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# Effectiveness of GASTROFIX on Duration of Diarrhea and Length of Hospitalization in Children with Acute Gastroenteritis: A Randomized Controlled Trial

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## *Abstract*

***Background:*** According to evidence, the main treatment plans for children with gastroenteritis include the use of an oral solution or intravenous infusion for hydration, continued nutrition; zinc supplementation. The aim of this study was to investigate the effectiveness of Gastro-Fix (registered nutritional supplement) versus placebo on length of hospitalization and duration of diarrhea in children with acute gastroenteritis.

***Materials and Methods:*** We conducted a double blind randomized placebo-controlled trial in children with acute gastroenteritis (age between 6 and 120 months). Three hundred eligible patients randomly allocated to one of two parallel groups, Intervention received Gastro-Fix, whereas the placebo group received baby food (cereal based on skimmed milk and wheat without mineral) for a total of 6 days. Gastro-Fix and baby food was administered as a same sachet that could be opened and mixed in water. The primary outcome was length of hospitalization and duration of diarrhea.

***Results:*** The Mean length of hospitalization in Gastro-Fix and placebo was 3.43± 0.57 and 4.70±0.59 day respectively (P<0.001). Median duration of diarrhea was 3 days (range: 3-5, IQR: 3–4 days) in the Gastro-Fix group and 5 days (range 3-6, interquartile range [IQR]: 4–5 days) in the placebo group which was statistically significant (P<0.001). The highest efficacy (diarrhea-free percentage of children) of the Gastro-Fix was observed at day 4 (relative risk [RR]: 0.28; 95% confidence interval [CI]: 0.23-0.35), and at day 5 (RR 0.08; 95% CI: 0.03-0.17) after the intervention.

***Conclusion:*** Finding of this study showed that Gastro-Fix can be effective in reducing duration of diarrhea and length of hospitalization in children with diarrhea. This product is suggested to be used in children with acute gastroenteritis.

***Key Words:*** Children, Diarrhea, Length of hospitalization, Gastro-Fix Gastroenteritis.

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## 1- INTRODUCTION

Diarrhea is one of the most important causes of children mortality around the world. Poverty, malnutrition, low health status and unfavorable living conditions are also risk factors (1, 2). The rate of this disease in developed and developing countries is in the range of 2 to 12 cases per person per year (3); it is estimated that diarrheal diseases in developing countries account for more than three million deaths among children every year and it will lead to malnutrition among children who have been treated (4). Diarrhea, among children with malnutrition, has more severe effects and the rate of mortality among them is eight to nine times higher than that of children with normal nutritional status (5). Treatment plans for these children include the use of an oral solution for hydration, continued nutrition, zinc supplementation and antibiotic administration in specific cases. According to the European Society for Pediatric Gastroenterology, Hepatology, and Nutrition and the European Society of Pediatric Infectious Diseases Expert Working Group, treatment of dehydration of these children with edible solution is considered as one of the most important methods of replacing liquid and electrolyte but it is less than needed in many cases, unfortunately (6).

According to some reports, roughly half of the children consume adequate amount of the oral rehydration solution (ORS) (7). Consumption of ORS and other recommended domestic liquids can reduce up to 69% of diarrhea's mortality (8). Since 2004, consumption of zinc supplementation for treatment of diarrhea has led to 46% mortality reduction and 23% children hospitalization (9). It is estimated that about 17.3 percent of the world's population have a zinc deficiency, which is more common among those children who are less than five years old. Therefore, based on guidelines, consumption of ORS and zinc plus continued diet is recommended to treat children's diarrhea (10). According to a systematic review study, it has been illustrated that taking vitamin A, can also reduce the mortality rate of children's diarrhea by 28% and reduce the incidence of this disease as much as 15% (11). There are many viewpoints about the relationship between the optimal nutritional status and the consumption of nutritional compounds to accelerate the recovery process and maintain the nutritional status of these children. Based on the extensive study of dietary strategies and nutrition-based interventions among many children, it has been noted that the duration of treatment of diarrhea and treatment failure among children who were consumed lactose-free foods was far lower than those who consumed lactose-based foods (12).

Other therapeutic interventions which are important in the development of diarrhea among children are the consumption of pro-biotic compounds and anti-vomiting drugs; as studies have shown that pro-biotic compounds has been effective in reducing of diarrhea by 14%. (13). Also, given that most children with diarrhea suffer from vomiting; it has been shown that using of ondansetron can reduce 54% of hospitalization and reduce 60% of intravenous fluid intake (14). Considering the nutritional status of children with diarrhea in developing countries is very important. Based on evidence, the prevalence of diarrhea is related to the growth rate of children and the lack of control of diarrhea cause growth disorders and the probability of persistent diarrhea (15). Based on above mentioned, it is clear that the consumption of a nutritional supplement containing the required electrolytes, calories, vitamins and some salts such as zinc can reduce the duration of diarrhea among children and prevent the consequences of diarrhea, such as long-term admission, intravenous fluid therapy, weight loss and malnutrition after diarrhea.

The Gastro-fix supplement is a special formula for feeding in case of diarrhea to cover children's nutritional needs during the recovery phase of diarrhea. In breastfeeding infants, in the phase of diarrhea recovery after ORS therapy, it can be given along with breast milk, and among non-breastfeeding infants, it replaces with the milk in the recovery phase. The aim of this study was to investigate the effectiveness of Gastro-fix (registered nutritional supplement) versus placebo on length of hospitalization and duration of diarrhea in children with acute gastroenteritis.

## 2- MATERIALS AND METHODS

### 2-1. Study design and population

This study was a single-center; double blind randomized placebo-controlled trial. This clinical trial was conducted in children with acute gastroenteritis (age between 6 and 120 months) referred to Shahid Bahonar Educational and Therapeutic Center in Karaj, Iran, between April to September 2017. Acute diarrhea was defined as the presence of three or more liquid or loose stools, as defined by Bristol criteria type ≥6 per day lasting for less than or equal to 7 days (16). In this study the sample size was determined according to previous studies (17, 18), and using two mean comparison formula and considering type I and II error 0.05 and 0.1 respectively. In this formula the mean (standard deviation [SD]) duration of diarrhea in intervention and placebo group was considered 3.4 (1.8) and 4 (1.9), respectively.

### 2-2. Inclusion and exclusion criteria

**Inclusion criteria:** an episode of mild to moderate acute diarrhea (more than four time [semi] watery stools/day according to Bristol criteria [Bristol criteria ≥6]), and at least lasting more than 24 h and less than 72 h, requiring hospitalization; we enrolled children with mild to moderate dehydration. Dehydration was evaluated using World Health Organization's dehydration scale (19).

**Exclusion criteria**: patients with any of the following conditions were excluded: acute diarrhea that contains blood, chronic diarrhea, severe dehydration, inflammatory bowel disease, necrotizing enterocolitis, immune deficiency, chronic disease and malnutrition, gastro-intestinal malformations and severe malnutrition.

### 2-3. Intervention

three hundred patients with acute gastroenteritis were assigned randomly into two groups and received one of the following interventions; 150 patients received Gastro-Fix (9g/kg, daily, in two to four divided doses per day), and 150 patients in control group received "baby food" (cereal based on skimmed milk and wheat without mineral) as placebo (9g/kg, daily, in two to four divided doses per day). All patients received regular standard treatment and routine care throughout the study (fluid/electrolyte replacement using hypo-osmolar ORS and/or or intravenous therapy based on the status of each patient).

### 2-4. Main outcome measures

The primary outcome variable in the study is the length of hospitalization. The secondary outcome measures includes the following: body weight, severity of diarrhea will be defined by the stool consistency score and frequency of diarrhea in 24 hours, the state of dehydration, using the World Health Organization's dehydration scale.

### 2-5. Procedures

All of the patients referred to the emergency department of the hospital. If the patient was hospitalized, the inclusion criteria for entering the study were evaluated by the co-researcher and then random allocation was made to the Gastro-Fix and placebo groups. A pediatrician,

who was responsible for the treatment of the child in the ward, as well as assessment of the primary and secondary outcome of the study, did not know about the type of intervention of the groups. Also the parents were blind to the real nature of the product. Parents recorded in a specific diary the number and consistency of the stools and the use of any other medication. The duration of diarrhea was defined as the time in hours from admission until cessation of diarrhea, which in turn was defined as the first normal stool according to the Bristol score (a score of <5 was considered as normalization of the stools) (**Table.1**). The parents received an individually education about recording of stool consistency by Bristol score. The visual form of this scale was used for teaching.

The tested Gastro-Fix was administered as a sachet that could be opened and mixed in water. The placebo was the same sachet as baby food (cereal based on skimmed milk and wheat without mineral). The content of packages (Gastro-Fix and placebo) was similar in color and smell. Both products were supplied by FASSKA Company, who was not involved in any of the stages of the design (design, conduct of the study, data analysis, and interpretation). Both the physicians and the patients were unaware of the real nature of the product. Patients were enrolled according to the computer-determined allocation to group A (Gastro-Fix) or B (placebo). Random allocation was made in blocks of ten to obtain groups of similar size. The sequence was concealed until treatments were assigned.

**Table-1**: Bristol stool score

Seven types of stool:

Type 1: Separate hard lumps, like nuts (hard to pass).
Type 2: Sausage-shaped, but lumpy.
Type 3: Like a sausage, but with cracks on its surface.
Type 4: Like a sausage or snake, smooth and soft.
Type 5: Soft blobs with clear cut edges (passed easily).
Type 6: Fluffy pieces with ragged edges, a mushy stool.
Type 7: Watery, no solid pieces. Entirely liquid.

Types 1 and 2 indicate constipation, with 3 and 4 being the 'ideal stools' especially the latter, as they are the easiest to defecate, and 5–7 tending towards diarrhea.

### 2-6. Ethical consideration

The study protocol was approved by the ethics committee of Alborz University of Medical Sciences. Informed consent was obtained from all parents. This trial was registered in Iranian Registry of Clinical Trials (IRCT2017091536195N1).

### 2-7. data analysis

Statistical analysis was performed using the SPSS software version 20.0 (SPSS Inc.; Chicago, IL, USA). Normal distribution of continuous variables was assessed using Kolmogrov-Smirnov test and due to lack of normality, continuous variable were presented as median (inter-quartile range [IQR]). Continuous variable without normal distribution were compared between (Gastro-Fix and placebo) groups using Mann-Withney U test. Categorical data were presented as number (percentage) and were compared using Chi-square test between study groups (Gastro-Fix and placebo). Relative risk (RR) and 95% confidence interval (CI) was calculated using Chi-square test to compare percentage of children with diarrhea in study groups at day 4 to 6. All analysis was performed based on per protocol analysis method. The threshold of statistical significance was set at $P < 0.05$ at least.

## 3- RESULTS

Totally 316 eligible subjects with diarrhea out of 376 invited subjects were included in the study. Among 316 eligible patients, 16 patients were excluded and finally 300 patients with acute diarrhea (150 in intervention and placebo group) were enrolled in this study. Eight patients from each group were excluded due to parental unwillingness to continue the study and lack of data after hospital discharge (**Figure.1**). Clinical and demographic characteristics of the study groups are presented in **Table.2**.

Age and gender distribution was not statistically different between groups ($p>0.05$). Median duration of diarrhea before intervention was 9 hours in both groups. Median duration of diarrhea was 3 days (range: 3-5, interquartile range [IQR]: 3–4 days) in the Gastro-Fix group and 5 days (range 3-6, IQR: 4–5 days) in the placebo group which was statistically significant ($p<0.001$). Mean (standard deviation [SD]) length of hospitalization in Gastro-Fix and placebo was 3.43(0.57) and 4.70 (0.59) day, respectively ($p < 0.001$) (**Figure.2**).**Table.3** shows median (IQR) number of stools per day in study groups. In all days except at day 5, there was a reduction in the number of stools in the Gastro-Fix group compared with the placebo group ($p<0.005$). In the Gastro-Fix and the placebo group the maximum duration of diarrhea was 5 and 6 days, respectively. At day 1 to day 3 all patients (100%) had diarrhea at both groups. The highest efficacy (diarrhea-free percentage of children) of the Gastro-Fix was observed at day 4 and at day 5 (**Table.4**). At day 4 and 5, 39.3% and 4% of the children in Gastro-Fix group still had diarrhea while in the placebo group these percentages were 99.3% and 64%, respectively which was statistically significant between groups (relative risk [RR] at day 4 and at day 5 was 0.28 and 0.08, respectively) (**Table.4**).

In terms of stool consistency, although at admission time all patients in both groups had diarrhea (Bristol scale > 5), at discharge time 126 (84%), and 43 (28.9%) patients in Gastro-Fix and placebo group had a normal stool consistency (Bristol scale ≤ 4) which was statistically significantly between groups ($p < 0.001$). No adverse effects (including rash, drug-related fever or nausea, etc.) were not reported by the parents.

**Table-2**: Clinical and demographic characteristics of the study groups

| Variables | Gastro-fix (n = 150) | Placebo (n = 150) | P-value |
|---|---|---|---|
| Gender (Male/Female) | 76/74 | 73/77 | 0.72 |
| Age (month)* | 17(12-24) | 15(11-24) | 0.55 |
| Duration of diarrhea before intervention (hours)* | 9(9-10) | 9(8-10) | 0.44 |
| Duration of vomiting before intervention (hours)* | 3(2-7.25) | 4(2-6) | 0.41 |
| Weight (kg)* | 10.8(9.7-12.12) | 10.8 (9.5-12.5) | 0.82 |
| % of Dehydration* | 8(7-9) | 8(7-9) | 0.99 |
| Length of hospitalization (days)* | 3(3-4) | 5(4-5) | <0.001 |
| Duration of diarrhea (days)* | 3(3-4) | 5(4-5) | <0.001 |

*Data are expressed as median ($25^{th}$-$75^{th}$), **According to Chi-square test, *** Mann-withney U test.

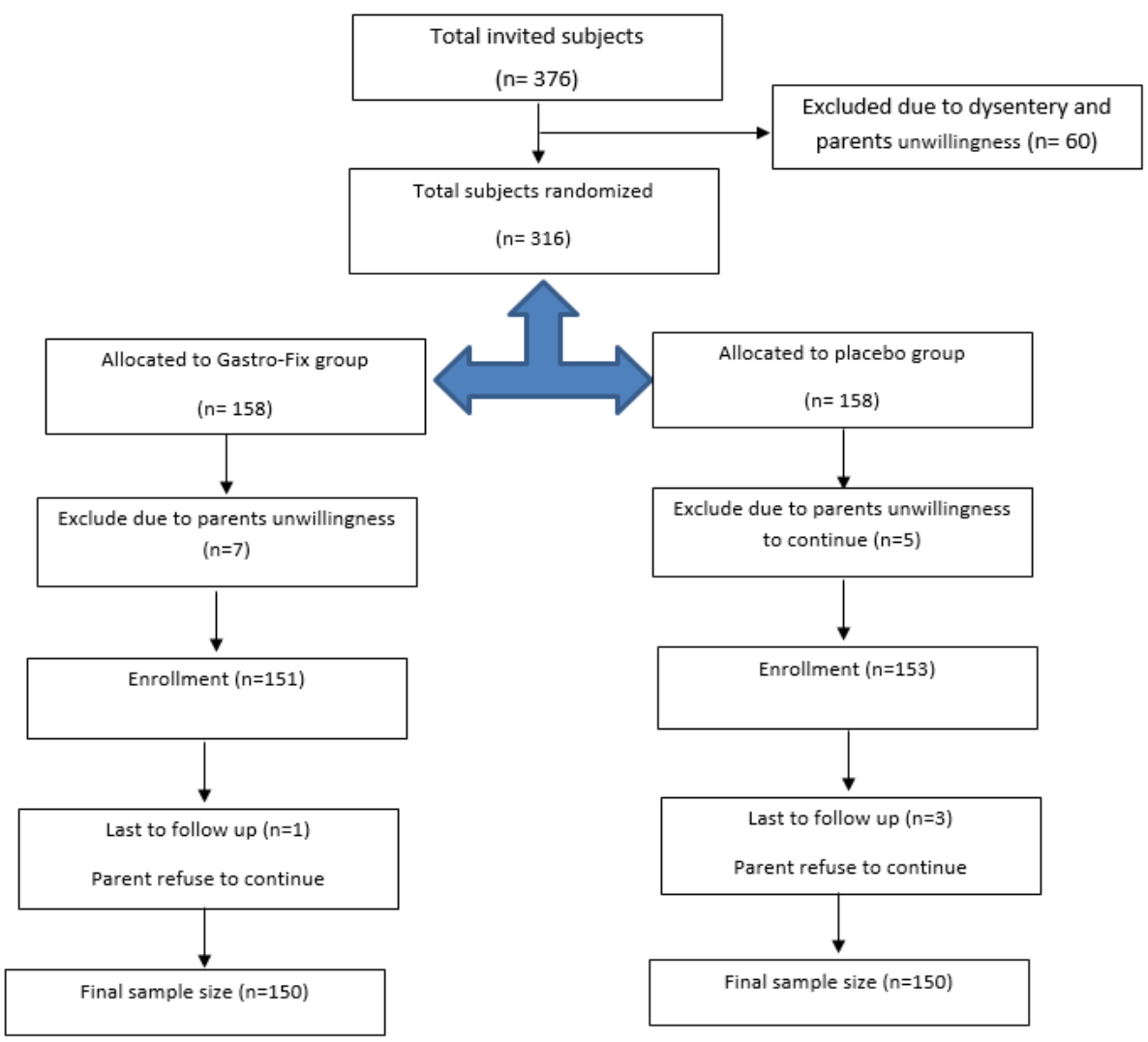


**Fig.1**: flow diagram of the subject participation in the study.

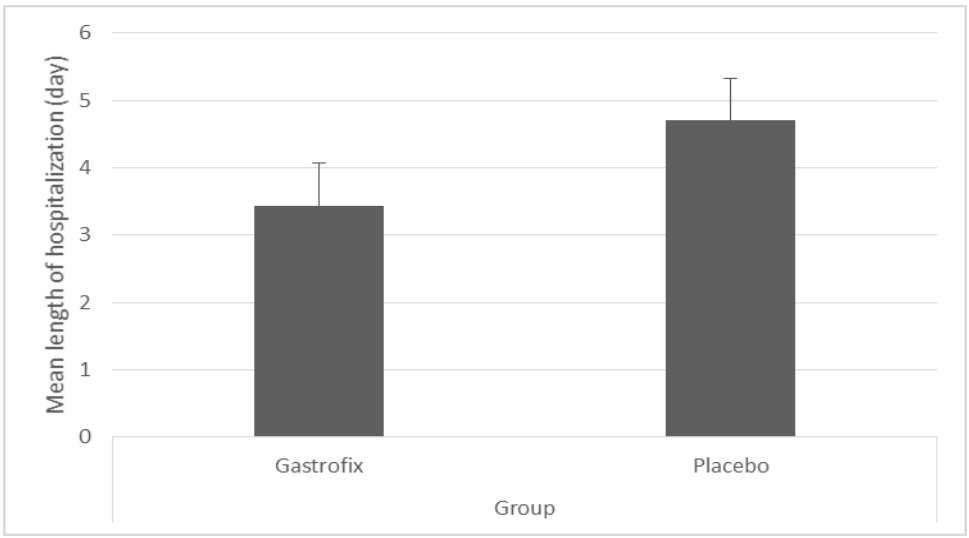


**Fig.2**: Comparison of mean length of hospitalization in study groups (Gastro-Fix and placebo).

**Table-3**: Number of stools per day in study groups

| Day | Gastro-Fix | | | Placebo | | | P-value* |
|---|---|---|---|---|---|---|---|
| | Median | IQR ($25^{th}$-75th) | Range | Median | IQR | Range | |
| Day 1 | 9 | 8-9 | 5-10 | 8 | 7-9 | 4-10 | 0.015 |
| Day 2 | 6 | 6-7 | 4-9 | 8 | 8-9 | 5-10 | <0.001 |
| Day 3 | 3 | 2-5 | 1-8 | 7 | 6-8 | 5-9 | <0.001 |
| Day 4 | 2 | 1-3 | 1-6 | 5 | 3-6 | 1-7 | <0.001 |
| Day 5 | 2 | 1-3 | 1-3 | 3 | 2-3 | 1-6 | 0.16 |
| Day 6 | ---------- | ---------- | ---------- | 2 | 2-3 | 1-3 | ------- |

*According to Mann-Withney U test. IQR: interquartile range.

**Table-4**: Percentage of children with diarrhea in study groups at day 4 to 6

| Day | Gastro-Fix (n=150) Number (%) | Placebo (n=150) Number (%) | RR (95% CI) | P-value* |
|---|---|---|---|---|
| Day 4 | 59 (39.3%) | 149 (99.3%) | 0.28(0.23-0.35) | <0.001 |
| Day 5 | 6 (4%) | 96 (64%) | 0.08(0.03-0.17) | <0.001 |
| Day 6 | 0 (0%) | 12 (7.4%) | ---------- | 0.001 |

At day 1 to day 3 all patients (100%) had diarrhea at both groups. *According to Chi-square test; RR: relative risk; CI: confidence interval.

## 4- DISCUSSION

The most important goal in the treatment of diarrhea in infants is diminution of the diarrhea duration and reduction hospitalization. ORS is the initial therapy that recommended for dehydration in individuals with diarrhea (20). However, ORS replaces fluid and electrolyte but does not substantially shorten diarrhea duration; so additional therapy methods have been widely assessed. In present study, the effect of Gastro-Fix was evaluated on recovery of individuals with diarrhea. In the current study, a significant difference was observed in duration of diarrhea, number of stools, and length of hospitalization between Gastro-Fix group and placebo group. Significantly, duration diarrhea and length of hospitalization in Gastro-Fix group were less than placebo group, also in Gastro-Fix group, number of stools significantly decreased more than placebo group. Gastro-Fix is a nutritional formula that its main characteristics are adapted carbohydrates (lactose free), specific fat and protein, enriched with electrolytes and minerals (Sodium, Potassium, chloride, Zinc, etc.). Previous studies have shown the efficacy of zinc for treatment of diarrhea, reduction of diarrhea duration, as well as frequency of stool (21-25). Sami Yazar et al. stated diarrhea duration was significantly decreased in the zinc group compared to the control group (approximately 28 hours) and at 72 and 96 hours of intervention, the zinc group had less diarrhea compared to the control group (26). The finding of a meta-analysis study (24) showed that zinc supplementation resulted in a shorter duration of diarrhea and less diarrhea at Day 3 and Day 5, approximately similar to our findings. Zinc is the one of main components of Gastro-Fix supplement that may be caused this supplement is useful for treatment of diarrhea. One of main components of Gastro-Fix supplement is adapted carbohydrates that including cooked rice, banana powder, and apple powder. The results of a double-blind trial study in Bangladeshi children showed that green banana and pectin significantly reduced amounts of stool, frequency of vomiting, and diarrheal duration (27).

Other study showed that a rice based diet containing green banana or pectin significantly improved stool consistency and decreased the diarrhea duration in infants with persistent diarrhea (28). A current met analysis study showed that ORS containing cooked rice powder instead of glucose substantially decrease the rate of stool loss in cholera diarrhoeal diseases (29). The results of our study were consistent with these studies and showed that adapted carbohydrates such as cooked rice and banana powder are useful for treatment of diarrhea.

## 5- CONCLUSION

In conclusion, the results of our study showed that Gastro-Fix reduced the duration of diarrhea and reduced the duration of hospitalization in infants with diarrhea. These children were more likely to be diarrhea-free at day 4 and at day 5 of intervention and passed significantly fewer stools. Gastro-Fix is can be used in infants with diarrhea and provided the nutritional needs during this period.

## 6- CONFLICT OF INTEREST: None.

## 7- ACKNOWLEDGMENT

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