supporting data

All the datasets analyzed during and/or the current study available from the corresponding author on reasonable request.

Competing interests

The authors declare that they have no competing interests.

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This study did not receive grant from any institution or organization.

Authors' contributions

IAN and ASA conceptualized, supervised and lead the study. HMA contributed to the data collection and data entry. MHT and HMA contributed to the data analysis and wrote the manuscript. All authors participated in the review of the manuscripts, read and approved the final manuscript.

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