Effect of Vitamin A on the Clinical Outcome of Acute Rotavirus Diarrhea in Preschool Children

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ABSTRACT

Background: Rotavirus infection is the most significant cause of severe dehydrating diarrhea, responsible for 5–10 million fatalities annually despite vaccinations. Acute rotavirus is the leading cause of vitamin A insufficiency by many mechanisms.

Aims: To study the acute prognostic clinical effect of the addition of vitamin A on treating preschool-age patients with confirmed infection with acute rotavirus diarrhea.

Materials and methods: A randomized, double-blind study of 55 children from 6 to 72 months aged in Al-Hussein hospital for children with positive acute rotavirus infection from October 2022 to May 2023 in Al-Diwaniya city in Iraq, was classified into two groups with a vitamin A dose of 100000 IU for those age less than 12 months and 200000 IU for those older given in the first day of involvement, while the other group received a placebo.

Results: Vitamin A significantly decreased stool consistency and frequency to significant levels and reduced the diarrheal severity of acute rotavirus and the period of hospitalization from 7.18 days to 5 days only.

Conclusion: Vitamin A intake in acute rotavirus infections significantly reduces the severity of diarrhea and hospitalization.

Keywords: gastroenteritis, rotavirus, vitamin A, children .

تأثير فيتامين أ على النتائج السريرية للإسهال الناجم عن فيروس الروتا الحاد لدى الأطفال في مرحلة ما قبل المدرسة

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الخلاصة

الخلفية: عدوى فيروس الروتا هي السبب الأكثر أهمية للإسهال الجفافي الوخيم، وهي مسؤولة عن ٥-١٠ ملايين حالة وفاة سنويًا على الرغم من التطعيمات. فيروس الروتا الحاد هو السبب الرئيسي لنقص فيتامين (أ) من خلال العديد من الآليات.

الأهداف: دراسة التأثير السريري النذير الحاد لإضافة فيتامين أ على علاج المرضى في سن ما قبل المدرسة المصابين بعدوى مؤكدة بالإسهال الفيروسي العجلي الحاد.

المواد والطرق: دراسة عشوائية مزدوجة التعمية أجريت على ٥٥ طفلاً تتراوح أعمارهم بين ٦ إلى ٧٢ شهرًا في مستشفى الحسين للأطفال المصابين بعدوى فيروس الروتا الحادة الإيجابية في الفترة من أكتوبر ٢٠٢٢ إلى مايو ٢٠٢٣ في مدينة الديوانية في العراق، وتم تصنيفها إلى قسمين: المجموعات التي أعطت جرعة فيتامين أ ١٠٠٠٠٠ وحدة دولية لمن تقل أعمارهم عن ١٢ شهرًا و٢٠٠٠٠٠ وحدة دولية لمن هم أكبر سنًا تم إعطاؤها في اليوم الأول من المشاركة، بينما تلقت المجموعة الأخرى علاجًا وهميًا.

النتائج: أدى فيتامين (أ) إلى انخفاض ملحوظ في تماسك البراز وتواتره إلى مستويات كبيرة وقلل من شدة الإسهال الناجم عن فيروس الروتا الحاد وفترة الاستشفاء من ٧.١٨ يومًا إلى ٥ أيام فقط.

الاستنتاج: إن تناول فيتامين أ في حالات العدوى بفيروس الروتا الحادة يقلل بشكل كبير من شدة الإسهال والاستشفاء.

الكلمات المفتاحية : التهاب المعدة والأمعاء، فيروس الروتا، فيتامين أ، الأطفال.

INTRODUCTION

Rotavirus infection produces the most common viral cause of diarrhea and lead to severe dehydrating diarrhea in infancy. In children, rotavirus and other gastroenteric viruses cause serious morbidity and mortality despite the involvement of rotavirus vaccine [1,2]. Rotavirus diarrhea claims the lives of 702,000 children globally. In addition, about 30%–40% of hospitalizations and deaths due to diarrhea among children under 5 years old, and about 5% of all child deaths, are attributed to rotavirus infection [3]. In Iraq, rotavirus is a major cause of nosocomial infectious diarrhea of nearly (18.5%), occurring primarily among children younger than 5 years of age [4,5].

In the treatment of viral enteritis, the primary objectives are to prevent dehydration and cure it if it occurs. The patient's nutritional state should be maintained as a secondary objective of the treatment [6]. In recent years, the improvement of Complementary Feeding Practices has significantly reduced mortality in children aged 6-11 months; malnutrition is an independent risk for the frequency and severity of diarrheal illness. Improved vitamin A status has been shown to reduce the frequency of severe diarrhea. Vitamin A supplementation reduces all-cause childhood mortality by 25% and diarrhea mortality alone by 30% [7].

Due to a response to acute phase, vitamin A level is impacted during infection. Because epithelium inflammation and absorption are impacted during an infectious episode, serum retinol levels may drop. It has been shown that a number of infectious episodes in children, including chickenpox, bronchitis, upper respiratory infection, tonsillitis, and diarrhea, are linked to low levels of vitamin A and retinol binding protein, with the effects being more pronounced in the presence of a high temperature [8]. Increased excretion of retinol in the urine may be one of the processes reducing vitamin A levels after illness. Severe infections significantly enhanced the loss of vitamin A and retinol-binding proteins. These losses might be due to several pathological changes associated with the febrile responses [9].

When children with acute diarrhea are given vitamin A, the amount of stool produced, the typical length of an episode, and the likelihood of persistent diarrhea are all significantly reduced. According to studies, when given in high doses, vitamin A is readily absorbed during severe diarrhea [10]. After administering the vitamin, acute diarrhea in children aged 1 to 5 shows a 70% reduction in persistent diarrhea lasting 14 days or more [11]. The underlying mechanisms are thought to relate to the maintenance of the intestinal epithelial lining and the regeneration of damaged mucosal epithelial cells [12].

The gut immune system's defense against infections and tolerance to food-derived antigens both benefit from vitamin A. In addition, vitamin A controls the production of genes that make anti-microbial peptides. [13]. Intestinal absorption of retinol occur in the lumen of the small intestine is high, with absorption efficacy of 70%-90% [14].

Vitamin A also affects intestinal epithelial renewal before and after acute enteric infections, which affects the absorption of water, electrolytes, and other nutrients. Vitamin A also regulates cell division in the gut and the generation of cell glycoprotein. [15].

METHODS

Study Design, Patients Recruitment, Setting and Timing

From October 2022 to April 2023, we performed a double-blind, randomized controlled research trial at the Al-Hussein Children's Hospital in Al-Diwaniyah, Iraq. Children between the ages of 6 months and 72 months who had acute onset rotavirus diarrhea lasting fewer than 5 days were eligible to participate.

Two hundreds diarrheal children were enrolled in the study with 55 children had positive rotavirus. We exclude any patient with severe dehydration or malnutrition or if the child already receives any vitamin A supplements before the infection or if the diarrhea caused by other than rotavirus infection. Diarrhea was defined as ≥3 passage of unformed or loose stools in the last 24 hours [16].

Children were randomly selected to receive either a single dose of vitamin A or a placebo in a sequence created by a person not directly involved in the execution of this study. According to WHO recommendations for vitamin A, vitamin A was administered at a dosage of 100.000 IU of retinol for individuals aged 6 to 12 months and 200.000 IU of retinol for patients aged 13 to 72 months. [17]. Vitamin A given in the first day of administration to the hospital. The other 28 children receive only the same treatment with placebo empty capsule.

Children with mild or moderate dehydration were rehydrated prior to patient enrolled in the study.

At every episode of diarrhea, the parents were instructed to monitor their child's stool frequency and consistency and other clinical symptoms that may appear during the trial. All subjects were monitored each day till healing.

Stool volume returning to normal (less than 200 ml/day), loose or soft stool consistency returning to normal, and frequency of diarrhea decreasing to fewer than three times per day were all considered signs of recovery from diarrhea. [18]. Acute rotavirus diarrheal illness usually resolves spontaneously within 7-10 days without treatment [19].

The number of days between the first and final abnormal (loose or liquid) stools before a normal stool production was used to describe the duration of acute diarrhea.

Stool consistency was rated as normal (1), loose (2), semiliquid (3), and liquid (4). The period from admission to discharge was used to determine the length of the hospitalization period. Frequency is the number of passages of stool times per day.

Questionnaire Formula

Prior to admission into the study, history, age, sex, weight, vaccination stat, days of diarrhea before admission and stool frequency and consistency each day after admission, on a prepared pro forma, information on the patient's physical examination, nutritional state, level of hydration, temperature, oral acceptance, and distention were noted. According to the WHO acute diarrhea guideline, case treatment was carried out. [16].

Ethical Considerations

The study was conducted after approval of the ethical committee, College of Medicine- University of Al-Qadisiyah, Iraq and Al-Hussein Hospital before administration. All patient's parents were informed both verbally and in writing about the procedure and the purpose of the study; Before participating in the research, every participant's parents provided written, informed permission.

Primers Used in the Current Study

One fresh diaper faeces sample was collected from each baby participating in the trial during the first few hours of arrival using a plastic spatula. The patient's basic information and the sample's code were recorded on a sterile plastic cup in which the faeces sample was collected, and it was sent within 30 minutes to the hospital's microbiological laboratory. Rotavirus was detected in this stool sample using an immunochromatographic test (RovA Rotavirus Antigen Rapid Test kit).

Statistical Analysis

We used SPSS version 26 and Microsoft Excel 2010 for data processing. The relation between vitamin A (nominal scale), diarrheal frequency and diarrheal duration (numeric scale) was examined using an independent T-test. The relation between vitamin A (nominal scale) and stool consistency (ordinal scale) was examined using the chi square test. If P values with a 95% CI were 0.05, then differences were deemed significant.

RESULTS

Two hundred children with acute diarrhea were recruited in this study. More than 145 children were excluded (133 children with negative rotavirus in their stool), and 12 children with positive rotavirus test were excluded because two of them were already received large doses of vitamin A in the form of drugs. Seven of them were presented with severe dehydration or malnutrition as their weight was less than the 3rd percentile on the growth chart. The other 3 children were excluded because they presented with diarrhea for more than 5 days until they reached the hospital.

Only 55 children were enrolled in the study with positive stool for rotavirus and reached all the criteria in this experiment. The remaining 55 children were randomized into two groups;27 children received vitamin A, and the other 28 received a placebo. The group that takes vitamin A on the first day of admission and another group receive the same treatment of diarrhea as in the previous group except for vitamin A. Both groups were insignificantly different in age, sex, weight, and type of feeding for those ages less than two years (p-value >0.05). (Table 1)

Table (1) The fundamental quality of study groups.

The characteristic	Vit. A group	Placebo group	P - value
Age (months)	11±5.4*	10.5±3.8*	0.9 (NS)
Male/Female	12/15 n (27)	15/13 n (28)	0.5(NS)
Breast/ Bottle Feeding	1/16 n(27)	4/24 n(28)	0.3(NS)
Weight (kg)	9.3±3*	8.5±2.6*	0.3 (NS)
Days before Admission	2.3±1*	2.8±1.1*	0.13(NS)
Fever	20 n(27)	26n(28)	0.1 (NS)
Vomiting	12 n(27)	16 n(28)	0.3(NS)
Abdominal Distension	12 n(27)	18 n(28)	0.14(NS)
Dehydration	22 n(27)	27(28)	0.075(NS)

*mean± SD

Stool consistency is the first clinical parameter used to assess the severity of acute diarrhea caused by acute rotavirus infection. All patients presented with liquid stool consistency for several days. The liquid stool period in children in the vitamin A group continues for a shorter time (2.3 days). In comparison, the children with liquid stool consistency in the placebo group require (3.28 days) to change the stool consistency to a semi-liquid phase in p-value <0.05. (Table 2)(Figure 1)

Table (2). Liquid stool consistency of All children following treatment:

Liquid stool consistency	No.	Mean (Days)	Std. Error Mean	P-value
vitamin A Group	27	2.333	0.13074	<0.005
Placebo Group	28	3.285	0.15307	<0.005

The semi-liquid stool period in children with vitamin A group continues for (0.5 days) while the children with semi-liquid stool consistency in the placebo group require (0.9 days) to change the stool consistency from semi-liquid phase to loose stool consistency in p-value 0.09. (Table 3) (Figure 1)

Table (3). Semi-liquid stool consistency of All children following treatment:

Semi-Liquid stool consistency	N	Mean	Std. Error Mean	P-value
vitamin A Group	27	0.5926	0.14381	0.09
Placebo Group	28	0.9643	0.15838	0.09

The loose stool period in children in the vitamin A group they were continued for a shorter time (2.14 days), while the children with loose stool consistency in the placebo group required (2.89 days) to change the stool consistency to normal stool consistency in p-value < 0.05. (Table. 4) (Figure. 1)

Table (4). Lose stool consistency of All children following treatment:

Loose stool consistency	N	Mean	Std. Error Mean	P-value
vitamin A Group	27	2.1481	0.1574	0.002
Placebo Group	28	2.8929	0.8751	0.002

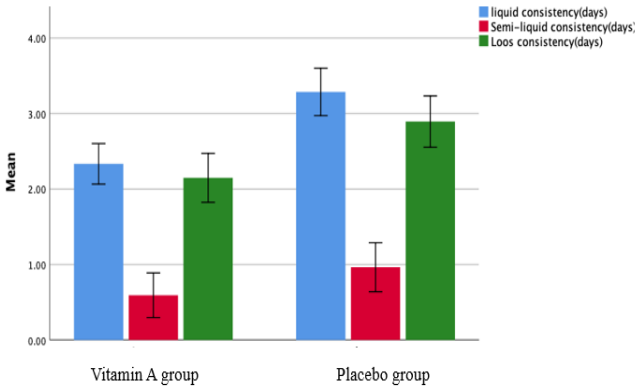

Figure 1: Stool consistency changes during the days of admission in both groups.

The second parameter is the frequency of stool passage per every day of study. Abnormal stool frequency is above 3 times per day. In the first two days of admission, the stool frequency number was non-significantly changed even after vitamin A administration to the children (p-value 0.131 and 0.014, respectively). In the next 4 days of vitamin A administration to the children in the vitamin A group, there was a significant drop in stool frequency compared to the children in the placebo group(p-value<0.05). (Table 5) (Figure 2)

Table 5: Daily diarrheal frequency of children following treatment.

Date	Group	No.	Mean	Std.Error	P-value
Day 1	vit A Group	27	12.56	0.521	0.131
	Placbo Group	28	13.82	0.636	0.131
Day 2	vit A Group	27	11.26	0.436	0.014
	Placbo Group	28	12.96	0.505	0.014
Day 3	vit A Group	27	8.59	0.414	<0.005
	Placbo Group	28	11.39	0.472	<0.005
Day 4	vit A Group	27	5.15	0.402	<0.005
	Placbo Group	28	9.71	0.554	<0.005
Day 5	vit A Group	27	3.19	0.302	<0.005
	Placbo Group	28	7.79	0.438	<0.005
Day 6	vit A Group	27	2.33	0.169	<0.005
	Placbo Group	28	5.89	0.346	<0.005

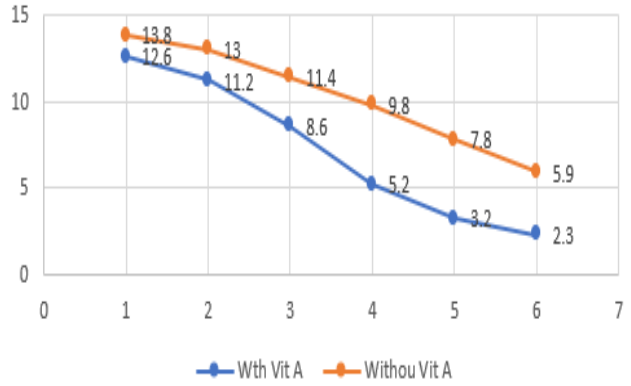

Figure 2: Stool frequency changes during the 6 days of children's admission after treatment in both groups.

In Figure (3), the children in both groups are divided into four categories according to the stool frequency. The first category for stool frequency more than 12 times per day in the first days of admission to the hospital (orange color). The second category is for children of 10-12 stool frequency/day in the next few days after admission (green color). The third category was for children of stool frequency from 7-9 times/day (red color). The last frequency was near the improvement and discharge in stool frequency less than 6 times/day (blue color).

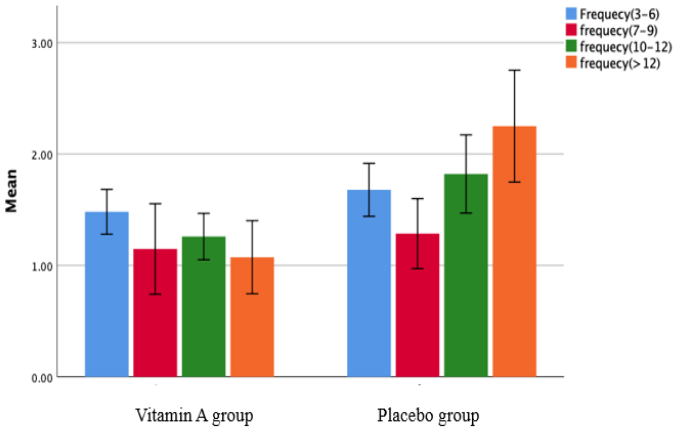

Figure 3: Stool frequency categories in both groups.

The days of hospitalization for children with acute rotavirus diarrhea changed significantly after administrations of vitamin A from mean of 7.18 days for those children with the same treatment except vitamin A to mean of 5 days for those group received vitamin A with P-value <0.001. (Table 6) (figure 4)

Table 6: Days of hospitalization in children with positive acute rotavirus diarrhea.

	Groups of study	No.	Mean Days	Standard Error mean	P - value
Duration of hospitalization	Vit. A group	27	5.00	0.214	<0.001
	Placebo group	28	7.18	0.225	

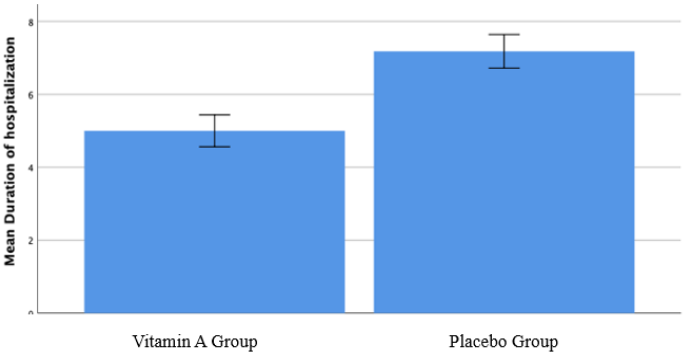

Figure 4: Distribution of days of hospitalization in children with positive acute rotavirus diarrhea in both groups.

DISCUSSION

Gastroenteritis remains the most common cause of morbidity and mortality in the first years of child age worldwide. Rotavirus is the most common viral cause gastroenteritis in these age group [1,3]. Of the 200 children who entered into the experiment, 67 were infected with rotavirus (33%). This indicates that a large number of children still suffer from rotavirus infection, despite the generalization of the periodic national program for vaccinations in Iraq.

Abood et al. (2013) discovered that 42.45% of the 384 infants with gastroenteritis admitted to Maternity and Child Teaching Hospital in three governorates (Al-diwaiya, Babylon and Najaf) were 214 infants infected with rotavirus [20].

The ages were enrolled from the category of less than seven years, due to the high incidence of diarrheas and rotavirus in this age group. It was taken into account that the ages in this study are similar for the two groups who received vitamin A (mean 11±5.4 months) and those received a placebo (mean 10.5±3.8 months). (Table 1)

The closeness of the selected numbers in terms of sex for males and females for vitamin A group (mean 12/15) and placebo group (mean 15/13) was taken into account, as well as the selected weights (mean 9.3±3 Kg 8.5±2.6 Kg respectively) were close to the corresponding ages. (Table 1)

Therefore, children who were underweight and severely dehydrated were excluded from the study.

According to Hasan (2013), among patients with diarrhea in Baqubah-Diyala province, females had an insignificantly higher infection incidence than men (22.1% vs. 18.9%). [21].

Children who are breastfed or formula-fed under two years of age represent 81% of the total number of children in the study, and this indicates that the method of feeding has a clear relationship with the number of cases of acute diarrhea, as well as the incidence of acute rotavirus infections as well, as the incidence of diarrhea decreased clearly after the second year of age (less than 19%), and it was difficult to find children infected with the virus after this age group.

The other observation related to the method of breastfeeding is the reluctance of mothers to breastfeed, only 5/45 or 11.2% (table 2) and the tendency to artificial feeding 40/45 or 88.8%, and this plays a major role in increasing the incidence of diarrhea and rotavirus cases as well, if we take into account that breastfeeding has a significant impact in increasing the acquired immunity for babies with breast milk due to the wide immune elements that are of great importance in reducing the incidence of diarrhea and other infections.

According to some studies, bottle feeding increases the risk of rotavirus infection due to improper feeding practices, poor sterilization techniques, infection risks, and cow's milk allergies. However, According to Hasan et al. (2011), the frequency of anti-rotavirus IgG antibodies was not statistically affected by bottle feeding (55.30%) in either the sick or healthy groups. [22].

In a research done by Al-khafagi et al. (2011), mixed feeding compared well to breast feeding in cases of acute infantile rotavirus diarrhea, with a very significant P-value of 0.05 [23].

The number of days during which the child was suffering from acute diarrhea at home was determined by less than five days for both groups (Vitamin A group 2.3±1 days and placebo 2.8±1.1 days)(Table1), as all cases of infection with rotavirus were neglected after reviewing the hospital within five days, because the patient is likely to have taken some different types of treatments that will affect the improvement and results. Also, the diarrhea will not be acute after this period, and some cases of diarrhea caused by rotavirus infection may be start to improve even without treatment.

High fever, vomiting, dehydration, and abdominal distension are common signs that can be used in association with the diagnosis of rotavirus diarrhea. The previous complications were recorded in the two groups very closely. There was a rise in temperature for children by 83.5%, vomiting by 52%, general mild to moderate dehydration by 89%, and flatulence by 54% in both groups and for all age groups that involved in this study.

Acute rotavirus, and after all the national efforts to contain it through the national periodic vaccination programs, still alone constitutes approximately 33% of all acute diarrhea occurrence in this study. This high percentage of rotavirus infections is the result of the parents' delay in adhering to the periodic schedule of vaccinations in the first few months of the child's life. This requires spreading more awareness and understanding among the people, as only this percentage needed hospitalization, except for the other numbers who were treated in the daily counseling unit and did not need hospitalization.

The other reason that led to an increase in the number of children infected with the rotavirus despite the national periodic schedule of vaccines is the presence of other different serotype strains of the virus, which are not covered by the schedule of vaccines, but fortunately, most cases gained complete recovery within a few days, especially if vitamin A was adopted in the study as therapeutic.

The clinical stool parameters that involved in this study were the stool consistency and frequency. After administration of vitamin A to children with positive rotavirus, the stool consistency changed from liquid to semi-liquid (in 2.33 days) then to loose stool (in 0.5 days) before return to the normal stool consistency (in 2.14 days) in a shorter period in comparison to those with placebo group stool consistency (3.28, 0.9, 2.89 days respectively). (Tables 2,3,4) (Figure 1).

Stool frequency is the second clinical stool parameter to assess the severity of diarrhea. The stool frequency of children with acute rotavirus diarrhea can reach more than 20 times per day in our study. The stool frequency of Vitamin A group of children with acute rotavirus diarrhea became improve (Significant P-value of frequency number decrease in the successive days) starting from the third day by mean of 8.5 times/day, while in placebo group, the stool frequency not improve (Non-significant P-value frequency decrease) until the 6th day of admission. (Table 5, Figure 2). Figure 3 illustrates that all stool frequency categories in placebo group, still higher than those of vitamin A group for the same period of diarrhea.

These results support previous findings of Fawzi et al (2003) [24], Marpaung et al (2013) [25] and Salazar-Lindo et al (2003) [26] about low vitamin A concentrations and its supplementation in diarrheal children may lessen the frequency and severity of the condition.

There are various ways that acute diarrhea might result in vitamin A deficiency: A generalized loss of

fat-soluble vitamins may result from steatorrhea. Damage to the brush border may prevent the brush border retinyl esterase, which is in charge of vitamin A's intestinal absorption, from performing its role. Lack of vitamin A negatively impacts the epithelium lining, resulting in reduced mucus production and impaired local infection defenses. Additionally, it could cause villous atrophy, aberrant villous architecture, and goblet cell depletion. Vitamin A supplementation, affecting humoral and cellular immune functions. All these points may lead to prolong and severe diarrhea.

The fact that the outcomes evaluation in this research was reliant on parents' accounts rather than our personal observations may be a reason for its limitations. We do not evaluate the effects of other risk variables, such as mothers' educational attainment levels, the quality of the water, or environmental elements that can affect the healing processes. The study period from October to May, not cover all the seasons of the year. More cases may be recorded through the second half of the year.

From all of the aforementioned, and due to the direct effect of vitamin A in accelerating the change in the consistency of stool, reducing the number of diarrheal frequencies per day led to a decrease in the hospitalization period for those with vitamin A group (5 days) to 7.1 days in those with placebo, with significant decrease of days of hospitalization. (P-value<0.001) (Table 6) (Figure 4).

The average length of diarrhea per episode was significantly shortened in a double-blind; placebo-controlled experiment in a Calcutta community of infants who got vitamin A, and who were the same age as the participants in our research [27].

Another double-blind, randomized trial in New Delhi studied the impact of vitamins on acute rotavirus diarrhea in children of a comparable age range and came to the conclusion that vitamin A could lessen the severity of the diarrhea [28].

According to a research by Kheirkhah et al (2016) [29], giving children aged 1 to 5 years old with acute watery diarrhea vitamin A intramuscularly may shorten their hospital stays as well as the duration of their diarrhea and frequency.

Yurdakok et al. (2000) [30] discovered that oral vitamin A treatment during episodic acute diarrhea in infants who do not exhibit indications of malnutrition had no impact on diarrheal duration, weight growth, or blood vitamin A levels. Gebremedhin (2017) [31] found that despite that vitamin A administration has an established benefit for the reduction in childhood mortality of diarrhea, vitamin A had no role in decreasing the complications or hospitalization of acute rotavirus diarrhea.

CONCLUSIONS

Acute rotavirus infection, despite the approved national periodic schedule of vaccines, still constitutes nearly third of the cases of acute gastroenteritis. There is an apparent mother's reluctance to breastfeed and the tendency to artificial feeding. Vitamin A supplementation in cases of acute diarrhea caused by acute rotavirus has a major and significant role in reducing diarrheal frequency and recovery of the stool consistency of diarrhea to normal form in a sooner and shorter period of time. Vitamin A supplementation has a significant role in acute decrease diarrhea of acute rotavirus severity and period of hospitalization.

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