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Original Article

The Impact of Oral Glutamine Supplementation on Prevention of Nosocomial Infections in Preterm Infants

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ABSTRACT

***Background*:** In the recent decades, the prevalence of nosocomial infections in neonates has grown and almost 21% of preterm neonates experience these kinds of infections. Some factors were proposed to have a protective effect against neonatal infections through promoting the development of the immune system of the newborn. This study aimed to evaluate the efficacy of oral glutamine supplementation in management of neonatal sepsis.

***Methods*:** Neonates were randomly allocated to case and control groups. The infants in the case group received 0.3 g/kg/day glutamine, every eight hours from three days of age to 28 days. Hospital stay duration and occurrence of necrotizing enterocolitis (NEC) as well as sepsis were recorded for each patient. Data were analyzed using SPSS version 16.

***Results*:** In general, 105 neonates were enrolled in the study, 52 of who were allocated to the glutamine group and 53 neonates assigned to the control group. The results showed that 52 (49.5%) cases were male and 53 (50.6%) were female with mean gestational age of 30±2 weeks. Life threatening infections occurred more commonly in the control group (P=0.036). Six neonates (11.5 %) in the glutamine group and eight (15.1 %) in the control group developed clinical sepsis (P=0.592). NEC occurred only in the control group (P=0.118). Mean durations of hospital stay in the glutamine and placebo groups were 20±12 days and 26±18 days (P=0.065), respectively. Mean durations of oxygen therapy were 6±5 days and 16±11 days for the glutamine and control groups, respectively (P=0.039).

***Conclusion*:** Oral glutamine administration reduced life threatening infections and duration of receiving supplemental oxygen.

Keywords: Glutamine, Neonate, Prevention, Sepsis

Introduction

Neonatal sepsis is one of the major causes of mortality and morbidity in preterm neonates. Approximately, 2% of fetuses and 10% of neonates are estimated to suffer from infection (1). The overall incidence of infection is 1-4 neonates per 1000 live births, while this value is greater in preterm neonates (2). Sepsis can lead to long-term complications such as hearing loss, pulmonary diseases, and cerebral palsy (3).

Early-onset sepsis occurs during the first 48-72 hours of life (4). However, late-onset sepsis is defined as the sepsis occurring during the first 3-7 days of life. In late-onset sepsis, infection is predominantly acquired through the infant's environment.

Infants become colonized with pathogenic bacteria that are ubiquitin in their physical environment including part of the flora of their caregivers. Prematurity is one of the greatest risk factors for late-onset sepsis. As overall care and survival rates of premature and low-birth-weight infants are improving, long hospital stay, indwelling vascular catheters, use of histamine-2 blocker, and proton pump inhibitors are additional infectious risk factors for these infants (5-7). Other risk factors for late-onset sepsis include tracheal intubation, mechanical ventilation, umbilical vascular catheterization, total parenteral nutrition, and poor hand hygiene.

Despite the recent advancements in antimicrobial therapy and intensive care services, neonatal sepsis and its complications remain the main causes of neonatal death (5, 6). Defense mechanisms are not fully developed in neonates and neutrophils are defected both qualitatively and quantitatively (7). Preterm neonates are suspected to fulminate bacterial infection. The rate of mortality and risk of neurologic

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complications, which correlates negatively with gestational age and increases in preterm neonates, are high in early-onset sepsis (8-10).

Macrophages, which use high levels of glutamine, play a crucial role in immune response (11). Arginine and glutamine are necessary for immunoprotein production and function, particularly in neonates (12). Glutamine regulates proliferation of lymphocytes during immune response. This amino acid assumes a protective role in oxidative stress. Some studies demonstrated that intravenous glutamine can reduce the need for ventilation and lower the incidence of pneumonia and bacteremia, and proposed its administration in critically ill patients (9).

Therefore, it can be concluded that glutamine plays a vital role in the immune system. There is limited evidence regarding the efficacy of glutamine administration in reducing neonatal infections (13). This study aimed to evaluate the effect of oral glutamine on preventing neonatal nosocomial infections.

Methods

This interventional study was conducted in neonatal intensive care unit (NICU) of Qaem Hospital, affiliated to Mashhad University of Medical Sciences, Mashhad, Iran. After obtaining approval of the Ethics Committee of Mashhad University of Medical University, all the preterm neonates with birth weight less than 1500 grams, gestational age lower than 32 weeks, and Apgar scores higher than 7 were enrolled in the study. In case of discharge before the end of treatment period, intraventricular hemorrhage (IVH), metabolic disease, or congenital anomalies the neonates were excluded from the study. The standard sample size was calculated to be 94 with regard to the formula below:

$$n = \frac{(1.96 + 0.84)^2 [0.12 \times 0.88 + 0.28 \times 0.72)}{(0.28 - 0.12)^2} = 94$$

After obtaining written constant from all the parents, the infants were divided into two groups randomized block design. The intervention group received glutamine (L-glutamine, Vitapnutrition, Iran) from the third day of life until the 28th postpartum day. In the case group, 0.3 g/kg/d glutamine was administered as a 5% solution, which was divided into three doses. The drug was not mixed with milk or other therapeutic agents. The samples received glutamine for at least one week. The control group received the routine and required care during hospital stay; both groups were tested and controlled carefully for infection during hospital stay.

Tachypnea (respiratory rate of more than 60 breaths/minutes), low blood pressure (lower than 2 SD from the mean arterial pressure), conjunctivitis defined as local infection, positive blood culture sepsis, and meningitis were considered as life threatening infections. Necrotizing enterocolitis (NEC), which is a common and devastating gastro-intestinal condition, primarily affecting premature infants, can present with hematochezia, emesis, increased gastric residual volume, abdominal distention, and lethargy.

Table 1. Characteristics of the neonates

		Mean±standard deviation	Mann-Whitney
Gestational age (weeks)	Glutamine	30.7±2.2	P=0.744 Z=-0.327
	Control	30.7±2.4	
	All	29.2±6.8	
Birth weight (grams)	Glutamine	1235.8±219.5	P=0.118 Z=-1.562
	Control	1298.1±175.9	
	All	1299.1±185.1	
Apgar score	Glutamine	8.5±1.2	P=0.189 Z=-1.297
	Control	8.1±1.8	
	All	7.3±1.6	
Maternal age (years)	Glutamine	26.5±5.2	P=0.135 Z=-1.494
	Control	28.2±5.1	
	All	26.0±9.4	
Parity	Glutamine	2.1±1.1	P=0.118 Z=-4.4
	Control	2.6±1.7	
	All	2.3±1.8	

Table 2. Mean hospital stay and oxygen administration duration

		Mean± standard deviation	Mann-Whitney P-value
Hospital stay duration (day)	Glutamine	12.3±20.9	P=0.065 Z=-1.59
	Control	18.7±26.7	
Oxygen administration by oxyhood (day)	Glutamine	5.9±6.2	P=0.039 Z=-1.62

Data were recorded using a checklist and were analyzed by SPSS, version 16. Kruskal-Wallis, t-test, Mann-Whitney, and Chi-square tests were performed. P-value less than 0.05 were considered as statistically significant.

Results

In this study, 105 neonates were admitted to the hospital due to prematurity. The control group consisted of 53 neonates and the glutamine group comprised of 52 infants. In general, 52 male (49.5%) and 53 female (50.5%) neonates were enrolled. The rates of normal vaginal delivery and cesarean section were 60.9% and 39.1%, respectively. The characteristics of the neonates are compared in Table 1, and mean hospital stay and oxygen administration duration are summarized in Table 2.

Overall, 60 neonates (25 in the glutamine group and 35 in the control group) developed manifestations of acquired sepsis during hospitalization. Sepsis and other infections were confirmed in both groups. Sepsis work-ups are compared in Table 3, and results of neonatal sepsis work-up are presented in Table 4.

Table 3. Infections in the glutamine and control groups

		Glutamine (n=52)	Control (n=53)	Odd (CI 95%)	Chi-square P-value
Clinical sepsis	+	6 (24%)	8 (22.9%)	1.364 (0.436-4.424)	0.918
	-	19 (76%)	27 (77.1%)		
Life threatening infections	+	0	6 (17.1%)	0.887 (0.805-0.975)	0.036
	-	25 (100%)	29 (89.2%)		
Conjunctivitis	+	5 (20%)	1 (2.9%)	0.181 (0.020-1.604)	0.073
	-	20 (80%)	34 (97.1%)		
Necrotizing enterocolitis	+	0	3 (8.6%)	0.943 (0.883-1.008)	0.258
	-	25 (100%)	32 (91.4%)		
Supplementary oxygen	+	9 (36%)	24 (68.6%)	1.645 (0.761-3.556)	0.018
	-	16 (64%)	11 (31.4%)		

Table 4. Results of neonatal sepsis work-up

		Mean±SD	T-test P-value
White blood cell count (/ml)	Control	14000.1±1928.9	P=0.88 Z=-1.88
	Glutamine	11004.4±878.9	
Neutrophil (%)	Control	41.2±15.5	P=0.764 Z=0.302
	Glutamine	40.1±13.5	
Lymphocyte (%)	Control	54.4±15.3	P=0.764 Z=0.302
	Glutamine	55.7±17.0	
Erythrocyte sedimentation rate (/min)	Control	5.8±4.3	P=0.281 Z=0.718
	Glutamine	6.5±3.8	
Immature neutrophil/total neutrophils	Control	0.03±0.02	P=0.78 Z=1.664
	Glutamine	0.06±0.04	

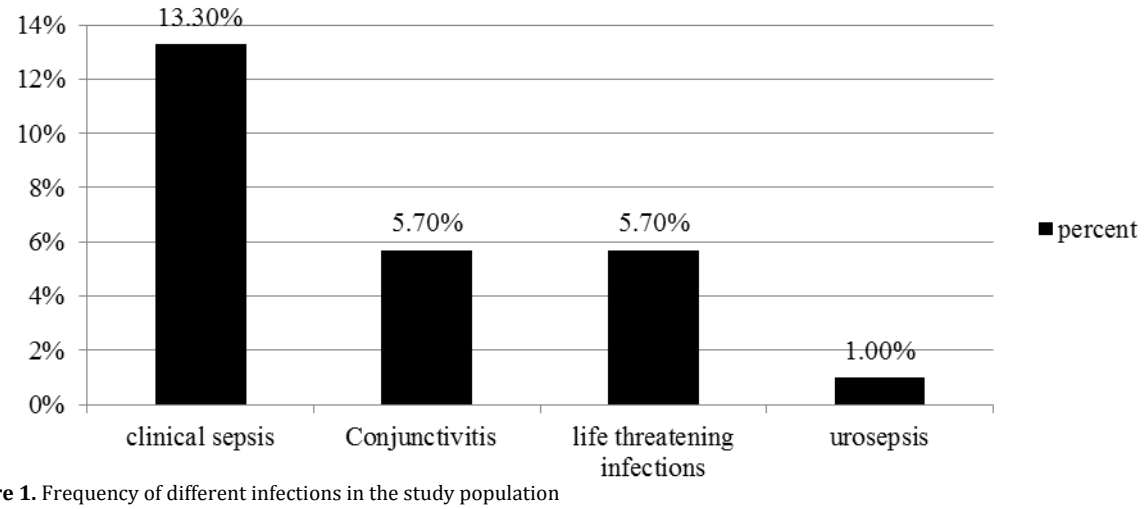

Figure 1. Frequency of different infections in the study population

Discussion

This study aimed to investigate the impact of orally administered glutamine on nosocomial infections in neonates admitted to NICU. In our study Life threatening infections occurred in 6 neonates (5.7%), clinical sepsis occurred in14 neonates (13.3%), conjunctivitis ocurred in6 neonates (5.7%) and urosepsis in 1 neonate (1%). (**Figure 1).** Life threatening infections (blood culture positive sepsis and meningitis) occurred in six neonates (17.1%) in the control group, and none of the neonates in the glutamine group, the difference between the groups was significant (P=0.036). This result was similar to those of the Neu study, conducted in 1997 (14), in which orally administered glutamine reduced the incidence rates of nosocomial infections and sepsis.

Chen in 2014 revealed that oral glutamine supplementation lowered the rate of nosocomial infections (15). Similarly, a study by Sevastiadou (16), conducted in 2011, evaluated 101 neonates (51 in case and 50 in control groups) and showed that oral glutamine supplementation decreased the rate of sepsis and NEC.

Glutamine can be easily transformed to glutamic acid to produce glutamine, which is an intra-cellular antioxidant. This product can protect oxidative stress and promote immune response to various microorganisms; on the other hand, glutamine diminishes insulin resistance. Glutamine is an important precursor of arginine, which is a crucial component in producing immune proteins in neonates that helps with growth and development of lymphocytes, regulates immune response, and reduces the risk of sepsis and other infections (17-19).

Mohammad (20) showed that intravenous glutamine could not prevent positive blood culture sepsis in neonates. This discrepancy in results might be secondary to different study population; we evaluated 105 preterm and low-birth-weight neonates, who were at high risk of sepsis development and required hospitalization for a longer period, while in that study, 270 neonates were studied. On the other hand, we investigated the efficacy of oral glutamine supplementation, whereas Mohammad administered intravenous glutamine.

In our study, 15.1% of the neonates in the case group and 11.5% infants in the control group developed clinical sepsis, but the difference between the two groups was not statistically significant (P=0.592). The incidence rates of purulent conjunctivitis in the two groups were 9.6% and 1.9%, respectively (P=0.113). Vaughn (21) in 2003 showed that oral glutamine could not diminish clinical sepsis in neonates (47.1% vs. 51.6%) significantly. Bober-Olesińska (22) could not confirm the efficacy of intravenous glutamine supplementation in preventing clinical sepsis in neonates. However, Chen revealed the impact of oral administration of glutamine on reducing the rate of clinical sepsis incidence (15). This difference might be due to different sample sizes; the study by Chen was a systematic review of 17 clinical trials and summarized the results of 3383 neonates, but we evaluated 105 neonates in a cohort design. There is some evidence on the efficacy of intravenous glutamine, as l-alanine-l-glutamine, in reducing leukocytes and natural killers, lowering inflammation and systemic inflammatory response, and improving cell

mediated immunity, particularly in critically ill patients (23).

In the current study, NEC was only observed in the control group (5.7% vs. 0%), but the difference between the two groups was not statistically significant (P=0.118). Mohammad conducted a study in Malaysia (20), which indicated that intravenous glutamine supplementation could not lower the rate of NEC incidence. Houdijk and Bober revealed that intravenous administration of glutamine could reduce NEC (22, 24). This discrepancy in findings might result from different sample sizes (we evaluated 105 neonates and Bober studied 55 ones), or the methods of glutamine administration (they evaluated the impact of intravenous glutamine). Sevastiadou (16) in Greece evaluated 101 neonates with birth weight less than 2 kilograms and found that oral administration of glutamine could reduce NEC in neonates. We evaluated neonates with birth weight less than 1500 grams.

Glutamine is the cardinal nutrition source of enterocytes, which can influence intestinal activity and its integration into the immune system. This amino acid can promote epithelial defense and reduce intestinal cell permeability, through which glutamine might prevent NEC (25).

Hospital stay in the glutamine group was six days shorter than the control group (20.9±12.3 vs. 26.7±18.7 days), but the difference was not significant (P=0.065). Chen showed that although sepsis rate was lower in glutamine group, hospital stay did not reduce significantly after glutamine administration (15). Li's findings were inconsistent with ours and neonates in the glutamine group were discharged sooner (26). In previous studies, it was proposed that glutamine could prevent multi-organ damage syndrome and might promote feeding tolerance in preterm neonates; thus, hospital stay might be curtailed (19, 24).

In the present study, dependence of the glutamine group to oxygen was six days shorter than the control group, which was statistically significant (P=0.039). This finding confirmed the previous report on the efficacy of glutamine in reducing ventilator dependency duration (21). We suggested that glutamine might influence pulmonary macrophage, improve pulmonary activity, and reduce supplementary oxygen dependency (21).

The main limitation of our study was not evaluating the long-term effects of glutamine and not comparing oral and intravenous administrations of glutamine.

Conclusion

Our study revealed that oral glutamine supplementation plays a major role in reducing life-threatening infections in premature neonates with birth weight less than 1500 grams, and decreases supplemental oxygen requirement, which might prevent further nosocomial infections and lower parental concern and treatment expenses.

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