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Effect of Glutamine Enteral Supplementation in Post-Operative Intestinal Obstruction Neonates: A Randomized Control Trial

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Abstract: Surgical treatments targeted for infants suffering congenital intestinal obstruction are advantageous to increase clinical outcomes. However, the post-surgical period might encourage them to depletion of glutamine (Gln). This study aims to evaluate the efficacy of Gln to supply feeding requirements for infants during post-gastrointestinal tract surgical recovery. It was conducted in infants with congenital anomalies involving gastrointestinal (GI) and undergoing surgery using a double-blind, randomized trial design. The population was divided into control and trial groups. Afterward, the comparison of outcomes following the intervention is analyzed to determine the benefits of Gln supplementation. Eighteen of 20 infants were diagnosed with a congenital malformation that involved the GI tract after birth. As reported in 10 infants, anorectal malformation accounted for most of the types of malformations. There was no significant difference in clinical outcomes shown by infants supplied with Gln enteral diet and those who were not, in their birth weight and median time to full-enteral feeding (FEF). Enteral nutrition support using Gln enriched diet does not improve feeding tolerance for infants with congenital GI anomalies during post-surgical care. Concerning the novelty, this study found that the effect of Gln supplementation on babies undergoing GI surgical management is not significantly different from placebo.

Keywords: birth weight, infants, full enteral feeding, glutamine, placebo.

谷氨酰胺腸內補充劑對術後腸梗阻新生兒的影響：一項隨機對照試驗

摘要：針對先天性腸梗阻嬰兒的手術治療有利於提高臨床結果。然而，手術後時期可能會促使他們消耗谷氨酰胺。本研究旨在評估谷氨酰胺在胃腸道手術後恢復期間為嬰兒提供餵養需求的功效。它是在患有涉及胃腸道的先天性異常並使用雙盲、隨機試驗設計接受手術的嬰兒中進行的。人群被分為對照組和試驗組。然後，分析干預後結果的比較，以確定補充谷氨酰胺的益處。二十名嬰兒中有十八名被診斷出患有出生後涉及胃腸道的先天性畸形。據報導，在十名嬰兒中，肛門直腸畸形佔大多數畸形類型。接受谷氨酰胺腸內飲食的嬰兒與未接受谷氨酰胺的嬰兒的出生體重和全腸內餵養的中位時間在臨床結果上沒有顯著差異。在術後護理期間，使用富含谷氨酰胺的飲食進行腸內營養支持不會提高先天性胃腸道異常嬰兒的餵

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養耐受性。關於新穎性，本研究發現補充谷氨酰胺對接受胃腸道手術治療的嬰兒的影響與安慰劑沒有顯著差異。

关键词：出生體重、嬰兒、全腸內餵養、谷氨酰胺、安慰劑。

1. Introduction

Neonatal intestinal obstruction, caused by a mechanical impediment in digestive tract anatomical structures, may impinge on the intestinal motility and present pertinent clinical presentations, namely recurrent bilious vomiting, subtle abdominal distention, and inability to excrete meconium on the first day of life [1]. The latter are subject to the anatomical site of obstruction and the blockage degree [2]. Congenital intestinal obstruction serves as a common surgical emergency in newborn infants [3]. Of all obstruction types, anorectal malformation, esophageal obstruction, and duodenal obstruction become the most prevalent [3, 4].

The supplementation of Glutamine (Gln) is assumed to benefit intestinal mucosal protection and promote the immune system [5, 6]. Moreover, on account of the endogenous synthesis of Gln that may not suffice to meet the increased demand in critically ill patients, Gln could be taken into account as an essential amino acid [7]. Nonetheless, a report from an animal study has shown that oral GLN could not forestall bacterial translocation in rats with intestinal obstruction in which *the Escherichia coli* challenge was in place. Furthermore, there was no specific organ protected by Gln supplementation [8]. Therefore, this randomized control trial study aims to investigate the effect of Gln-supplemented enteral nutrition on feeding tolerance and weight gain in infants with mechanical intestinal obstruction who have undergone surgical procedures.

2. Materials and Methods

With a double-blind, randomized trial design, this experimental study was carried out between May 2020 and January 2021 in the Neonatal Intensive Care Unit (NICU) at Dr. Soetomo General Hospital Surabaya. This study enrolled a sample that comprised infants with mechanical intestinal obstruction who had received surgical procedures at Dr. Soetomo General Hospital based on eligibility criteria. The inclusion criteria applied in this study were infants whose body weight was more than 2000 grams, gestational age of more than 35 weeks, and those with consent approval by the guardians. The exclusion criteria were infants with multiple congenital abnormalities, infants with coexisting sepsis, and those with complications following surgical procedures. Meanwhile, the dropout criteria of this study were infants who presented feeding intolerance, infants whose guardians withdrew their consent, or infants who died during the study period. The sample size of this study was determined using quota sampling, which was to recruit ten samples each for the respective group. The subjects were divided into two groups, the trial group and the control group. The trial group received breast milk supplemented with capsules containing Gln with a dose of 400 mg/kg/day from the initial day of enteral feeding tolerance to the day on which full-enteral feeding had been reached.

On the other hand, the control group received breast milk supplemented with placebo capsules containing 400 mg/kg/day of glucose from the initial day of administering enteral feeding to the day the infants had developed full-feeding tolerance. Weight accretion was observed in each enrolled infant during the administration of either Gln supplemented capsule or placebo capsule. Daily body weight measurements were performed in recruited infants since obtaining approval from the guardians until the enrolled infants had culminated in full-enteral feeding tolerance. Before the study conduction, ethical approval was gained from the Ethics Committee of Dr. Soetomo General Hospital (Ethics Committee Approval Number: 1888/KEPK/III/2020), which complied with the principles of Helsinki.

The guardians gave their informed consent ahead of their inclusion in the study. Before signing the informed consent form, information on informed consent was given. In this study, the SPSS version 21 program for Windows IBM., Corp., Armonk, NY, USA) was used to analyze the data. At first, the analysis of subjects' characteristics was determined by Chi-square, Mann-Whitney, and Fisher Exact test. Then, to assess the normality of the samples, we ran Shapiro-Wilk.

Regarding the analysis aiming to compare the babies' birth weight before and after the administration of placebo and glutamine, we conducted one way ANOVA test and compared means commands. Meanwhile, the control group, babies given a placebo, was also evaluated for their birth weight during pre and post administration of the placebo. The independent-test command was used to compare babies' birth weights from both placebo and control groups. The p-value must be less than 0.05 to determine the significant increase of BW in both groups.

Furthermore, the median time needed for full enteral feeding was compared in both groups by using cox

regression analysis. If the p-value is less than 0.05, the difference will be considered significant.

3. Results and Discussion

As shown in Table 1 that indicates the subjects' characteristics, the intervention and control groups consist of 10 subjects per group. Of the 20 subjects recruited in this study, almost all babies were male (90%). There were eight babies born via cesarean section. From the total population, two babies were identified with anomalies during the antenatal diagnosis procedure, while the other 18 babies had anomalies diagnosed after birth. Concerning the types of anomalies found, suffered by 12 of 20 babies, the most common congenital disorder was anorectal malformation with rectourethral fistula. Another common congenital anomaly, namely duodenal obstruction, was also reported in three babies. Collectively, subjects in this study were born at term (Mean = 38.35 weeks of gestational age), with excellent APGAR score (Mean = 7.95), and had normal birthweight (Mean = 2885 grams). Infants receiving Gln enriched diet were initiating and attaining the supplementation at a younger age than infants from the placebo group.

Table 1 Baseline characteristics

Parameters	**n/Mean**	**(%)/ SD**
Intervention	10	50
Control	10	50
Sex		
Male	18	90
Female	2	10
Delivery		
Vaginal Birth	12	60
Cesarean Section	8	40
Diagnostic Establishment Period		
Anorectal Malformation without Firstly	10	50
Anorectal Malformation with Perineal Firstly	1	5
Anorectal Malformation with Rectourinary (RU) Firstly	2	10
Down Syndrome + Anorectal Malformation + RU Firstly	1	5
Down Syndrome + Duodenal Obstruction	1	5
Duodenal obstruction	3	15
Duodenal Web	1	5
Gastric Outlet Obstruction	1	5
APGAR Score in 5th minute	7.95	0.76
Gestational Age (Weeks)	38.35	0.87
Body Weight (gram)	2885	456.85
Age when initiating enteral Gln (days)		
Intervention group	8	7.26
Placebo group	15	21.6
Age when attaining (days)		
Intervention group	14	7.83
Placebo group	21.6	13.14

Before starting the bivariate model analysis to compare the birthweight of babies during pre and post-interventions of placebo and Gln enriched enteral feeding, the normality of data was evaluated. Throughout the statistical program, the identified variables had been distributed normally (Table 2).

Table 2 Birth weight

	Gln Supplementation	**Placebo Supplementation**	**p-value**
Birth Weight (g) [before intervention]	2858.70 $\pm$ 372.03	2915.90 $\pm$ 437.99	0.84
Birth Weight (g) [after intervention]	2949.80 $\pm$ 449.45	3028.10 $\pm$ 468.43	0.86

Table 3 Full-enteral feeding (hazard risk = 1, no significant association between Gln-enriched nutrition with median time to FEF)

	Gln	**Placebo**	**HR (95%CI)**	**p-value**
Time to FEF (days)	6.5 (3-10)	6 (4-12)	1.157 (0.47, 2.85)	0.75

Then, the statistical program that would be used to further analyze the differences in birth weight was paired t-test. On both groups of control and intervention, according to Table 3, it was found that there were no significant differences in babies' birth weight before administering the placebo and glutamine (p-value = 0.84), nor the birth weight changes after being given both placebo and glutamine (p-value = 0.86), respectively. Another comparison to evaluate the differences of birth weight increase in both intervention and control groups by performing an independent t-test resulted in the higher birth weight significantly seen in the control group. Meanwhile, concerning the median time required to obtain full-enteral feeding, the intervention group needed a shorter period (SD = 3-10 days) than the control group (SD = 4-12 days). However, the difference was not significant (p-value = 0.75).

Our previous study on Indonesian infants with low birth weight had reported the efficacy of enteral Gln supplementation to accelerate birth weight increase velocity, encouraging return to optimum birth weight [9]. We intend to use Gln enteral nutrition to promote better clinical outcomes showed by infants undergoing post-surgical care through this study. After that, Gln depletion elevation is induced by the limitation of intestinal reserves and fasting period during surgical actions. In consequence, Gln synthesis cannot exceed consumption and lead to the high demands of Gln supplementary [10]. Nonetheless, this study revealed no significant benefit of the Gln enteral diet in increasing the birth weight of infants with surgical GI diseases. Even the group of infants not given a Gln enriched diet t experienced the same increase in their birth weight as the control group instead. There are still plenty of previous studies that addressed the efficacy of a Gln enriched diet on infants with GI tract problems

before and after surgery. Gln supplementation unexpectedly turns out to be more beneficial in children and teenagers with short bowel syndrome following intestinal resection or dysfunction. A study in China on children suffering from short bowel syndrome found that the exogenous treatment using Gln and growth hormone supplementation could improve the growth parameters of patients aged 2 to 17 years old, indicated by the increase in participants' body weights [11]. Moreover, another meta-analysis performed to determine the benefits of Gln supplementation for adult patients following surgery due to GI cancer provided evidence that Gln enteral supplementation may benefit patients by reducing the infection rate and length of hospital stay [10]. In addition, a control trial study implies that Gln supplementation is effective in shortening the length of hospital stay for adult patients undergoing gastrointestinal surgery [12].

Our study also did not find any benefit of nutritional support using the Gln diet to shorten the period needed to start enteral feeding. Then, this finding supports a study done by Ong et al. [13] that showed no significant difference in the amount of time to first and full enteral feeding witnessed in participants consist of post GI surgical infants aged less than three years old [13]. Also, similar results of a randomized clinical trial in the Netherlands had reported no increase in time to full enteral feeding, nor improving the feeding tolerance in very low birth weight infants after administering Gln-enriched enteral nutrition [14]. In contrast to our findings, Vaughn et al. [15] and Neu et al. [16], examining enteral Gln supplementation, reported the benefits of Gln supplementation could induce a better tolerance to enteral feedings, decreasing the number of days of restraining full enteral feeding. However, these two studies not directly reported the time to reach full enteral feeding. The failures of achieving full enteral feeding were associated with gestational age < 32 weeks, low birth weight, and male sex [15].

4. Conclusion

To infer, this study of Gln supplementation in babies with congenital GI diseases after the surgical management utterly address the insignificant of Gln supplementation, indicating that there are no significant differences in both control and trial groups.. the main limitation of this study was the variation of infants' age in receiving Gln initiation and attaining full enteral feeding, due to the urgency of performing elective surgeries, infants' age while receiving surgical management, pre-surgical condition, post-surgical fasting period, and the time needed to achieve full enteral feeding. Besides, the number of eligible patients recruited for this study was scarce, and the time to include the patients was also limited. The authors' perspective of this study is that a similar study should be done longer to observe the effect of Gln supplementation during post-surgical conditions while recruiting more patients to be included in the study.

Post-surgical care may cause the feeding tolerance of young babies because of the limitation of intestinal reserves and fasting periods when surgery was performed. Nutritional support is needed to improve the feeding tolerance, thus enabling infants to return to the targeted birth weight range and start enteral feeding earlier. However, the Gln supplementation cannot yet be proved to benefit nutritional support patients with this condition.

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