Int J Clin Exp Med 2021;14(2):1208-1216
www.ijcem.com /ISSN:1940-5901/IJCEM0123982

Original Article

Octreotide combined with probiotics can improve the immunity of children with necrotizing enterocolitis and promote their rehabilitation

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Received October 12, 2020; Accepted November 24, 2020; Epub February 15, 2021; Published February 28, 2021

Abstract: Objective: To explore whether octreotide combined with probiotics can improve the immunity of children with necrotizing enterocolitis (NEC) and promote their rehabilitation. Methods: A total of 126 children with NEC treated in our hospital from January 2016 to March 2019 were recruited as the study cohort and divided into two groups according to the treatment method each received. The children in the regular group (RG, 60 cases) were treated with octreotide, and the children in the joint group (JG, 66 cases) were treated with octreotide plus probiotics. The clinical symptoms, curative effects, and adverse reactions of the children after the treatment were compared, as well as their nutritional status (serum albumin, ALB, and serum prealbumin, PAB), their intestinal flora improvement, their immune function, and their humoral immune indexes before and after the treatment in the two groups. Results: After the treatment, the diarrhea remission times, the abdominal distension remission times, the enteral nutrition recovery times, and the children's lengths of stay in the JG were notably shorter than they were in the RG, and their expressions of ALB and PAB in the JG were notably higher than they were in the RG. Also, the JG had notably higher $CD4^+$ and $CD4^+/CD8^+$ expressions, and lower $CD8^+$ expressions than the RG. The IgA, IgG, and IgM expressions in the JG were significantly higher than they were in the RG. The total effective rate in the JG was significantly higher than it was in the RG, but there was no difference in the rates of adverse reactions in the two groups. Conclusion: The administration of octreotide combined with probiotics can improve the adverse signs and abdominal symptoms of children with NEC and improve their nutritional status, immune function, and intestinal flora.

Keywords: Octreotide combined with probiotics, necrotizing enterocolitis, immunity of children, promoting rehabilitation

Introduction

NEC is an acquired disorder that affects preterm or ill neonates [1, 2], with lesions occurring in the terminal ileum. Premature infants have vulnerable intestinal tracts that allow microbial pathogens to invade their tissues, leading to severe morbidity and mortality [3]. Clinical evidence suggests that in neonates who develop NEC, three factors of persistent intestinal ischemic damage, bacterial colonization, and substrate in the intestinal lumen are usually present in the small intestine, with their clinical signs presenting as abdominal distension and intestinal obstruction, vomiting of bile after feeding, and bloody stools [4, 5]. Therefore, finding a safe and effective treatment has become the primary clinical task.

Octreotide is a synthetic octapeptide cyclic compound that has a function similar to natural endogenous somatostatin. It has longer drug action, longer efficacy, and a longer half-life than natural somatostatin [6]. Studies have shown that octreotide can also inhibit the release of growth hormones, insulin, and glucagon, reduce the secretions of the pancreas, intestines and bile, inhibit gallbladder contraction and gastrointestinal motility, and reduce visceral blood flow [7]. Octreotide has been successfully used to treat neonatal chylothorax, chylous ascites, congenital lymphedema, lymphangiectasia, gastrointestinal bleeding, enterocutaneous fistula, and so on [8]. Martini [9] gave octreotide to critically ill and perforated NEC children with extremely low birth weights and observed no adverse effects during the

treatment. After withdrawing the octreotide, the children's conditions gradually improved, the peritoneal outflows gradually decreased, and their pneumoperitoneum was successfully cured without recurrence. Children with NEC usually have intestinal flora imbalances and an excessive reproduction of pathogenic bacteria, which leads to the apoptosis of the intestinal epithelial cells. Therefore, it is of great significance to reconstruct normal strains in children to prevent and control NEC [10]. Probiotics are living microorganisms that, when ingested, provide health benefits to the host. They have been widely studied and used to improve the health status of premature infants, and they can reduce morbidity and mortality. Probiotics have been studied as a treatment method to reduce the risk of NEC [11].

At present, there are few studies on the efficacy of octreotide combined with probiotics in the treatment of NEC. We will evaluate the curative effects of the two and their impacts on the improvement of children's clinical symptoms, hoping to provide effective clinical information on NEC treatment.

Materials and methods

General data

A total of 126 children with NEC treated at Northwest Women and Children's Hospital from June 2015 to March 2019 were divided into two groups. The children who received octreotide treatment were enrolled in the regular group (RG, 60 cases), and the children who received octreotide combined with probiotics treatment were enrolled in the joint group (JG, 66 cases). Inclusion criteria: children who met the clinical diagnostic criteria for NEC [12], children who had diarrhea, vomiting, abdominal distension, and other symptoms, children who had positive fecal occult blood test results, children who had complete case data, and children who underwent follow-up treatment in our hospital after their diagnoses. This study was conducted with the approval of the ethics committee of our hospital, and all the patients' guardians were informed and signed an informed consent form. Exclusion criteria: children with severe metabolic disease complications, congenital heart disease, a congenital malformation of the digestive tract, an allergic constitution, and children transferred to other hospitals or who quit the experiment halfway.

Therapeutic intervention steps

Both groups of children were given routine treatment: the children fasted for 7 days and received total parenteral nutrition: 10% fat milk 1-2 g/(kg·d), glucose 10-15 g/(kg·d), compound amino acids 2-3 g/(kg·d), compound vitamins 100-150 g/(kg·d), Na^+ 2 mol/(kg·d), $Ca2^+$ 0-18 mg/(kg·d), K^+ 1.5-2.0 mol/(kg·d) and an intravenous drip of 120-150 ml/(kg·d), as well as gastrointestinal decompression.

The children in the RG were treated with octreotide injections. Thirty ml/kg octreotide and 50 ml sodium chloride were continuously and evenly intravenously instilled using infusion pump for 24 hours, once a day.

The children in the JG were treated with probiotics in addition to the treatment the RG received, which was Live combined *B. Subtilis* and *E. Faecium* granules with multivitamins (Hanmi Pharm. Co., Ltd., SFDA approval number: J20100161), and different dosages were given according to the children's body masses. Children with a body mass less than 1.5 kg were given a bag twice a day. Children with a body mass of 1.5-2.0 kg were given 1-2 bags twice a day. Children with a body mass > 2.0 kg were given 2 bags twice a day. The duration of the treatment in both groups was 2 weeks.

Outcome measures

Clinical symptoms: diarrhea remission times, abdominal distension remission times, enteral nutrition recovery times, and the two groups' lengths of hospital stays after the treatment were observed, recorded, and compared.

Condition of the nutrition and immune status: five mL venous blood was drawn from the children in both groups before and after the treatment, centrifuged at 1500×g at 4°C for 10 min, and placed in a freezer at -70°C for later use. The children's nutritional status (the expressions of serum albumin, ALB, and serum prealbumin, PAB) was measured using immunoturbidimetry. The children's immune function ($CD4^+$, $CD8^+$, $CD4^+/CD8^+$) in the two groups was measured using flow cytometry (FCM). Enzyme-linked immunosorbent assays (ELISA) were

Table 1. Comparison of the children's general datain the two groups [n (%)] (mean ± SD)

Classification	Joint group (n=66)	Regular group (n=60)	t/χ^2 value	*P* value
Gender			0.014	0.905
Male	37 (56.06)	33 (55.00)		
Female	29 (43.94)	27 (45.00)		
Body mass (g)	1358.04±11.65	1356.76±11.35	0.624	0.534
Gestational age (week)	30.46±3.17	31.05±3.15	1.047	0.297
Age (days)	7.75±1.32	7.63±1.25	0.523	0.602
Production mode			0.168	0.682
Caesarean	31 (46.97)	26 (43.33)		
Eutocia	35 (53.03)	34 (56.67)		
Parental drinking history			0.001	0.986
Present	32 (48.48)	29 (48.33)		
Absent	34 (51.52)	31 (51.67)		
Parental smoking history			0.019	0.892
Present	30 (45.45)	28 (46.67)		
Absent	36 (54.55)	32 (53.33)		

used to determine the children's humoral immune indexes (IgA, IgG, IgM) in the two groups.

Intestinal flora: the intestinal flora changes before and after the treatment in the two groups were determined, including the total number of bacteria, cocci, bacilli, and the ratio of cocci to bacilli.

Clinical efficacy: Marked response: after the treatment, the children were routinely X-rayed, and their clinical symptoms disappeared. Effective response: after the treatment, children had mild vomiting, made gurgling sounds, and had improved adverse signs and abdominal symptoms. No response: after the treatment, the children's adverse signs and abdominal symptoms were unchanged. Total effective rate = (marked response + effective response)/total cases * 100%.

Adverse reactions: the adverse reactions in the two groups of children during the treatment were observed and recorded.

Statistical analysis

SPSS 22.0 (Beijing EasyBio Co., Ltd., China) was used for the statistical analysis. The count data were expressed as the number of cases/percentage [n (%)]. Chi-square tests were used to compare the count data in the two groups. When the theoretical frequency in a chi-square test was less than 5, a continuity correction chi-square test was used. The measurement data was expressed as the mean ± SEM. The measurement data in the two groups were compared using independent sample t-tests, and paired t-tests were used for intra-group comparisons before and after the treatment. When $P < 0.05$, a difference was statistically significant.

Results

General data

There were no significant differences in the general baseline data, such as gender, body weight, gestational age, age, production mode, parental drinking history, or parental smoking history between the JG and the RG ($P > 0.05$), as shown in **Table 1**.

Comparison of the clinical symptom relief in the two groups of children after the treatment

After the treatment, the diarrhea remission times, the abdominal remission times, and the enteral nutrition recovery times of the children in the JG were notably shorter than the corresponding times in the RG, and their hospital stays were also shorter than the hospital stays in the RG, with a significant significance ($P < 0.05$), as shown in **Table 2**.

Comparison of the nutritional statuses in the two groups of children before and after the treatment

The ALB and PAB expressions showed no significant differences between the two groups

Table 2. Comparison of the clinical symptom relief between the two groups after the treatment (mean ± SEM)

Group	n	Remission time of diarrhea	Remission time of abdominal distension	Recovery time of enteral nutrition	Length of stay (d)
Joint group	66	1.87±0.19	1.43±0.15	3.72±0.28	5.83±0.35
Regular group	60	2.85±0.23	2.09±0.18	6.42±0.43	8.19±0.51
t	-	26.160	22.430	42.130	30.520
P	-	< 0.001	< 0.001	< 0.001	< 0.001

Table 3. Comparison of the nutritional statuses between the two groups before and after the treatment (mean ± SEM)

Group	n	ALB (g/L)		PAB (μg/ml)	
		Before treatment	After treatment	Before treatment	After treatment
Joint group	66	25.17±2.16	42.18±4.03	85.37±8.12	114.82±10.22
Regular group	60	25.24±2.18	31.27±3.19	85.92±8.16	100.73±10.09
T	-	0.181	16.740	0.379	7.776
P	-	0.857	< 0.001	0.706	< 0.001

Table 4. Comparison of the intestinal flora between the two groups of children before and after the treatment (mean ± SEM)

Group	N	Total number of bacilli (cfu/ml)		Total number of cocci (cfu/ml)		Ratio of cocci to bacilli	
		Before treatment	After treatment	Before treatment	After treatment	Before treatment	After treatment
Joint group	66	26.32±2.17	73.18±6.32	74.98±7.54	267.36±20.11	2.93±0.28	3.68±0.31
Regular group	60	26.28±2.14	52.63±5.05	75.16±7.84	159.32±15.27	2.97±0.26	3.04±0.29
t	-	0.104	20.030	0.131	33.700	0.829	11.930
P	-	0.917	< 0.001	0.896	< 0.001	0.409	< 0.001

before the treatment (P > 0.05), but their expressions after the treatment were notably elevated (P < 0.05), and their expressions were higher in the JG than they were in the RG, with a significant statistical difference (P < 0.05), as shown in **Table 3**.

Comparison of the intestinal flora in the two groups of children before and after the treatment

Before the treatment, there were no differences in the total number of bacilli, total number of cocci, or the ratio of cocci to bacilli in intestinal the flora of the two groups of children (P > 0.05), but after the treatment, the three values were significantly higher than they were before the treatment (P < 0.05), and they were higher in the JG than they were in the RG (P < 0.05), as shown in **Table 4**.

Comparison of the immune function in the two groups before and after the treatment

In terms of immune function, there was no significant difference in the $CD4^+$, $CD8^+$ or $CD4^+/CD8^+$ expressions in the two groups before the treatment (P > 0.05). After the treatment, these expressions were considerably better than they were before the treatment (P < 0.05), with notably higher $CD4^+$, $CD4^+/CD8^+$ expressions, and a notably lower $CD8^+$ expression in the JG compared to the RG. The differences were statistically significant (P < 0.05), as shown in **Figure 1**.

Comparison of humoral immune indexes between the two groups of children before and after the treatment

The IgA, IgG, IgM expressions in the two groups of children showed no significant differences

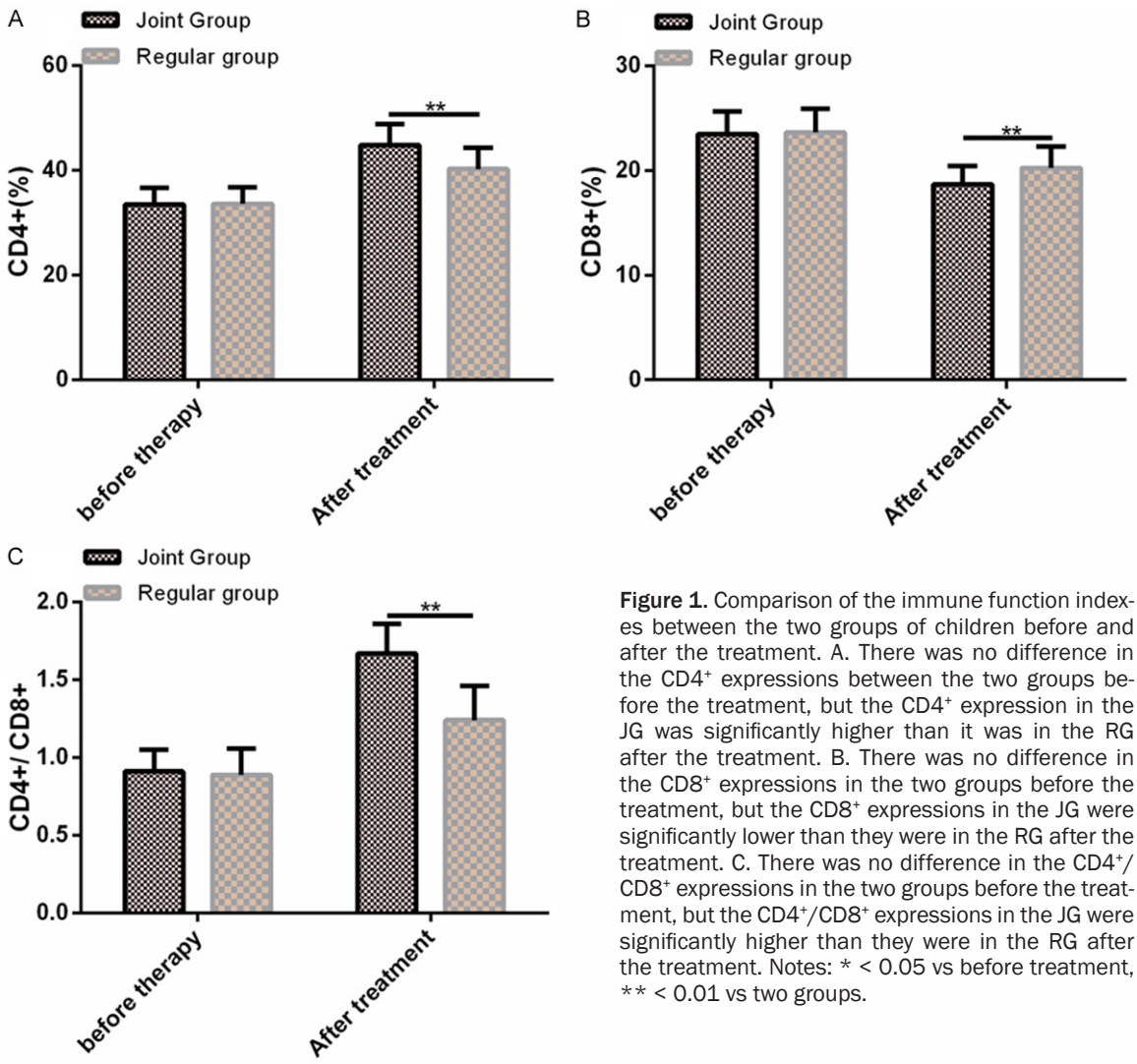

Figure 1. Comparison of the immune function indexes between the two groups of children before and after the treatment. A. There was no difference in the $CD4^+$ expressions between the two groups before the treatment, but the $CD4^+$ expression in the JG was significantly higher than it was in the RG after the treatment. B. There was no difference in the $CD8^+$ expressions in the two groups before the treatment, but the $CD8^+$ expressions in the JG were significantly lower than they were in the RG after the treatment. C. There was no difference in the $CD4^+/CD8^+$ expressions in the two groups before the treatment, but the $CD4^+/CD8^+$ expressions in the JG were significantly higher than they were in the RG after the treatment. Notes: * < 0.05 vs before treatment, ** < 0.01 vs two groups.

before the treatment (P > 0.05), but the expression levels of the three were significantly higher after the treatment (P < 0.05), and they were higher in JG than they were in the RG (P < 0.05), with statistically significant differences, as shown in **Figure 2**.

Comparison of the curative effects in the two groups of children after the treatment

After the treatment, the total effective rate in the JG was 95.45%, and in the RG the total effective rate was 78.33%. The total effective rate in the JG was significantly higher than it was in the RG (P < 0.05), with a statistically significant difference (**Table 5**).

The adverse reactions in the two groups of children during the treatment

Adverse reactions, such as pneumonia and hypoglycemia, occurred in both groups during the treatment, but they were all controlled. There was no significant difference in adverse reactions between the two groups (P > 0.05).

Discussion

NEC is an acute inflammatory disease of the intestinal tract that primarily affects preterm infants, and it is a major cause of morbidity and mortality in neonatal intensive care units [13]. Its pathogenesis is extremely complex [14, 15]. The children's clinical symptoms often include vomiting, abdominal distension, diarrhea, and bloody stools. It has been noted that gastrointestinal inflammation, gastrointestinal pathogenic flora disorders, and enteral feeding play important roles in NEC [16]. It also has been suggested that NEC is associated with poor systemic immune function and intestinal barrier function in children [17]. Therefore, it is of great clinical significance to improve the intesti-

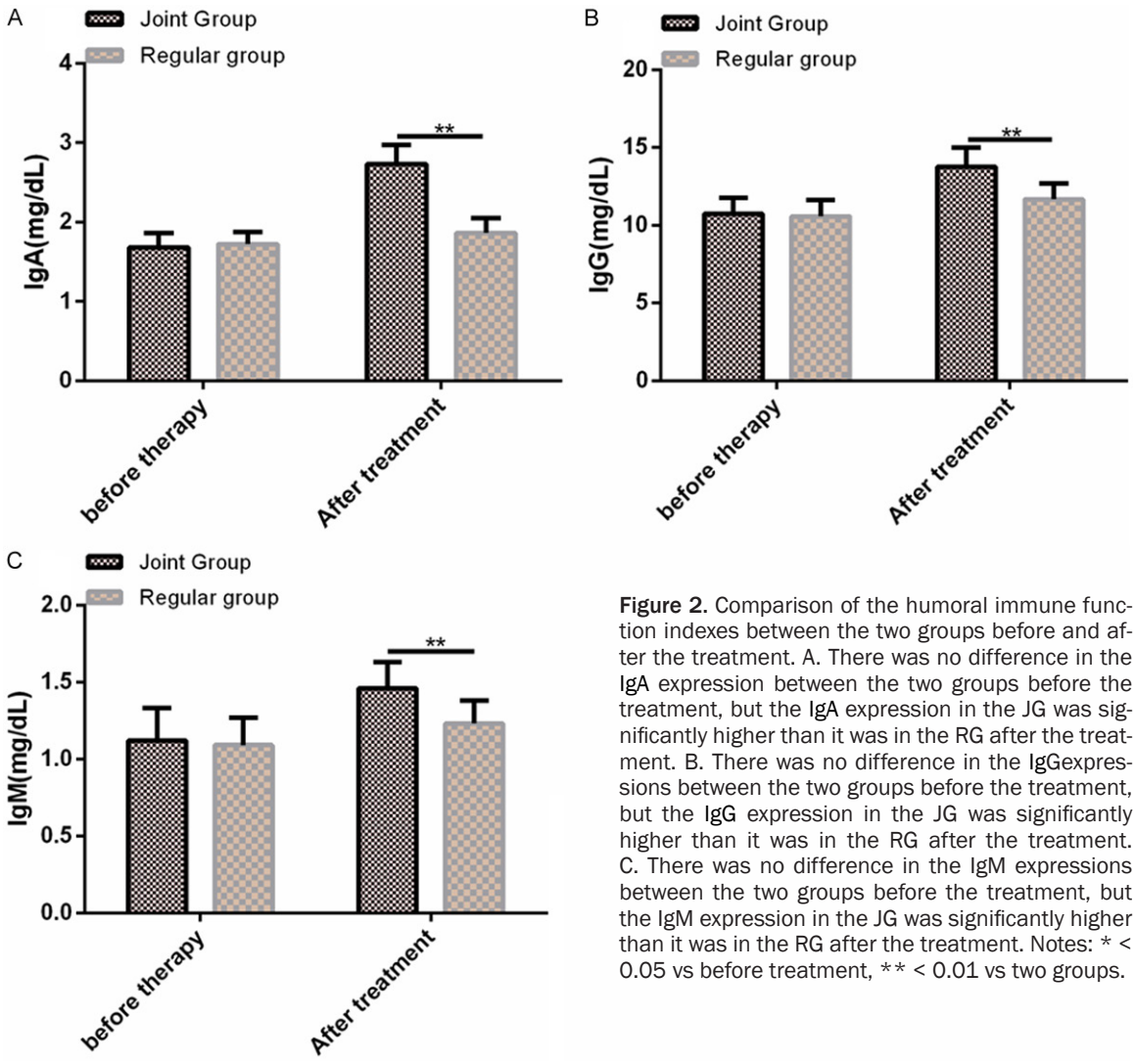

Figure 2. Comparison of the humoral immune function indexes between the two groups before and after the treatment. A. There was no difference in the IgA expression between the two groups before the treatment, but the IgA expression in the JG was significantly higher than it was in the RG after the treatment. B. There was no difference in the IgGexpressions between the two groups before the treatment, but the IgG expression in the JG was significantly higher than it was in the RG after the treatment. C. There was no difference in the IgM expressions between the two groups before the treatment, but the IgM expression in the JG was significantly higher than it was in the RG after the treatment. Notes: * < 0.05 vs before treatment, ** < 0.01 vs two groups.

Table 5. Comparison of the curative effects in the two groups of children after the treatment [n (%)]

Group	n	Marked response	Effective response	No response	Total effective rate %
Joint group	66	42 (63.64)	21 (31.82)	3 (4.55)	63 (95.45)
Regular group	60	20 (33.33)	27 (45.00)	13 (21.67)	47 (78.33)
T	-				8.310
P	-				0.004

nal flora and the immune function of children in the prevention of neonatal NEC.

Octreotide can inhibit gastrointestinal peristalsis, reduce intestinal hypersecretion, and enhance the intestinal absorption of NA^+ [18]. In recent years, octreotide has been increasingly used in the treatment of neonatal diseases such as gastrointestinal bleeding, neonatal enterocutaneous fistula, NEC, neonatal chylothorax, and the like [19, 20]. A balance in the complex interactions of the intestinal microbial community is essential to intestinal health. Probiotics can improve the balance of bacteria and prevent NEC [21]. In this study, octreotide combined with probiotics was used to treat NEC, and it was found that the children's conditions improved significantly after this treatment intervention. The results of this study show that the diarrhea remission times, the abdominal distension remission times, the enteral nutrition recovery times, and the lengths of the hospitals stay of the children in the JG were notably shorter than the corresponding values in the RG, which indicates that

octreotide combined with probiotics can effectively alleviate children's clinical symptoms and promote their recovery from NEC. Clinical research shows that enteral nutrition intervention should be given to children with extremely low birth weight as early as possible, in order to effectively reduce the occurrence of NEC [22]. Also, according to this study, the ALB and PAB expressions in the JG were notably higher than they were in the RG after the treatment, suggesting that the administration of octreotide combined with probiotics can effectively increase the ALB content in NEC children, thus effectively promoting intestinal function recovery in the children.

One study suggested [23] that the lack of intestinal flora in newborns leads to an imbalance of the normal intestinal flora, which is also a reason why newborns suffer from NEC. Therefore, the timely supplementation of intestinal probiotics has an auxiliary role in preventing NEC. Probiotics can stimulate beneficial bacteria and reduce adverse bacteria, balancing the intestinal flora, a finding similar to this study's results, namely that the expressions of the intestinal flora in the two groups of children after the treatment were remarkably higher than they were before the treatment, and the total number of bacilli, the total number of cocci, and the ratio of cocci to bacilli in the JG after the treatment was remarkably higher than it was in the RG, indicating that the use of octreotide combined with probiotics intervention can help children have normal intestinal flora as soon as possible and can promote the formation of the normal intestinal microbial balance, thus better promoting patient recovery [24]. Newborns with low immune function are more prone to NEC, so we should pay attention to improving patients' immune function when treating diseases [25]. One study [26] found that cellular immunity and humoral immunity are involved in the NEC immune response process at the same time, in which IgA is an important mediator of humoral immune function, and T lymphocytes are an important mediator of cellular immune function. Octreotide is a commonly-used drug in the clinical treatment of gastrointestinal diseases, and it can promote the secretion of peptide hormones in the intestinal tract, thus increasing intestinal function [27]. Probiotics, however, can regulate the function of the innate/acquired immune system functions, triggering the mucosal and systemic immune responses, leading to significant changes in the intestinal flora, and regulating the Th1/Th2 balance to avoid allergies [28]. Here, the $CD4^+$, $CD4^+/CD8^+$, IgA, IgG, and IgM levels in the NEC children were decreased, while the $CD8^+$ level increased. After the treatment, the immune function and humoral immune indexes of the children improved significantly in both groups, and the $CD4^+$, $CD4^+/CD8^+$, IgA, IgG, and IgM expressions in the JG were significantly higher than they were in the RG, but the $CD8^+$ in the JG were lower than they were in the RG, indicating that octreotide intervention can improve the immune function, and the probiotic intervention can further enhance the above effects. One study suggested that octreotide has a high curative effect on patients with acromegaly complicated with ulcerative colitis, and the patients experienced a steady clinical remission in both diseases after the intervention [29]. This above result is also the same as the result obtained from this study, that the total effective rate was notably higher in the JG after the treatment in comparison with the RG, indicating that octreotide combined with probiotics intervention can improve the nutritional status and immune function of children with NEC and alleviate their conditions, which has a high therapeutic effect. Adverse reactions, such as pneumonia and hypoglycemia, occurred in both groups during the treatment, but they were all controlled, and no difference could be found between the two groups, indicating the high curative effect of the two treatment methods.

To sum up, octreotide combined with probiotics can improve the adverse signs and abdominal symptoms in children with NEC and improve their nutritional status, immune function, and intestinal flora. However, there is some room for improvement in this study. For example, we can add basic experiments on the therapeutic mechanisms of the two treatments and explore the risk factors affecting the patients' treatment effects at the molecular level. Also, we can also add pathological studies on inflammation related to children with NEC. In the future, we will progressively improve our research from the above perspectives.

Disclosure of conflict of interest

None.

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