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Original Article

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Impact of a New Preoperative Immune-Nutrition Protocol Using Zinc on Hospital Outcomes of Children with Hirschsprung's Disease: A Novel Randomized Controlled Trial

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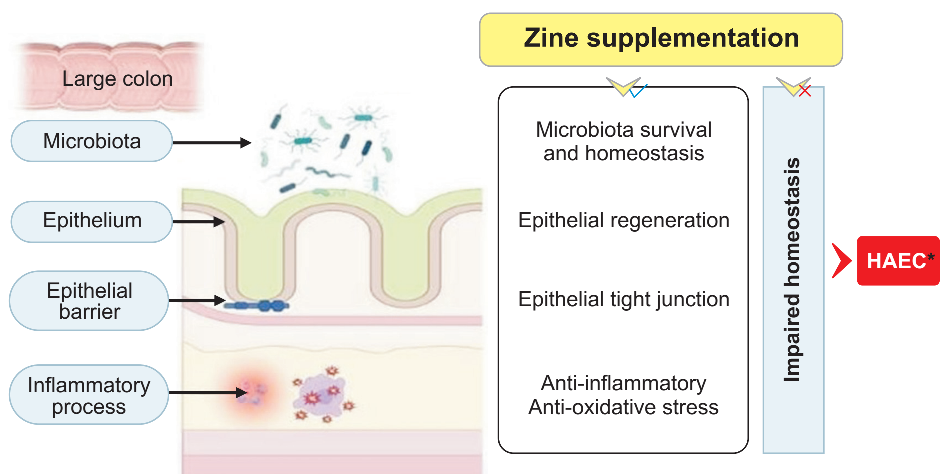

· Hirschsprung-associated enterocolitis*

ABSTRACT

Purpose: Research proved the beneficial effect of Zinc on human health and Gastrointestinal tract inflammatory diseases. We propose that zinc would be of value in children with Hirschsprung's disease (HD) undergoing elective pull-through surgery. This study was carried out to determine the influence of preoperative zinc intake on postoperative outcomes, especially the hospital length of stay in patients diagnosed with HD as a primary outcome. Other outcomes include identification of the nutritional and inflammatory status including the nutritional and inflammatory markers in children with HD with possible impacts on hospital outcomes.
Methods: This is a randomized interventional control study that was applied to 50 children diagnosed with HD who underwent elective pull-through surgery. We randomly allocated 25 diagnosed with HD who underwent elective pull-through surgery. We randomly allocated 25 patients to zinc treatment.

Conflict of Interest

The authors have no financial conflicts of interest.

AUTHORS CONTRIBUTIONS

Hoda Atef Abdelsattar Ibrahim: Conceptualization, data and results interpretation, formal statistical and clinical analyses, arranging diagnostic investigations, project methodology, project administration, supervision, data validation, visualization, literature review, manuscript drafting/writing, and editing; Sherif Kaddah: Resources and supervision; Rawan Mohamed El-Hussein Mohamed: Resources, data collection and literature review; Sayed Khedr: Resources, visualization, and supervision. All authors read and approved the final manuscript.

Results: The results demonstrated that the interventional group had a lower incidence of complications (20%) when compared to the control group (64%), with a significant *p*-value of 0.002. In addition, less incidence of Hirschsprung's associated enterocolitis (HAEC) (12% vs. 40%) and skin excoriation (8% vs. 32%) were documented in the interventional group compared to the controls respectively.

Conclusion: Pre-operative zinc supplementation may have a beneficial impact on HD children undergoing elective pull-through surgery as regards outcomes such as HAEC and skin excoriation.

Keywords: Hirschsprung disease; Enterocolitis; Zinc; Child

INTRODUCTION

Hirschsprung's disease (HD) is a neurocristopathy, an enteric nervous system developmental disorder, which is defined by the absence of ganglion cells [1]. The most noticeable initial sign is an atypical/delayed passage of meconium, which prompts additional clinical assessment and ultimately establishes the diagnosis using imaging methods and biopsy [2].

Hirschsprung's-associated enterocolitis (HAEC) remains the most common and most severe complication of HD and is a potential cause of death, with a varying incidence of 6–60% prior to surgical correction and 25–35% after [3].

Zinc can interact with gut microbiota and affect the natural course of gastrointestinal diseases. Zinc has a critical effect on homeostasis through its effect on immune system function via improving response to pathogens, and reducing inflammatory responses through interacting with cytokines release. Zinc also shows preliminary viral anti-replicative effects [4-6]. Besides, zinc is known to be the main physiological inducer of metallothionein (MT) expression which are a superfamily of the small stress-responsive proteins. The expression of MTs in different tissues (including the gastrointestinal tract [GIT]) is favored by various stimuli, including infection and inflammation. MTs act as an antioxidant and radical scavengers. Additionally, MTs have an impact on a variety of cellular functions, such as gene expression, apoptosis, proliferation, and differentiation. In humans, the MTs exist in a variety of isoforms, with MT-1 and MT-2 being particularly prevalent in the gastrointestinal tract [7-9]. The current working theory is that MTs guard against colitis. It has been discovered that MTs are often increased in a number of models of experimentally induced colitis as a response to colonic damage [10,11] and it may be crucial for controlling mucosal inflammation [12]. High-dose dietary zinc supplementation induces MT-encoding genes and increased MT-1 and MT-2 expression in the intestine. It is notable that zinc greatly induced MT2 compared to MT1. Also, it has been discovered that, in the colon, zinc supplementation was linked to a substantial impact on the gene expressions that are involved in a number of aspects of intestinal protection, including the production of mucin, the integrity of the intestinal epithelium and immune cell function. Additionally, taking zinc was linked to considerable goblet cell suppression, reduced crypt loss, diminished inflammatory infiltrates (mostly neutrophils), and minor changes in colon thickness during colitis. In that light, low serum zinc concentrations may increase inflammation via loss of the previously mentioned protective mechanisms against the increased levels of pro-inflammatory cytokines and oxidative stress, according to translational research [13,14].

Tight junctions (TJs), are junctional complexes gathered at the lateral membrane of intestinal epithelial cells and signify a key component of the intestinal barrier. Although the underlying molecular mechanisms are yet unknown, studies revealed that intracellular zinc is involved in the modulation of the intestinal TJ barrier through its significant function as a catalytic cofactor for enzymatic activity and a structural component inside particular proteins. Zinc supplementation improves transepithelial electrical resistance (TER) and mannitol flux, all of which are markers of TJ integrity. Additionally, it was demonstrated that a zinc shortage in intestinal cells results in immature differentiation and reduced TER [15,16].

The main research question is to address if preoperative zinc supplementation would have a positive effect on postoperative outcomes in children with HD. Till now, this proposed role of zinc has not been investigated, hence our study was carried out.

MATERIALS AND METHODS

This study is a parallel randomized controlled trial (RCT) study with an allocation ratio of 1:1 using a random-numbers table, that was conducted on 50 children admitted to Paediatric Surgery Department at the Children Hospital Cairo University (CHCU) who were diagnosed with Hirschsprung's disease, underwent elective pull-through surgery and followed from April 2023 to June 2023.

Inclusion criteria

Patients diagnosed with Hirschsprung's disease with rectal biopsy, whose parents or caregivers approved for the participation in the study, who had the recto-sigmoid disease (short segment) that was confirmed by contrast study and patients' selection was limited to non-customized patients. The type of surgery: trans-anal pull-through and laparoscopic-assisted endo-rectal pull-through.

Exclusion criteria

Patients with emergency situations such as acute obstruction or perforation and patients with evidence of enterocolitis or sepsis at the time of planned surgical intervention

Data collection

After the selection of the children according to the eligibility criteria, the following data was collected from each child:

Preoperative assessment

1. Preoperative sociodemographic and nutritional assessment including age in months, sex, and the anthropometric Z scores encompassing weight, height, and Body Mass Index, which were interpreted according to World Health Organization child growth standards [17-20]. The interventional group received pre-operative zinc supplementation (15 mg/day) for the immediate preceding 7 days before the elective surgeries [21,22], flow chart of the study (**Fig. 1**).

2. Preoperative clinical assessment including history taking e.g., past history of Hirschsprung-associated enterocolitis and abdominal examination for abdominal distension with a digital rectal exam.

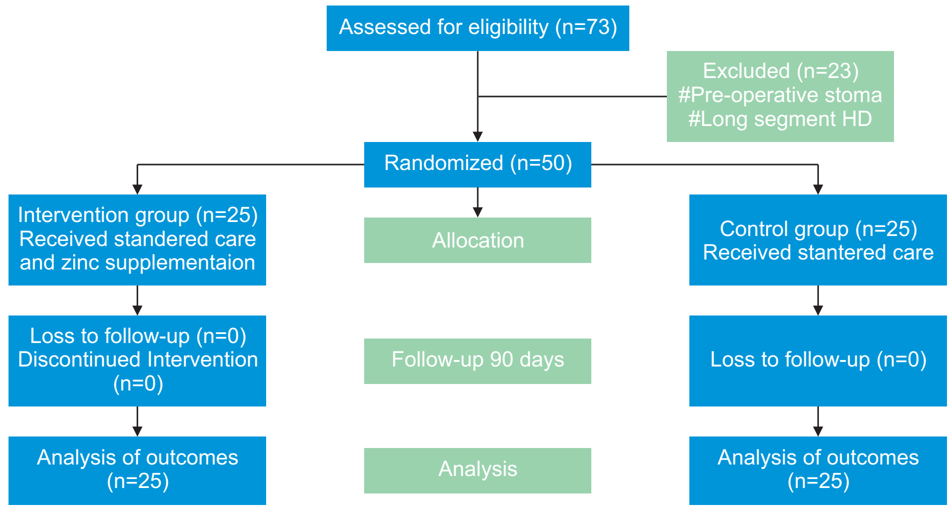

Fig. 1. Flow chart of the study.
HD: Hirschsprung's disease.

3. Preoperative biochemical nutritional and inflammatory markers including: CBC, albumin, C-reactive proteins (CRP), and CRP/albumin ratio as prognostic factors for the outcome.

Measurement of prognostic nutritional index (PNI), The Glasgow prognostic score (GPS), neutrophil-lymphocyte ratio (NLR), and platelets lymphocyte ratio (PLR) as inflammation-based prognostic scores.

Operational definitions

1. The PNI was evaluated and calculated as 10×albumin+0.05×the lymphocytes count [23].

2. The GPS was identified based on CRP and albumin. Children with elevated CRP (>0.3 mg/dL) and low serum albumin (<3.5 mg/dL) were assigned a score of 2. Children with either one of these 2 laboratory outliers were assigned a score of 1. Children with neither of these laboratory outliers were assigned a score of 0 [24].

3. The NLR was calculated as the absolute neutrophil count divided by the absolute lymphocyte count [25].

4. The PLR was calculated as platelet count divided by absolute lymphocytic count [26].

Operative technique

The operative management of HD was in the form of trans-anal pull-through or laparoscopic-assisted endorectal pull-through. The level of aganglionosis was confirmed by frozen section pathology and also with gross identification of the funnel in laparoscopic-assisted pull-through.

Postoperative assessment including in-hospital follow-up after surgery to record any complications including duration of hospital length of stay and outpatient-clinic follow-up to record late complications. Complications included postoperative skin excoriation, postoperative anastomotic leak, and development of HAEC, whose diagnosis was based on the score of 4 proposed by Frykman [27]. Clinical grading of HAEC was observed, which was based on history, physical examination, and imaging studies as proposed by Gosain [28].

Quality service improvement

Parents are instructed to pay attention to the development of any features that suggest the development of HAEC as fever, vomiting, abdominal distension, the passage of fluid offensive stool, and lethargy.

Outcome measures

For the primary outcome, the hospital length of stay was measured in days and compared between the interventional and control groups. In addition, frequencies of postoperative complications including HAEC were observed and compared between the two groups. For the secondary outcomes, the anthropometric Z scores were evaluated and interpreted. Moreover, the preoperative biomarkers were assessed and correlated with the postoperative outcomes as the hospital length of stay.

Sample size calculation

The primary objective of the study was to assess the effect of zinc supplementation on postoperative outcomes by measuring postoperative hospital length of stay, Rerksuppaphol et al. [29] reported that patients who received zinc supplementation had a mean hospital stay duration of 3.8±1.3 days compared to 6.1±3.2 days in control patients who received placebo. By setting α as 0.05, power of 0.80, and confidence level of 95%, and using the following formula:

$$n = \frac{\left(Z_{\frac{\alpha}{2}} + Z_{\beta}\right)^2 \times 2\sigma^2}{d^2}$$

Where $Z_{\alpha/2}$ was the critical value of the normal distribution at α/2 (e.g. for a confidence level of 95%, α is 0.05 and the critical value is 1.96), Z_β was the critical value of the normal distribution at β (e.g. for a power of 80%, β is 0.2 and the critical value was 0.84), σ^2 was the pooled standard deviation, and *d* was the difference between the two means.

The minimum required sample size was 20 patients per group, by adding 25% of the sample size as expected follow-up losses, then the required sample size for the study was 25 patients per group.

Statistical analysis

Data were statistically described in terms of mean±standard deviation for parametric data, median and interquartile range for non-parametric data, or frequencies (number of cases) and percentages when appropriate. Tests of normality were done for all the numerical variables. The comparison of numerical variables between the study groups was done using Mann-Whitney U-test for non-parametric data. For comparing categorical data, Chi-square (χ^2) test, and Fisher's exact test were performed. Spearman correlation was performed and receiver operator characteristic (ROC) curve was done to detect sensitivity and specificity. Logistic regression was done to detect significant predictors. Two-sided *p*-values less than or equal 0.05 was considered statistically significant [30-32]. All statistical calculations were done using computer program using IBM SPSS Statistics for Windows, Version 25.0 (IBM Co.).

Clinical trial registration

The protocol of the study was registered on ClinicalTrial.gov with ClinicalTrials.gov Identifier: NCT05785013.

Ethical approval

The present study was carried out according to the principle of Helsinki. The study protocol was revised and approved by the Scientific Committee of the Surgical Department at Cairo University. The study protocol was revised and approved by the local ethics committee of Cairo University. The ethical approval number is MS 277-2022. Informed consent was obtained from each parent or caregiver.

RESULTS

Numerical data were tested for normality

Table 1 shows that most of the data were non-parametric. Age, hospital length of stay, and biochemical lab assessment (except albumin and PNI) were not normally distributed (*p*-value≤0.05).

Table 2 shows the sociodemographic and clinical criteria of the study participants, including matching cases (interventional group) with controls

The median age of the study participants was 7 months with no significant difference between the interventional and control groups (*p*-value=0.465). Besides, the male gender predominates in our study with no significant difference in the gender distribution between the interventional and control groups (*p*-value=0.107). As regards the possible risks for the development of HAEC, two risk factors are compared between the two groups. First, malnutrition generally occupies a considerable number in our study with no statistically significant difference between the two groups (*p*-value=0.087). In addition, a statistical (*p*-value=0.017) and a clinically significant difference was found between the interventional and control group as regards the presence of a past history of HAEC that was more prevalent in the interventional group, the observation which is of value as the incidence of postoperative HAEC was significantly less in the interventional group compared to the control as illustrated in **Table 3** (*p*-value=0.024). This observation may disclose the impact of preoperative zinc supplementation as it seems that the interventional group was riskier for the development of postoperative HAEC (as the past history of HAEC predominated in them) and despite this risky feature, they developed fewer frequencies of postoperative HAEC as compared to the control group.

Table 3 shows the hospital outcomes of the study participants

Generally, postoperative complications predominated significantly in the control groups as compared to the interventional group (*p*-value=0.002). Specifically, frequencies of HAEC and skin excoriations were more in children within the control group (*p*-value=0.024 vs. 0.034

Table 1. Examination of the numerical data of interest for normality to detect the suitable statistical tests

Numeric data of interest	*p*-value*	Reject null or fail to reject	Distribution
Age	<0.001	Reject null hypothesis	Non-parametric
Hospital length stay in days	<0.001	Reject null hypothesis	Non-parametric
NLR preoperative	0.007	Reject null hypothesis	Non-parametric
PNI preoperative	0.2	Fail to reject null hypothesis	Parametric
Plat to lymphocyte ratio preoperative	0.002	Reject null hypothesis	Non-parametric
Albumin preoperative	0.2	Fail to reject null hypothesis	Parametric
CRP preoperative	<0.001	Reject null hypothesis	Non-parametric
CRP/albumin preoperative	<0.001	Reject null hypothesis	Non-parametric

NLR: neutrophil-lymphocyte ratio, PNI: prognostic nutritional index, CRP: C-reactive proteins.
A statistically significant test result (*p*≤0.05) means that the test hypothesis is false or should be rejected.
*The significance of the Kolmogorov-Smirnov test for normality.

Table 2. The sociodemographic and clinical Criteria of the study participants, including matching cases with controls

Sociodemographic Criteria of the study participants			
Age (mo), median (IQR)	7 (20)		
Minimum–Maximum	1–54		
Sex distribution of the study participants			
Male	37 (74.0%)		
Female	13 (26.0%)		
Distribution of malnutrition among the study participants			
Coexistence of malnutrition	28 (56.0%)		
Absence of malnutrition	22 (44.0%)		
Types of malnutrition: the patient may have more than one type			
Underweighting	15 (34.0%)		
Short stature	19 (43.0%)		
Wasting	10 (23)		
Matching the interventional group with controls			
Studied variable	Interventional group	Control group	p-value
Age, median (IQR)	11 (24)	7 (16)	0.465†
Sex			
Female	9 (36.0%)	4 (16.0%)	0.107‡
Male	16 (64.0%)	21 (84.0%)	
Risk factors for subsequent HAEC (Co-existence of malnutrition and past history of HAEC as risk factors)			
Coexistence of malnutrition	17 (68.0%)	11 (44.0%)	0.087‡
Absence of malnutrition	8 (32.0%)	14 (56.0%)	
Presence of past history of HAEC	9 (36.0%)	2 (8.0%)	0.017*,‡
Absence of past history of HAEC	16 (64.0%)	23 (92.0%)	

Values are presented as median (interquartile range) or number (%).
HAEC: Hirschsprung's associated enterocolitis.
*A statistically significant test result when ($p \leq 0.05$). †Mann-Whitney test. ‡Chi-square test.

Table 3. The hospital outcomes of the study participants

Studied variables among the study participants	Intervention group (n=25)	Control group (n=25)	p-value
Development of any postoperative complication in general	5 (20.0%)	19 (76.0%)	0.002*,†
Post-operative HAEC	3 (12.0%)	10 (40.0%)	0.024*,†
Grade of enterocolitis			
Grade 1	3 (100.0%)	6 (60.0%)	0.497‡
Grade 2	0 (0.0%)	4 (40.0%)	
Skin excoriation	2 (8.0%)	8 (32.0%)	0.034*,†,‡
Anastomotic leak	0 (0.0%)	1 (4.0%)	0.312‡
Post-operative hospital length of stay in days, median (IQR): N.B: The effect Size regards the postoperative length stay is moderate to large (0.6)	7 (4.88)	5 (3.5)	0.146

Studied variables among the malnourished children	Intervention group (N=17)	Control group (N=11)	p-value
Development of any postoperative complication in general	3 (17.6%)	9 (81.8%)	0.001*,‡
Development of HAEC	1 (5.9%)	5 (45.5%)	0.012*,‡

Values are presented as median (interquartile range) or number (%).
HAEC: Hirschsprung's associated enterocolitis.
*Statistically significant at $p \leq 0.05$, The effect size was detected using G*Power version 3.1. †Chi-Square test.
‡Fisher's exact test.

respectively). On the other hand, durations of postoperative hospital length of stay didn't seem to differ significantly between the two groups (p-value=0.146). However, it shows a

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moderate effect size which means a moderate practical application. Unlike significance tests, effect size is independent of sample size. Therefore, it may be worth mentioning here [33].

Notably, the outcomes were observed within the malnourished children. Out of the total malnourished children in each of the interventional and control groups, the proportion of the control children who developed postoperative complications including HAEC was higher than the case in the interventional group with significant differences as shown in **Table 3**.

As a trial to detect the possible covariates and predictors for longer postoperative hospital length of stay among children with HD in our study

Spearman correlations were done between the preoperative nutritional and inflammatory markers and the duration of hospital length of stay as shown in **Table 4**. Furthermore, the hospital stay was dichotomized into short and long stays according to the median hospital stay (5.5 days) to detect predictors of prolonged length of hospital stay (PLOS) using the logistic regression model as shown in **Table 4**. Out of the preoperative labs, preoperative GPS, PLR, and CRP showed positive significant linear correlation, negative significant linear correlation, and positive significant linear correlation respectively. Upon investigating these significant covariates through logistic regression to detect predictors of prolonged length of hospital stay, PLR was the only significant predictor (*p*-value=0.044). To detect the cut-off value of PLR for PLOS, ROC analysis was done which revealed the highest sensitivity and specificity at 107.8 with a *p*-value of 0.011, **Fig. 2** shows the ROC curve.

Table 4. A: Correlation between some variables and postoperative hospital stay in days of the studied patients
B. Logistic regression of significant covariates for prediction of possible predictors of prolonged length of hospital stay (PLOS)
C. Sensitivity and specificity of preoperative platelet to lymphocyte ratio for in detection of prolonged postoperative hospital stay

A. Correlation between some variables and postoperative hospital stay in days of the studied patients

Studied variable	Postoperative hospital stay in days	
	rs	*p*-value
Preoperative NLR	−0.024	0.870
Preoperative PNI	−0.061	0.675
Preoperative GPS	0.276	0.050*
Preoperative platelet to the lymphocytic ratio	−0.308	0.029*
Preoperative CRP	0.278	0.050*
Preoperative albumin	−0.049	0.516
Preoperative CRP/albumin ratio	0.268	0.060

B. Logistic regression of significant covariates for prediction of possible predictors of (PLOS)

	Exp (B)	Wald	*p*-value	Odds ratio	95% CI for odds ratio	
					Lower	Upper
Preoperative GPS (1)(reference)	4.3	1.769	0.183	0.127	0.006	2.661
Preoperative GPS (2)	5.2	0.390	0.532	0.446	0.036	5.608
Preoperative platelet-to-lymphocyte ratio	0.98	4.067	0.044*	0.973	0.947	0.999
Preoperative CRP	1.02	0.223	0.637	1.021	0.937	1.112

C. Sensitivity and specificity of preoperative the significant predictor, platelet to lymphocyte ratio, for in detection of prolonged postoperative hospital stay

Platelet to lymphocyte ratio	AUC	*p*-value	Cut off point	Sensitivity	Specificity	95% CI	
	0.71	0.011*	107.8	88%	56%	0.566	0.855

NLR: neutrophil-lymphocyte ratio, PNI: prognostic nutritional index, GPS: Glasgow prognostic score, CRP: C-reactive proteins, AUC: area under the curve, rs: Spearman correlation, CI: confidence interval, PLOS: prolonged length of hospital stay.
*Statistically significant at $p \leq 0.05$.

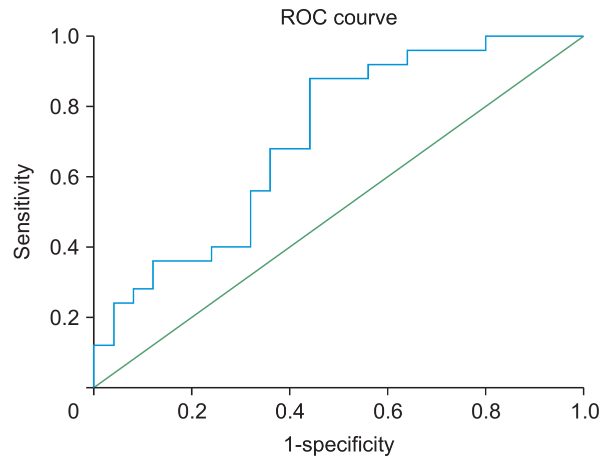

Fig. 2. ROC curve for PLR regarding PLOS.
ROC: receiver operator characteristic, PLR: platelet-to-lymphocyte, PLOS: prolonged length of hospital stay.

DISCUSSION

Our study was a randomized interventional control study that was carried out to explore the effect of the application of a new preoperative immuno-nutrition-based preventive strategy using zinc for children with HD. Zinc may have a role in the alteration of the gut microbiota which is known to be one of the recommended preoperative protocols for nutrition optimization prior to surgery [34,35]. This was sounded in our study as it seems that zinc supplementation might decrease the risk of HAEC in the interventional group significantly compared to controls. The results of several previous randomized clinical studies yielded that zinc decreases the time period and severity of prolonged diarrhea [36,37]. It is proven that zinc can improve the absorption of water and electrolytes, the early regeneration of gastrointestinal mucosa, the renewal of enteral enzymes, and can increase both humeral and cell immunity. Therefore, this can be the reason for the significantly lower levels of zinc in patients with enterocolitis compared to those in healthy controls in preceding research [38]. Furthermore, the occurrence of enterocolitis was significantly higher in the control group who didn't receive zinc supplementation in former studies [39,40].

In our study, postoperative complications didn't only include HAEC, but also included skin excoriations in 20% of the enrolled participants. Comparative analysis may disclose the impact of oral zinc supplementation as the interventional group had significantly lower frequencies of skin excoriations compared to controls. Skin bioavailability of the dietary zinc has been studied by Richelle in 2006 and Souyoul in 2018 [41,42]. Zinc can play an essential role in three skin functions such as morphogenesis, repair, and maintenance which can deliver defense and protection through the proteins and enzymes which are involved in these processes [43].

The effect of preoperative zinc supplementation on the hospital length of stay was desired to be outlined in our current study which revealed longer periods of hospitalizations in the control group compared to the interventional one though the difference was not statistically significant, yet of practical implication. Many studies examined the effect of zinc supplementation on the hospital length of stay of the admitted children which may have contrary results to ours [44,45]. However, our study may be the first to examine its role in the field of surgery regards the postoperative hospital length of stay. The absence of agreement may be attributed to practice style differences among hospitals and physicians and the effect of surgery [46].

Malnutrition is predominant among children with HD. It was observed that malnutrition may be a silent epidemic; >15% of pediatric patients with HD had malnutrition on admission for primary surgery [47]. This result was close to ours as a considerable number of children were malnourished

Despite the burden of malnutrition in the enrolled children, zinc supplementation may have a role in ameliorating their clinical outcomes in terms of HAEC, a closely stated finding [48]. In other words, malnourished children who received preoperative zinc supplementation experienced less frequencies of HAEC, compared to controls in our study. Therefore, we can suppose that zinc supplementation can prevent undesirable postoperative outcomes in malnourished children.

Laboratory markers' use for prognostication in the surgical field is a hot and new area in the current research. They have been examined on how to help predict the progression and the outcome. Numerous biomarkers were identified to reflect the severity of the underlying inflammatory diseases, the host reactions, and the immune response of children [49-53]. The platelet-to-lymphocyte (PLR) ratio is an interesting example of these markers. Low values were addressed to be associated with undesirable outcomes as recently found [54]. This is sounded in our study as PLR values were significantly inversely correlated with the hospital stay of length.

Another laboratory marker is the inflammation-based Glasgow prognostic score (GPS) that was developed by Forrest et al. [55] consisting of two simple components: serum levels of CRP and albumin. GPS was not only incorporated in cancers but was also involved in other fields as sepsis [55-57]. Our study explored the impact of preoperative GPS which was significantly correlated with postoperative hospital length of stay, suggesting its promising role as a preoperative marker in children with HD.

Strength of the study

To the best of our knowledge, our study may be the first to explore the effect of preoperative zinc supplementation on postoperative outcomes of elective surgeries for children diagnosed with HD. Besides, nutritional and inflammatory markers including GPS and PLR are outlined in our study through which GPS and PLR may be considered as nutritional and inflammatory biomarkers in the pediatric surgical field including HD. In addition, carrying out the study in one hospital removes any bias due to differences in hospital practices and postoperative care.

Study limitations

One major limitation is the absence of laboratory zinc levels due to the absence of availability in the study setting. However, we clinically excluded infants and children with zinc deficiency based on the known symptoms as diarrhea, bilateral symmetrical eczematous skin rash, and hair loss [58].

Recommendation

Our study may recommend the importance of preoperative zinc supplementation as adjuvant prophylactic therapy in children with HD. GPS and PLR may be used in risk stratification in these children.

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Conclusion

Zinc may have a great role at the level of GIT and skin microbiota through which the interventional group had lower frequencies of postoperative HAEC and skin excoriation. This may increase the awareness of surgeons about the importance of zinc supplementation preoperatively in infants and children with Hirschsprung disease. Prediction of other postoperative outcomes as PLOS could be outlined using GPS and PLR.

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