THE EFFECT OF ENTERAL LACTOFERRIN SUPPLEMENTATION IN PREVENTION OF MORBIDITY ASSOCIATED WITH IMMATURE DIGESTIVE TRACT IN PREMATURE INFANTS: PROSPECTIVE COHORT STUDY

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თანამშრომლობითა და მისი პატრონაჟით

ЕЖЕМЕСЯЧНЫЙ НАУЧНЫЙ ЖУРНАЛ

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7. სამამულო ავტორების გვარები სტატიაში აღინიშნება ინიციალების თანდართვით, უცხოურისა – უცხოური ტრანსკრიპციით.

8. სტატიას თან უნდა ახლდეს ავტორის მიერ გამოყენებული სამამულო და უცხოური შრომების ბიბლიოგრაფიული სია (ბოლო 5-8 წლის სიღრმით). ანბანური წყობით წარმოდგენილ ბიბლიოგრაფიულ სიაში მიუთითეთ ჯერ სამამულო, შემდეგ უცხოელი ავტორები (გვარი, ინიციალები, სტატიის სათაური, ჟურნალის დასახელება, გამოცემის ადგილი, წელი, ჟურნალის №, პირველი და ბოლო გვერდები). მონოგრაფიის შემთხვევაში მიუთითეთ გამოცემის წელი, ადგილი და გვერდების საერთო რაოდენობა. ტექსტში კვადრატულ ფჩხილებში უნდა მიუთითოთ ავტორის შესაბამისი N ლიტერატურის სიის მიხედვით. მიზანშეწონილია, რომ ციტირებული წყაროების უმეტესი ნაწილი იყოს 5-6 წლის სიღრმის.

9. სტატიას თან უნდა ახლდეს: ა) დაწესებულების ან სამეცნიერო ხელმძღვანელის წარდგინება, დამოწმებული ხელმოწერითა და ბეჭდით; ბ) დარგის სპეციალისტის დამოწმებული რეცენზია, რომელშიც მითითებული იქნება საკითხის აქტუალობა, მასალის საკმაობა, მეთოდის სანდოობა, შედეგების სამეცნიერო-პრაქტიკული მნიშვნელობა.

10. სტატიის ბოლოს საჭიროა ყველა ავტორის ხელმოწერა, რომელთა რაოდენობა არ უნდა აღემატებოდეს 5-ს.

11. რედაქცია იტოვებს უფლებას შეასწოროს სტატია. ტექსტზე მუშაობა და შეჯერება ხდება საავტორო ორიგინალის მიხედვით.

12. დაუშვებელია რედაქციაში ისეთი სტატიის წარდგენა, რომელიც დასაბეჭდად წარდგენილი იყო სხვა რედაქციაში ან გამოქვეყნებული იყო სხვა გამოცემებში.

აღნიშნული წესების დარღვევის შემთხვევაში სტატიები არ განიხილება.

Содержание:

THE EFFECT OF ENTERAL LACTOFERRIN SUPPLEMENTATION IN PREVENTION OF MORBIDITY ASSOCIATED WITH IMMATURE DIGESTIVE TRACT IN PREMATURE INFANTS: PROSPECTIVE COHORT STUDY

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Prevention of necrotizing enterocolitis (NEC), late infectious complications, including late-onset sepsis, and other diseases associated with disorders of postnatal adaptation of the immature digestive tract, is one of the most pressing problems of neonatology of the 21st century. These morbidities are especially dangerous for premature babies with very low birth weight (<1500 g) at birth. The incidence of NEC in this population of infants reaches 8-10% [1] with a mortality rate of 30-50% [2]. Neonatal sepsis is diagnosed in 20-36% [3, 4] of premature babies, leading to death in 20% of children who became ill [5]. In addition to high mortality, these diseases significantly increase the risk of other serious complications of preterm birth, such as bronchopulmonary dysplasia (BPD), intraventricular hemorrhage (IVH), retinopathy of prematurity (ROP), etc. [6].

Although the pathogenesis of NEC remains incompletely understood, it is known that the occurrence of this disease is associated with immaturity of the digestive tract (insufficient local immunity, increased permeability, reduced motility, and excessive inflammatory response), enteral nutrition, insufficient intestinal blood supply, as well as abruption of the physiological formation of intestinal microbiota [7,8]. Besides NEC, these factors may play a role in the pathogenesis of other diseases, primarily sepsis, due to the entry of microorganisms into the bloodstream through the affected intestinal mucosa [9]. It should also be noted that one of the leading mechanisms of severe neonatal diseases, including NEC, ROP, BPD, and CNS lesions (IVH and periventricular leukomalacia (PVL)) in premature infants, is oxidative stress [10,11].

An important prevention strategy for these diseases is considered to be immune nutrition, one of the components of which may be lactoferrin (LF) supplementation [12]. LF is a polyfunctional iron-binding glycoprotein that in the largest amounts is present in breast milk and plays a key role in innate immunity. The ability of LF to bind iron molecules prevents the growth and reproduction of numerous pathogens, which causes a wide range of bactericidal, antiviral, and antifungal activities of this biologically active glycoprotein [13]. Since ferric iron promotes the formation of active oxygen molecules [10,14], LF potentially reduces the effects of oxidative stress, which may be an important mechanism for preventing major complications associated with preterm birth, including neuroprotection [10]. The immunomodulatory properties of LF are determined by its ability to bind to pathogen-associated molecular patterns (PAMPs), in particular lipopolysaccharides (LPS) of gram-negative bacteria [15]. The formation of such bonds blocks the binding of LPS to Toll-like receptors 4 (TLR4) and L-selectin, thereby preventing the occurrence of the excessive inflammatory response [16]. LF is also able to stimulate the processes of proliferation and differentiation of the epithelium of the small intestine, which in turn affects its mass and length, as well as the production of digestive enzymes in it [17, 18]. The described properties allow considering LF as a potential modulator of postnatal adaptation of the digestive tract in premature infants and, as a means for the prevention and treatment of diseases associated with its disorders.

The results of the first randomized clinical trials of LF performed by Manzoni et al. indicated a significant reduction in the incidence of late-onset sepsis (LOS) and NEC in preterm infants [19,20]. At the same time, the power of these studies was insufficient to detect a statistically significant decrease in the frequency of NEC [19,20]. The results of 6 randomized trials involving about 1,000 preterm very low birth weight infants, summarized in the Cochrane systematic review in 2017, showed a reduction of the incidence of LOS and NEC in the infants, who received LF, however, without significant impact on overall mortality [21]. These findings substantiated the need for new large-scale multicenter randomized trials. The ELFIN study [22], which involved 2,203 preterm VLBWI, found no significant reduction in the incidence of late-onset infections in infants who received LF. Similarly, the results of the LIFT study [23], which involved 1,542 infants from the same population, showed no significant differences in the NEC stage II-III and LOS occurrence, as well as in overall mortality and morbidity. However, the results of the Cochrane systematic review and meta-analysis published in 2020 [24], as well as the findings of a special sequential meta-analysis performed by Yao Gao et al. [25], indicated a possible reduction in the incidence of LOS in preterm infants who received LF prophylactically, but no effect on the incidence of clinically apparent NEC and overall mortality. This gave rise to a new wave of discussions about the effectiveness of LF in premature infants.

This study was aimed to evaluate the effect of prophylactic enteral administration of bovine LF on the incidence of severe neonatal diseases and the overall mortality of premature infants with gestational age (GA) ≤ 32 weeks.

Material and methods. A prospective cohort study included 126 preterm infants with a gestational age of < 32 weeks, a birth weight of < 1,500 g, who were admitted to specialized neonatal units of the Lviv Regional Clinical Hospital within 72 hours of age. An additional inclusion criterion was a tolerance of minimal enteral feeds (MEF). Exclusion criteria: the presence of significant congenital malformations, the need for total parenteral nutrition, the presence of complications and conditions at the time of involvement in the study, which significantly reduce the chances of survival (e.g., IVH grade 3-4), and the lack of informed parental consent. The study was approved by the Ethics Commission of Danylo Halytsky Lviv National Medical University. Appropriate written informed consent was obtained from all parents whose children were involved in the study.

A total of 126 preterm infants were enrolled in the study. 9 patients (2 in the lactoferrin group and 7 in the control group) died at <7 days of age and were excluded from the final analysis. The final cohort included 117 preterm infants, 27 of whom were randomized to receive LF (lactoferrin group), and 90 infants were included in the control group. The randomization phase of the study was completed prematurely due to the sudden cessation of lactoferrin supplies to Ukraine. After that, all hospitalized patients who met the inclusion criteria were consistently included in the control group. 4 patients (1 from the lactoferrin group, 3 from the comparison group) were transferred to another institution for surgical treatment, 3 of them (1 from the LF group, 2 from the control group) – due to confirmed NEC.

Table 1. Definition and diagnostic criteria of LOS (European Medicines Agency consensus criteria and the predictive model) [29]

Late-onset sepsis (LOS) – diagnosed after 72 hours of life for the first 3 months (89 days). Caused mainly by hospital pathogens.
• ***Diagnostic criteria for late-onset sepsis:***
• Need to increase the % of oxygen in the inhaled mixture or use respiratory support
• Increased incidence of apnea and/or bradycardia
• Unstable body temperature
• Feeding intolerance and/or bloating.
• Decreased urine output <1 ml/kg/h.
• Signs of decreased peripheral perfusion (symptom of "white spot" longer than 3 s, marble pattern of the skin)
• Hypotension (with the clinical need to prescribe additional fluid or inotropes)
• Signs of tactile hyperesthesia, lethargy or muscular hypotension
• Increased serum C-reactive protein (CRP) > 15 mg/l.
• White blood cells < 4 or > 20 $x10^9$/l or thrombocytopenia < 100 $x10^9$/l.
• Leukocyte index > 0,2.
• Decreased glucose tolerance (glucose level <2.2 or >10 mmol/l)
• Metabolic acidosis (BE > -10 mmol/l).
And/or positive blood culture obtained after 72 hours of life.

Randomization was performed using a computer-generated sequence of random numbers. LF was administered in the first 72 hours of life after inclusion in the study at a dose of 100 mg once daily enterally (with breast milk or formula) until reaching postmenstrual age (PMA) 36 weeks or discharge (at least 4 weeks). A suspension of bovine LF "Lactoferyl" produced by LLC "EcoKids" was used, 1 drop of which contained 10 mg of LF. Infants in the control group received standard treatment.

The primary study outcome was the occurrence of LOS. The secondary outcomes were the incidence of necrotizing enterocolitis (NEC), retinopathy of prematurity (ROP), severe brain injury, bronchopulmonary dysplasia (BPD), and overall mortality. Age of achieving full enteral feeds, duration of antibacterial therapy, length of stay in NICU, and the total duration of hospitalization were compared between the groups as well. NEC was diagnosed according to Bell criteria, modified by Kleigman [26]. LOS was diagnosed based on the prognostic model of the European Medicines Agency (Table 1). The diagnosis of BPD was made according to the criteria of the National Institute of Child Health and Human Development [27]. All infants involved in the study underwent brain ultrasound screening. The severity of IVH was classified based on the criteria, proposed by Papile et al. [28]. All patients were also screened by a pediatric ophthalmologist. Standard protocols of respiratory support,

Table 2. Demographic and baseline clinical characteristics

	LF group (n=27)	**Control group (n=90)**	**P**
Birth weight, g	1095,0 (860,0–1300,0)[1]	1150 (870,0–1300,0)	0,80
Gestational age, weeks	28,5 (27,0-31,0)	29,0 (27,0-30,0)	0,72
Gestational age < 28 weeks	9 (33,3)[2]	26 (38,9)	0,66
Males	13 (48,1)	52 (57,8)	0,37
Multiple pregnancy	9 (33,3)	20 (22,2)	0,24
Mother`s age, years	29 (22-36)	30 (27-35)	0,47
Antibacterial treatment during pregnancy	2 (7,4)	18 (20)	0,12
Any antenatal steroids during pregnancy	17 (62,9)	67 (74,4)	0,25
Full course of antenatal steroids during pregnancy	16 (59,2)	55 (61,1)	0,66
C-section	14 (52)	50 (55,5)	0,73
Intubation after birth	17 (62,9)	52 (59,7)	0,63
APGAR score < 7 at 5 min	18 (66,6)	68 (75,5)	0,39
APGAR score < 4 at 5 min	0 (0)	2 (2,3)	0,79
Age of admission, hours	6 (2-10)	23 (5-44)	**< 0,005**
Surfactant	16 (59,3)	65 (72,2)	0,39
Intubation and mechanical ventilation required	14 (51,9)	43 (47,8)	0,71
Secondary intubation required	7 (25,9)	15 (16,7)	0,28
Umbilical vein catheter	6 (22,2)	3 (3,3)	***0,001***
Any postnatal steroids	3 (11,1)	6 (6,8)	0,47
Blood transfusions	14 (51,9)	46 (51,1)	0,95

notes. 1 – here and below data is presented as the median, in parentheses - the upper and lower quartiles; 2 – here and further the number of cases is indicated, in parentheses – the percentage of the total count

ensuring stable hemodynamics, parenteral and enteral nutrition, prescribing antibiotics and antifungal medications, correction of anemia, metabolic disorders, etc. were used in the NICU. All children were being continuously monitored for vital signs.

Statistical analysis of the obtained data was carried out with the application of standard descriptive and comparative methods using the χ^2 and Mann-Whitney criteria, as well as Kaplan-Meyer survival analysis. Nonparametric data are presented as medians (lower and upper quartiles) unless otherwise indicated. All results were considered significant if $p < 0.05$.

Results and disdussion. The groups did not differ significantly in demographics and the frequency of perinatal risk factors, but infants from the LF group were admitted to the units significantly earlier (Table 2). Also, an umbilical vein catheter was used in this group more often (Table 2). MEF were introduced on the first day of life, but somewhat sooner in the lactoferrin group. At the same time, the duration of MEX did not differ between the groups. The proportion of infants fed with both formula and breast milk was not significantly different in the groups, although breastmilk was introduced sooner in the lactoferrin group. The numbers of feeding intolerance episodes were similar in both groups (Table 3).

Table 3. Enteral nutrition

	LF group (n=27)	**Control group (n=90)**	**P**
Age of MEF introduction, hours	7 (6,0-11,0)[1]	10,0 (6,0-16,0)	0,02
Duration of MEF, days	3,0 (2,0-5,0)	3,0 (2,0-5,0)	0,75
Infants fed only with formula	17 (63)[2]	48 (53,3)	0,55
Infants fed with formula and breast milk	10 (37)	42 (46,7)	0,55
Age of breast milk introduction, days	14,0 (12,0-23,0)[1]	22,5 (16,0-30,0)	0,15
Episodes of feeding intolerance	1,0 (0-2,0)	1,0 (1,0-3,0)	0,44

notes. 1 – here and below the data is presented as the median, in parentheses - the upper and lower quartiles; 2 – here and further the number of cases is indicated, in parentheses – the percentage of the total count; MEF – minimal enteral feeds

Table 4. Main neonatal morbidity

	LF group (n=27)	**Control group (n=90)**	**p**
LOS			
All infants	8 (29,6)[1]	28 (22,2)	0,85
<28 weeks	3 (30,8)	14 (48,8)	0,29
≥28 weeks	5 (27,8)	14 (22,2)	0,62
NEC Bell`s stage II+			
All infants	4 (14,8)	5 (5,6)	0,11
<28 weeks	2 (22,2)	3 (12)	0,43
≥28 weeks	2 (11,1)	2 (3,1)	0,17
Overall mortality			
All infants	5 (18,5)	6 (6,7)	0,06
<28 weeks	3 (30,8)	5 (14,6)	0,39
≥28 weeks	2 (11,1)	1 (1,6)	0,06
Severe ROP treated surgically			
All infants	3 (11,1)	7 (7,8)	0,59
<28 weeks	2 (22,2)	5 (19,2)	0,84
≥28 weeks	1 (5,6)	2 (3,1)	0,63
IVH grade 3-4			
All infants	5 (18,5)	8 (9,1)	0,17
<28 weeks	3 (33,3)	5 (19,2)	0,39
≥28 weeks	2 (11,1)	3 (4,8)	0,33
PVL			
All infants	3 (11,1)	2 (2,3)	0,05
<28 weeks	2 (22,2)	1 (4,0)	0,10
≥28 weeks	1 (5,6)	1 (1,6)	0,35
All BPD			
All infants	4 (14,8)	23 (25,6)	0,25
<28 weeks	3 (33,3)	15 (57,7)	0,20
≥28 weeks	1 (5,6)	8 (12,5)	0,41
Medium and severe BPD			
All infants	1 (3,7)	6 (6,6)	0,57
<28 weeks	1 (11,1)	3 (11,6)	0,97
≥28 weeks	0	3 (4,7)	0,35

notes. 1 – here and further the number of cases is indicated, in parentheses – the percentage of the total count

Table 5. Secondary outcomes

	LF group (n=27)	Control group (n=90)	p
Achievement of full enteral feeds, days[a]			
All infants	14 (10-17) [1]	19 (13-32)	0,007
<28 weeks	16,5 (15,0-18,0)	34 (19,0-43,0)	0,02
≥28 weeks	13 (8-17)	18 (12-27)	0,03
Duration of AB treatment, days[a]			
All infants	23,5 (18-32)	31,5 (22,5-36,5)	0,16
<28 weeks	35 (29-40)	52 (38-70)	0,13
≥28 weeks	28 (18-34)	32 (23-38)	0,22
Duration of NICU stay, days[a]			
All infants	9 (5-25)	12 (7-32)	0,35
<28 weeks	28 (16-38)	45 (29-62)	0,21
≥28 weeks	8 (3-11)	10 (6-15)	0,41
Duration of hospitalization, days[a]			
All infants	61 (48-72)	69 (50-89)	0,22
<28 weeks	74 (68-89)	98 (83-109)	0,048
≥28 weeks	57 (45-66)	61,5 (47-74)	0,33

notes: 1 – here and below data is presented as the median, in parentheses - the upper and lower quartiles; a – the data is shown for infants who survived and were discharged from the institution

Prophylactic LF supplementation did not reduce the incidence of LOS and major morbidities classified as secondary outcomes, as well as overall mortality. However, the frequency of PVL was higher in the lactoferrin group (p=0.05). The analysis in the subgroups also showed that the incidence did not decrease with the prophylactic use of LF, regardless of gestational age (Table 3). A comparative analysis of survival by Kaplan-Meyer showed earlier deaths in the lactoferrin group compared to the control group (Fig. 1). The LF supplementation was associated with a significantly faster achievement of full enteral feeds and a shorter duration of antibacterial therapy, as well as the total length of hospital stay (p>0.05) and the length of stay in NICU (p>0.05). Subgroup analysis showed a significantly faster achievement of full enteral feeds in the lactoferrin group regardless of gestational age. Also, a shorter length of stay in NICU, general hospitalization, and use of antibacterial therapy was observed among extremely premature infants in the lactoferrin group (Table 5).

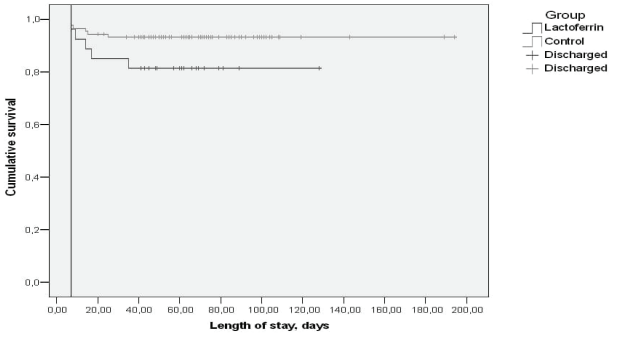

Fig. Kaplan-Meyer comparative analysis of survival in groups (F-Cox test p = 0.049)

The results of the study did not show a reduction in the morbidity associated with gastrointestinal immaturity and overall mortality in infants who received supplemental LF. However, a lower incidence of LOS was observed in infants <28 weeks of GA in the lactoferrin group, but the difference from the control group was not significant. The data obtained coincide with the results of LIFT and ELFIN [30,31] and differ from the results of the study by Manzoni et al. [19,20], the first study by Ochoa et al., conducted in Peru [32], and the study by Sherman et al. [33], which showed a significant reduction in the incidence of LOS and NEC in infants receiving LF. It should be noted that Ochoa et al. performed the second clinical study of the effectiveness of prophylactic LF published in 2020, which did not reveal a decrease in the incidence of LOS among infants receiving LF [34].

The positive effect of enteral LF on the faster achievement of full enteral nutrition was associated with a reduction in the total duration of hospitalization only in the subgroup of infants with GA <28 weeks. A similar trend was observed in the study by Sherman et al. [33], in which the authors found a shorter period to achieve full enteral feeding in infants fed with formula supplemented with LF. Infants who received LF in a study by Ochoa et al. [34], required a shorter duration of parenteral nutrition and fewer days of NPO.

Higher mortality rates, the incidence of NEC and PVL in the lactoferrin group were associated with a cluster of NEC cases in infants who were sequentially recruited into this group during several days according to a randomization plan. The rapid course of the disease led to severe CNS damage and death, which could affect the differences between the groups, especially given the small number of patients in the lactoferrin group. We reviewed the incidence of NEC in infants < 32 weeks of gestation admitted to our units in the calendar years of 2018-2020, finding the rates were not significantly different over these longer sample periods. Also taking into account the fact that in previous randomized studies, including the last 2, which involved 3745 patients [22,23], no such associations were found, this effect in our study can be considered as a random one.

Our study has certain shortcomings, the main of which was the unexpected change in its design and loss of power due to the unavailability of the study medication, which suddenly arose at the onset of the SARS-CoV-2 pandemic. Accordingly, the number of infants in the lactoferrin group was much smaller than in the control group. Also, to provide a power of 80% of the effect of reducing the incidence of LOS by 20%, the required sample should be 620 patients, 310 in each group.

A feature and strength of this study was its implementation in a country with a lower middle income. The prevention of late infections is especially important in such settings, and prophylactic LF supplementation is considered to be an affordable and effective mean of implementing the preventive strategy. In particular, a decrease in the incidence of LOS in infants receiving LF was observed in studies conducted in India and Peru [32,35].

It is possible, that the clinical effectiveness of enteral LF supplementation may vary from the type of enteral nutrition of preterm infants, the breastfeeding. In the LIFT study, which showed no effect of LF in reducing the incidence of NEC and LOS, as well as overall mortality, 94% of infants were fed exclusively with breast milk. Unfortunately, the relevant data are not described for the ELFIN study. In contrast, in a study by Manzoni et al., less than 30% of infants were fed exclusively with breast milk, and it did find the reduction of the incidence of NEC and overall mortality among infants receiving LF [20]. Subsequently, Manzoni et al. found that LF was more effective in formula-fed infants than in infants receiving breast milk [36], which was also confirmed by studies of Sherman and Ochoa [33,34]. Given the early transfer from the obstetric hospitals, we began to feed our patients with formula with a gradual transition to partial or complete feeding with breast milk, as soon as it became possible. At the same time, the vast majority of infants in both groups were fed with formula, which does not explain the lack of effectiveness of LF due to the effects of breastmilk feeding.

One of the possible future directions of the clinical LF investigation is to study the feasibility and effectiveness of its supplementation to infants who do not receive maternal or donor milk, as well as in the settings of low-income countries with higher infectious morbidity. Also, the study of the effect of LF supplementation on the formation of the microbiota of the digestive tract in premature infants remains relevant. Thus, Sherman and co-authors found that the use of Tal-lactoferrin reduced the abundance of Enterobacter and Klebsiella bacteria but increased the abundance of Citrobacter [37].

Conclusions. Enteral supplementation with LF at a dose of 100 mg/day did not reduce the incidence of LOS, NEC, ROP, severe CNS lesions, and overall mortality in preterm very low birth weight infants enrolled in our study. However, patients who received LF supplementation were more likely to achieve full enteral nutrition faster, and the most immature of them (with GA of <28 weeks) were more likely to be discharged from the hospital faster. Enteral supplementation with LF was also associated with a shorter duration of antibacterial therapy and length of stay in NICU.

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SUMMARY

THE EFFECT OF ENTERAL LACTOFERRIN SUPPLEMENTATION IN PREVENTION OF MORBIDITY ASSOCIATED WITH IMMATURE DIGESTIVE TRACT IN PREMATURE INFANTS: PROSPECTIVE COHORT STUDY

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Premature infants are at high risk for diseases associated with impaired adaptation of the immature digestive tract, such as necrotizing enterocolitis (NEC) or late-onset sepsis (LOS), as well as severe neonatal morbidities associated with these diseases. This study was aimed to evaluate the effectiveness of prophylactic enteral use of bovine lactoferrin for the prevention of severe neonatal diseases in premature infants.

The prospective cohort study included 117 premature infants with gestational age (GA) of ≤32 weeks, a birth weight of ≤1,500 g, and an age of ≤72 hours. 27 infants who were receiving enteral feeds were randomized to receive lactoferrin at a dose of 100 mg/day until postmenstrual age (PMA) of 36 weeks or discharge (at least 4 weeks). 90 infants formed the control group and received standard treatment. The primary outcome was the incidence of LOS, the secondary outcomes were the incidence of necrotizing enterocolitis (NEC), retinopathy of prematurity (ROP), severe brain damage, bronchopulmonary dysplasia (BPD), overall mortality, as well as the age of achieving full enteral feeds, duration of antibacterial therapy, length of stay in NICU and the total length of hospital stay.

Enteral lactoferrin supplementation did not reduce the incidence of LOS (29.6% in the lactoferrin group against 22.7% in the control group; p=0.85), NEC (5.6% vs. 1.8%, respectively; p=0.11) and overall mortality (18.5% vs. 9.1%, respectively; p=0.06), as well as the incidence of severe intraventricular hemorrhages (18.5% vs. 9.8%, respectively; p=0.17), PVL (11.1% vs. 2.2%, respectively; p=0.17) and BPD (14.8% vs. 25.6%, respectively; p = 0.25). Infants receiving lactoferrin were achieving full enteral feeds significantly faster compared to the control group (14 (10-17) days vs. 19 (13-32) days, respectively; p=0.007). The total length of hospital stay of infants with GA ≤28 weeks in the lactoferrin group was significantly shorter compared to the control group (74 (68-89) vs. 98 (83-109) days, respectively; p=0.048).

Enteral lactoferrin supplementation at a dose of 100 mg/day does not affect the main morbidity and mortality of prematurely born infants with GA ≤ 32 weeks but may facilitate significantly faster achievement of the full enteral feeds and the reduction of the length of hospital stay in the tiniest infants.

Keywords: bovine lactoferrin, preterm infants, late-onset sepsis, NEC, immune nutrition.

РЕЗЮМЕ

ЭФФЕКТИВНОСТЬ ЭНТЕРАЛЬНОГО ПРИМЕНЕНИЯ ЛАКТОФЕРРИНА С ЦЕЛЬЮ ПРОФИЛАКТИКИ ВОЗНИКНОВЕНИЯ ЗАБОЛЕВАЕМОСТИ, СВЯЗАННОЙ С НЕЗРЕЛОСТЬЮ ПИЩЕВАРИТЕЛЬНОГО ТРАКТА У НЕДОНОШЕННЫХ ДЕТЕЙ: ПРОСПЕКТИВНОЕ КОГОРТНОЕ ИССЛЕДОВАНИЕ

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Преждевременно рожденные младенцы имеют высокий риск возникновения заболеваний, связанных с нарушениями адаптации незрелого пищеварительного тракта (некротизирующий энтероколит - НЭК или поздний неонатальный сепсис - ПНС), а также тяжелой неонатальной патологии, связанной с этими заболеваниями.

Целью исследования явилась оценка эффективности профилактического энтерального применения бычьего лактоферрина в профилактике тяжелых заболеваний неонатального периода у преждевременно рожденных младенцев.

В проспективном когортном исследовании принимали участие 117 преждевременно родившихся детей со сроком гестации (СГ) ≤32 недели, массой тела при рождении ≤1500 г и в возрасте ≤72 часа. 27 младенцам, которых кормили энтерально, рандомизированно назначали лактоферрин в дозе 100 мг/сут до момента достижения постменструального возраста (ПМВ) 36 нед. или выписки из стационара (не менее 4 нед.). 90 младенцев, получавшие стандартное лечение, составили контрольную группу. Основным критерием эффективности была частота возникновения ПНС, вторичными критериями являлись частота развития НЭК, ретинопатии недоношенных, тяжелого поражения мозга по данным нейросонографии, частота и тяжесть бронхолегочной дисплазии (БЛД) в постменструальном возрасте, смертность, а также возраст к моменту достижения полного объема энтерального питания, продолжительность антибактериальной терапии, пребывания в отделении интенсивной терапии и общая госпитализация.

Энтеральное применение лактоферрина в дозе 100 мг/сут не влияет на основную заболеваемость и смертность преждевременно рожденных младенцев с СГ≤32 нед., однако сопровождается достоверно более скорым достижением полного объема энтерального питания и сокращением продолжительности общей госпитализации у младенцев.

რეზიუმე

ლაქტოფერინის ენტერული გამოყენების ეფექტურობა საჭმლის მომნელებელი ტრაქტის მოუმწიფებლობასთან დაკავშირებული ავადობის პროფილაქტიკის მიზნით დღენაკლულ ბავშვებში: პროსპექტული კოჰორტული კვლევა

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კვლევის მიზანს წარმოადგენდა ხარის ლაქტოფერინის პროფილაქტიკური ენტერული გამოყენების ეფექტურობის შეფასება ნეონატალური პერიოდის მძიმე დაავადებების პროფილაქტიკისათვის ნაადრევად დაბადებულ ახალშობილებში.

პროსპექტულ კოჰორტულ კვლევაში მონაწილეობდა 117ნაადრევად დაბადებული ბავშვი, გესტაციის ვადით ≤32 კვირა, დაბადებისას სხეულის მასით - ≤1500 გ და ასაკით - ≤72 საათი. 27 ახალშობილს, რომლეთაც კვებავდნენ ენტერულად, რანდომულად დაენიშნათ ლაქტოფერინი, დოზით 100 მგ/დღე-ღამეში პოსტმენსტრუალური ასაკის მიღწევამდე (36 კვირა) ან სტაციონარიდან გაწერამდე (არანაკლებ 4 კვირისა). 90 ახალ-შობილმა, სტანდარტული მკურნალობით, შეადგინა საკონტროლო ჯგუფი. ეფექტურობის ძირითად კრიტერიუმს წარმოადგენდა გვიანი ნეონატალური სეფსისის განვითარების სიხშირე, მეორად კრიტერიუმს კი – მანეკროზებელი ენტეროკოლიტის, დღენაკლული ახალშობილების რეტინოპათიის განვითარების სიხშირე, ასევე, ტვინის მძიმე დაზიანება ნეიროსონოგრაფიის მონაცემების მიხედვით, ბრონქულ-პულმონური დისპლაზიის სიხშირე და სიმძიმე პოსტმენსტრუალურ ასაკში, სიკვდილობა, ასაკი ენტერული კვების სრული მოცულობის მიღწევისას, ანტიბაქტერიული თერაპიის ხანგრძლივობა, ინტენსიური თერაპიის განყოფილებში დაყოვნების და საერთო ჰოსპიტალიზაციის ხანგრძლივობა.

კვლევის შედეგების მიხედვით, ლაქტოფერინის ენტერული გამოყენება, დოზით 100 მგ/დღე-დამეში არ მოქმედებს დღენაკლული ახალშობილების (გესტაციის ვადით ≤ 32 კვირა) ძირითად ავადობასა და სიკვდილობაზე, მაგრამ თან ახლავს ენტერული კვების სრული მოცულობის მიღწევის სარწმუნოდ ხანმოკლე ვადა და ახალშობილების საერთო ჰოსპიტალიზაციის ხანგრძლივობის შემცირება.

БОЛЕЗНЬ ГИРШПРУНГА У ПОДРОСТКОВ

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Нарушение дефекации у детей является одной из актуальных проблем педиатрии и детской хирургии. Задержка стула может наблюдаться как при функциональных расстройствах желудочно-кишечного тракта, соматической патологии, так и при врожденных аномалиях развития толстой кишки. Болезнь Гиршпрунга (БГ) – врожденная патология, характеризуется отсутствием ганглиев в межмышечных и подслизистых нервных сплетениях (аганглиоз) толстой кишки, что приводит к обструкции кишечника [13,15]. Аганглиоз - холинэргическая гиперинервация, дефицит обеспечения нервов нитрид-оксид синтетазой, нарушения интерстициальных клеток Кахаля, которые играют значимую роль в регуляции моторики желудочно-кишечного тракта, в совокупности являются патогенетическим механизмом болезни Гиршпрунга [8,12,14].

БГ в большинстве случаев выявляется в первые месяцы и годы жизни ребенка. Поэтому вопросы патогенеза, диагностики и лечения заболевания разработаны педиатрами и детскими хирургами. У взрослых и детей старшего возраста БГ является редкой патологией. В литературе описаны единичные случаи заболевания у подростков и взрослых пациентов. Этот клинический вариант врожденной патологии, при котором запоры появляются в подростковом возрасте и постепенно прогрессируют, представляется как «латентный вариант болезни Гиршпрунга у взрослых» и мало известен детским хирургам [2]. Несмотря на то, что в понимании этиопатогенеза и лечения болезни Гиршпрунга достигнуты значительные успехи, вопрос диагностики и лечения детей старшего возраста с этой патологией по сей день остается актуальным.

Термин “adult Hirschsprung’s disease» обычно применяется в случаях БГ у пациентов старше 10 лет [4]. Другие авторы [7] используют этот термин применительно к пациентам старше 18 лет. Первый задокументированный случай БГ у взрослого описан J.D. Rosin в 1950 г. у 54-летнего мужчины с коротким аганглионарным сегментом [17].

Miyamoto M. et al. [11] провели метаанализ англоязычной литературы за 50-летний период и описали 229 случаев БГ у взрослых. Среди них мужчин было в 3 раза больше, чем женщин, возраст варьировал в пределах от 10 до 73 лет, средний возраст составил 24,1 г. Основным симптомом были длительные запоры, начавшиеся еще в детском возрасте и боли, ассоциируемые с пальпируемыми каловыми массами. Частота дефекации составила от 1 раза в неделю до 2 раз в месяц. Все пациенты регулярно применяли слабительные средства и клизмы. У 46 (20%) пациентов ирригоскопия выявила короткие и ультракороткие формы БГ.

Выполненный R. Doodnath и P. Puri [10] метаанализ, который охватывал период с 1950 по 2009 гг., включал 490 случаев БГ у взрослых, из них 341 (69,5%) мужчина, 129 (26,4%) женщин и 20 (4,1%) пациентов, пол которых не обозначен. У 390 (79,6%) больных имела место ректальная локализация аганглиоза, у 60 (12,3%) – ректосигмоидная, у 2 (0,4%) – субтотальная, у 2 (0,4%) – тотальное поражение толстой кишки.

Данные о встречаемости БГ у взрослых лиц в литературе представлены весьма скудно. Согласно А.М. Аминеву [1], распространеннсть БГ среди лиц в возрасте от 10 до 73 лет составляет 5-7%, а по данным других авторов – большинство пациентов с БГ были моложе 30 лет, соотношение мужчин к женщинам – 4:1 [19-21].

Малоизученность проблемы БГ у подростков и детей старшего возраста диктует необходимость более углубленного изучения этого вопроса.

Цель исследования - проанализировать клинические проявления болезни Гиршпрунга у детей старшего возраста для разработки адекватной лечебной тактики.

Материал и методы. В исследование включено 26 детей, проходивших лечение в хирургических отделениях Киевской городской детской больницы №1 (n=11), Областной детской клинической больницы г. Черновцы (n=8) и Городской детской клинической больницы г. Львова (n=7) с болезнью Гиршпрунга, у которых заболевание впервые диагностировано в возрасте 10 лет и старше.

Согласно классификации Фонда ООН в области народонаселения [6], обследованные дети и подростки были распределены в следующие возрастные группы: 10-14 лет (ранний подростковый возраст) – 17 (65,39%) пациентов и 15-17