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COMPARISON BETWEEN EFFICACY OF PRO-BIOTICS AND ZINC SUPPLEMENTATION IN PREVENTION OF ACUTE WATERY DIARRHEA IN CHILDREN UNDER 5 YEARS

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Abstract

Objective: *To compare the efficacy of oral pro-biotics and zinc supplementation given to children less than 5 years of age for prevention of acute watery diarrhea by studying the mean duration and frequency of the disease*

Study Design: *Randomized controlled trial*

Place and Duration of Study: *Department of Pediatrics, Combined Military Hospital, Rawalpindi from Jan 2023-Jun 2023.*

Methodology: *Patients in Group Z received 20 mg elemental zinc as Zinc sulphate syrup per day in 4 divided doses. Patients in Group P received 2 pro-biotic tablets daily (age >1 year) mixed with yogurt or sachets mixed in milk (age <1 year). Primary variables studied were mean number of diarrhea episodes at 24-, 48- and 72-hour intervals and frequency of patients with non-resolving acute diarrhea after 72 hours.*

Results: *Mean number of diarrhea episodes at 24 hours on treatment showed 6.80±0.69 episodes in Group Z versus 6.80±0.70 episodes in Group P (p=1.00). When seen at 48 hours on treatment, mean diarrheal episodes were 3.82±0.75 in Group Z versus 6.62±0.48 episodes in Group P (p<0.001), the episodes were 0.67±0.47 in Group Z versus 3.97±0.66 episodes in Group P when observed at 72 hours (p<0.001). Number of patients still having episodes of persistent diarrhea were 03 (3.3%) Group Z versus 32 (35.6%) in Group P when seen after 72 hours on treatment*

Conclusion: *Zinc supplementation results in decreased stool frequency, better recovery, less hospital stay, and better satisfaction rates compared with pro-biotic supplementation.*

INTRODUCTION

Diarrhea remains one of the major contributors to childhood debility and mortality especially in the developing countries[1]. According to recent estimates, it accounts for 1.6 million deaths in children less than 5 years of age[2]. The incidence has been steadily declining in the developed world due to improved healthcare, childhood nutrition and control against childhood gastric diseases but it still accounted for 9% of all childhood deaths under the age of 5 years according to UNICEF estimates[3]. According to the standard definition, childhood diarrhea is defined as more than 3 stools in 24 hours[4]. It results in severe dehydration and electrolyte imbalance resulting in weakness, lethargy, failure to tolerate feeds and maybe associated with other gastrointestinal symptoms like vomiting and cramps[5]. The disease follows an acute course and

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rapidly progresses if left untreated. It is imperative that the best possible and effective care be provided to ensure early patient recovery.

The addition of zinc supplementation has been proposed to improve the stability of the gut mucosa and improve the absorption of water and minerals through the intestines. Its immunomodulatory role in prevention of gut infection and resistance against bacteria and viruses has been documented extensively[6]. Zinc deficiency plays a key role in diarrhea in children and its early supplementation is proposed to decrease the acute phase and prevention of chronic diarrhea in children. Pro-biotics contain essential gut flora and microorganism thought to act as a defense and barrier in the intestinal mucosa to bacterial, viral, and fungal infections[7]. Their role in children have been an area of interest in the last decade but studies done have shown disparity in their efficacy in limiting and preventing diarrhea in children[8].

Whether or not these treatment options are effective in controlling the frequency and sequelae of diarrhea in children form the aim of our study.

METHODOLOGY:

This randomized controlled trial was carried out at the Department of Pediatrics, Combined Military Hospital Rawalpindi from Jan 2023-Jun 2023 after approval from the ethical review board vide letter no. The sample size for two groups was calculated keeping the confidence interval at 95%, power of test at 80% with mean difference of diarrhea persistence between both groups, one receiving zinc supplementation and once receiving pro-biotics being 36.12±4.56 hours[9]. Minimum sample size for one group came out to be 61 (population variance 5000). We assessed 200 patients for eligibility and included 90 patients in each group, one to receive zinc supplementation and once to receive pro-biotics supplementation after randomization using non-probability consecutive sampling via lottery method.

Inclusion criteria included all children less than 5 years of age presenting with acute diarrhea (>3 episodes in 24 hours) with moderate or severe severity.

Exclusion criteria included patients less than 6 months and more than 5 years of age, history of antibiotic intake in the last two weeks, patients with congenital anomalies of the heart or gastrointestinal system, patients with advanced cardiac or respiratory compromise, patients on oxygen at admission, patients with dysentery and non-consent of the parents to be included in the study.

The study method included all patients as per the inclusion criteria furnished. The patients were randomized into two groups of 90 patients each. Group Z (n=90) to receive oral zinc supplementation and Group P to receive oral pro-biotics supplementation. The patients were initially counseled in detail about the study protocol and need for regular follow-up for the next 1 week in case of discharge <7 days and a written informed consent was taken before enrolment in the study protocol.

Patients in Group Z received 20 mg elemental zinc as Zinc sulphate syrup per day in 4 divided doses along with meals to reduce the incidence of zinc administration associated nausea and stomachache. Patients in Group P received 2 pro-biotic tablets daily (age >1 year) mixed with yogurt or sachets mixed in milk (age <1 year) containing Bifidobacterium lactis, Lactobacillus and Bifidobacterium bifidum, and Lactobacillus rhamnosus.

Primary variables studied were mean number of diarrhea episodes at 24-, 48- and 72-hour intervals and frequency of patients with non-resolving acute diarrhea after 72 hours. Mean hospital stay and median satisfaction scores to treatment tabulated on follow-up after 7 days on a 7-point Likert scale. Improvement in weight gain from baseline weight measured at admission and complications to treatment including vomiting, stomachache and cramps were recorded as secondary variables.

Demographic data were statistically described in terms of mean and SD, frequencies, and percentages when appropriate. Independent samples t-test was used to compare statistically significant means. Median values were compared

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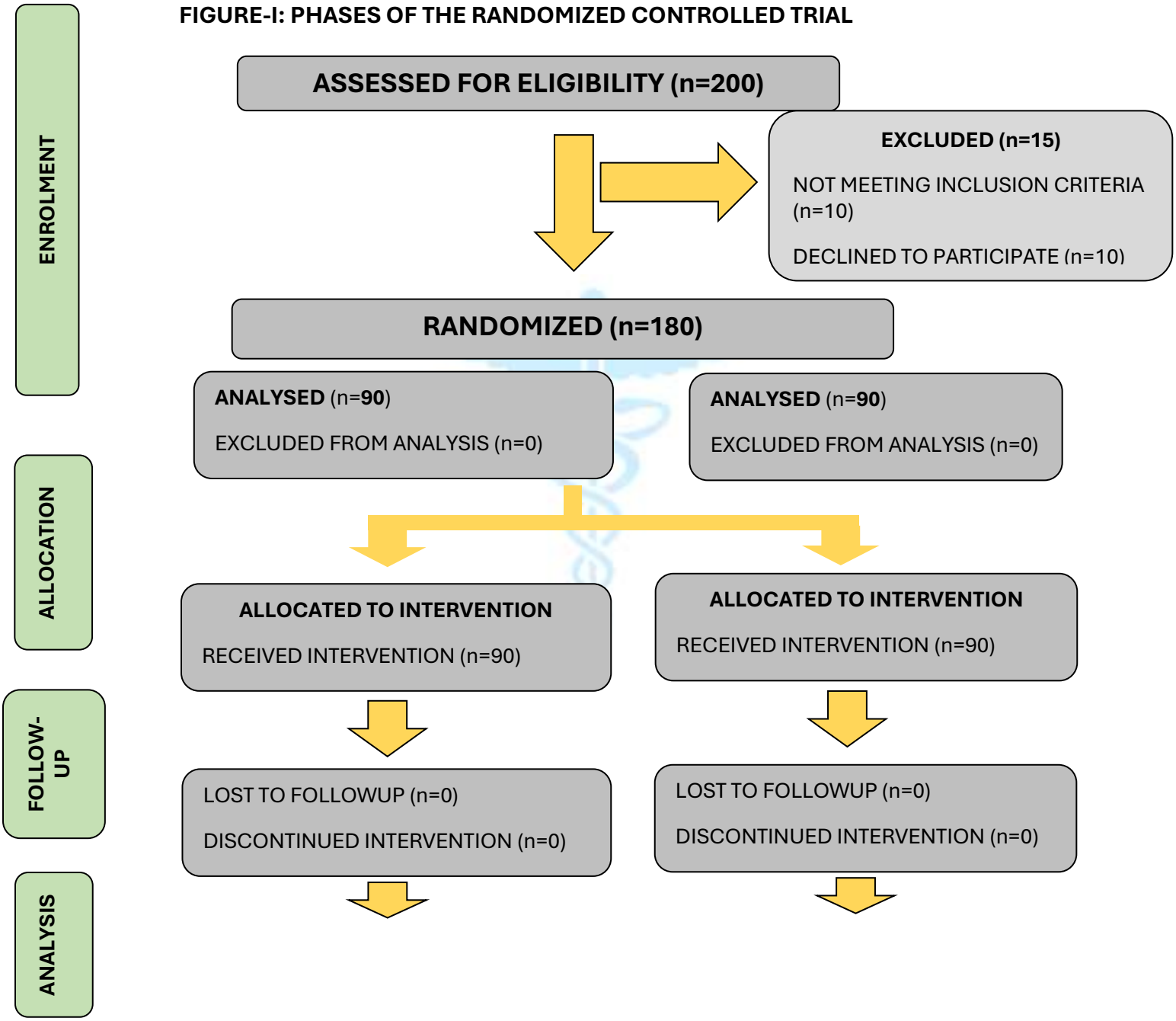
using the Mann-Whitney U test. Chi-square test was used to compare frequency variables. A p value of ≤0.05 was considered statistically significant. All statistical calculations were performed using Statistical Package for Social Sciences 26.0.

FIGURE-I: PHASES OF THE RANDOMIZED CONTROLLED TRIAL



RESULTS:

A total of 190 patients were included after assessment and randomization in two groups, Group Z received zinc supplementation (n=95) and Group P received pro-biotic supplementation. Mean age of patients was

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2.96±0.92 years in Group Z versus 2.91±0.97 years in Group P (p=0.754). Mean weight was 11.49±3.18 kg in Group Z versus 11.50±3.12 kg in Group P (0.981). Gender distribution showed 68 (75.6%) males and 22 (24.4%) females in Group Z versus 64 (71.1%) males and 26 (28.9%) females in Group P (Table-I).

Living status of the patients showed that 56 (62.2%) patients were from rural areas and 34 (37.8%) were from urban areas in Group Z versus 55 (61.1%) patients were from rural and 35 (38.9%) were from urban areas. When inquiry about the type of milk being given to the two groups, 60 (66.7%) patients were breastfed, 15 (16.7%) were on formula and 15 (16.7%) patients were consuming milk taken from anima origin in Group Z. Similarly, 45 (50%) patients in Group P were breastfed while 20 (22.2%) were on formula and 25 (27.8%) were on milk from animal origin (Table-I).

When primary and secondary variables were compared between both groups, mean number of diarrhea episodes at 24 hours on treatment showed 6.80±0.69 episodes in Group Z versus 6.80±0.70 episodes in Group P (p=1.00). When seen at 48 hours on treatment, mean diarrheal episodes were 3.82±0.75 in Group Z versus 6.62±0.48 episodes in Group P (p<0.001), the episodes were 0.67±0.47 in Group Z versus 3.97±0.66 episodes in Group P when observed at 72 hours (p<0.001). Number of patients still having episodes of persistent diarrhea were 03 (3.3%) Group Z versus 32 (35.6%) in Group P when seen after 72 hours on treatment (Table-II).

Mean hospital stay was 2.38±0.51 days in Group Z versus 5.40±0.66 days in Group P (p<0.001). Median satisfaction scores were 7.00 (IQR=1.00) on the Likert scale in Group Z versus 4.00 (IQR=1.00) in Group P (p<0.001) when tabulated 7 days post-therapy on follow-up visit. When weight gain was assessed after therapy for 72 hours, it showed mean weight gain of 1.41±0.49 kg in Group Z versus 0.84±0.23 kg in Group P (p<0.001). Treatment associated complications were seen in 03 (3.3%) patients in Group Z versus 06 (6.7%) patient in Group P (Table-II).

TABLES

TABLE-I DEMOGRAPHIC CHARACTERISITICS BETWEEN BOTH GROUPS (n=180)

VARIABLE	GROUP Z (n=90)	GROUP P (n=90)	p VALUE
MEAN AGE (YEARS)	2.96±0.92	2.91±0.97	0.754
MEAN WEIGHT (KG)	11.49±3.18	11.50±3.12	0.981
GENDER			
• MALE	68 (75.6%)	64 (71.1%)	-
• FEMALE	22 (24.4%)	26 (28.9%)	-
LIVING DEMOGRAPHIC			
• RURAL	56 (62.2%)	55 (61.1%)	-
• URBAN	34 (37.8%)	35 (38.9%)	-
TYPE OF MILK BEING GIVEN			
• BREAST-MILK	60 (66.7%)	45 (50%)	-
• FORMULA	15 (16.7%)	20 (22.2%)	-
• ANIMAL ORIGIN	15 (16.7%)	25 (27.8%)	-

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TABLE-II COMPARISON OF PRIMARY AND SECONDARY VARIABLES (n=180)

VARIABLE	GROUP Z (n=90)	GROUP P (n=90)	p VALUE
MEAN NUMBER OF DIARRHEA EPISODES			
• AFTER 24 HOURS	6.80±0.69	6.80±0.70	1.00
• AFTER 48 HOURS	3.82±0.75	6.62±0.48	<0.001
• AFTER 72 HOURS	0.67±0.47	3.97±0.66	<0.001
PATIENTS WITH PERSISTENT DIARRHEA AFTER 72 HOURS	03 (3.3%)	32 (35.6%)	<0.001
MEAN HOSPITAL STAY (DAYS)	2.38±0.51	5.40±0.66	<0.001
MEDIAN SATISFACTION SCORES TO TREATMENT	7.00 (IQR=1.00)	4.00 (IQR=1.00)	<0.001
MEAN WEIGHT DIFFERENCE FROM BASELINE MEAN WEIGHT ON ADMISSION AFTER 72 HOURS (KG)	1.41±0.49	0.84±0.23	<0.001
TREATMENT RELATED COMPLICATIONS EXPERIENCED	03 (3.3%)	06 (6.7%)	-

DISCUSSSION:

This study was carried out to assess the efficacy of the two treatment regimens and whether their proposed theoretical benefits provided any practical benefit in patients. Our study was aimed at children less than 5 years of age since they require very aggressive therapy if left untreated and better options of limiting the disease would prove beneficial in patient survival. Zinc deficiency has been implicated to cause atrophy of the thymus gland, reduced production of lymphocytes and reduced initiation of antibody responses of both the primary and secondary type resulting in widespread immune suppression and increase propensity to acquire infections[10]. Zinc has also taken importance in the early growth and pre-pubertal weight gain and linear growth of children. Intestinal ion and water secretion is the main mechanism in childhood diarrheal diseases and the use of zinc supplements can reduce the intensity and frequency of diarrhea by inhibiting intracellular pathways through various mechanism resulting in reduction in ion secretion from the intestine. The mechanism of ion channels inhibited include those controlled by AMP (adenosine monophosphate), nitric oxide, and calcium[11].

Probiotics are recommended in literature to be used to shorten the length and duration of diarrhea in children as well. The gut mucosa contains beneficial bacteria which are imperative for mucosal integrity, normal peristalsis and immune responses to infection and external stress factors. It has been seen that the balance of these gut bacteria is in a state of dis-equilibrium in children with acute and chronic diarrhea and supplementation with pro-biotics would help shorten the length and duration resulting in better patient outcomes[12]. Presently, there is no one single study that recommended the mandatory use of these supplements so we aimed to see whether our study can strengthen or refute the use of these supplementations for diarrhea in children.

Mean age and baseline weight was comparable in both groups after randomization in the study protocol. Majority of the patients in our study were of male gender. More than 50% of the patients presenting to our hospital belonged to the rural setups. When the primary variables were compared, there was a marked improvement in the frequency of stool episodes after being on treatment for 24 hours in the zinc supplementation group. The frequency decreased subsequently and there was <1 episode in the zinc supplementation group on the third day of treatment. More than 95% of the patients had complete resolution within three days of

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treatment for the zinc group. These findings were consistent with studies done by Ahmadipour et al[9] and local studies done by Shahzad et al[13] and Jabeen et al[14]. The pro-biotic group on the other hand showed a marginal improvement after the second day but more than 30% of the patients in our study still had persistent diarrhea in the pro-biotic group after 72 hours on treatment. These findings were also confirmed by Huang et al[15] which also showed modest improvements in stool frequency with pro-biotics after 48 hours on therapy but the duration was not lessened in the group. Another study done by Yang et al[16] also showed marginal improvement in frequency when pro-biotics were given in the treatment regime to treat diarrhea.

Since the frequency of stool episodes decreased in the zinc supplementation group, it was associated with a significantly shorter hospital stay, better satisfaction of the parents, early discharge and better weight gain when assessed after 7 days of therapy in the OPD. These findings are in-line with studies done to assess the same parameters by Sadiq et al[17], Maheshwari et al[18] and Kakkar et al[19]. These local studies provide important justifications for the use of zinc supplementation for good recovery, early discharge and less chances of complications when treating acute diarrhea in children. We also studied the complication profile for both groups, but they were limited to mild cramps, nausea and rarely vomiting but none severe enough to warrant cessation of therapy.

RECOMMEDATIONS:

The study recommends the use of supplemental zinc as superior to pro-biotic supplementation in limiting acute diarrhea in children.

CONCLUSION:

We conclude that zinc supplementation results in decreased stool frequency, better recovery, less hospital stay, and better satisfaction rated when compared with pro-biotic supplementation.

LIMITATIONS:

The limitations are that the study is single center only.

CONFLICT OF INTEREST:

None.

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