Comparing the Response to Pedilact in Term and Preterm Neonates under Phototherapy

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Abstract

Introduction: Hyperbilirubinemia is a common neonatal problem that occurs in about 60% of term and 80% of preterm infants during the first week of life. The increase of intestinal enteropathic cycle by intestinal beta-glucuronidase is one of the main mechanisms in the exacerbation of jaundice. Despite the relative lack of bacterial flora in the intestines of neonates during the first week of life and considering the differences in intestinal bacteria in term and preterm neonates, the present study evaluated the therapeutic response to pedilact in two groups of neonates.

Materials and Methods: This clinical trial study was performed on 97 term and preterm neonates aged 2 to 15 days after obtaining the approval of the Ethics Committee and parental consent. Inclusion criteria included age 3-14 days, serum bilirubin 15-22mg/dl, exclusive breastfeeding, and no risk factor for hemolysis. In addition to phototherapy, all infants received 5 drops of pedilact daily. Phototherapy conditions were the same in both groups. Serum bilirubin checked daily. The variables of sex, gestational age, and daily bilirubin level were recorded and compared.

Results: The minimum and the maximum gestational age of the neonates were 35 and 41 weeks, respectively. There was no difference between median, mean, and standard deviation of bilirubin reduction during hospitalization days between two groups (P= 0.451).

Conclusion: The results of this study indicate that the Micrococcus luteus SEHD031RS strain can be used as an effective microorganism in removing chromium from industrial wastewater or environmental bioremediation.

Keywords:
Hyperbilirubinemia, Microbiota, Phototherapy, Premature birth, Synbiotics, Term birth

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Introduction

Hyperbilirubinemia is a common and often benign neonatal problem that occurs in about 60% of term and 80% of preterm infants during the first week of life. Neonatal jaundice is a serious neonatal disease and is one of the most important causes of neonatal hospitalization worldwide, which is considered to be an increase in total bilirubin serum (TBS) levels above the 95th percentile for age in the first week of life. Bilirubin is one of the end products active in the catabolism of hemoglobin in the reticuloendothelial system and its clinical significance in infants is its tendency to deposit in the skin and mucous membranes that cause visible jaundice. One of the main mechanisms in the development and exacerbation of physiological jaundice is an increase in the intestinal enteropathic cycle. An important point in the mechanism of enteropathogenic circulation is beta-glucuronidase enzyme, which is present in term and preterm neonates at high concentrations. One of the causes of elevated bilirubin in neonates is the lack of conversion of conjugated bilirubin to stercobilin, which results in a lack of bacteria in the gut during the first week of life. Infants have relatively high concentrations of unconjugated bilirubin in their intestines, which is attributed to enterohepatic circulation. Intestinal bilirubin results from increased production of bilirubin, excessive hydrolysis of bilirubin glucuronide, and high concentrations of bilirubin in meconium. Also, the relative lack of bacterial flora in the intestines of infants to reduce the conversion of bilirubin to urobilinogen increases the intestinal storage of bilirubin compared to older children and adults.

The relative lack of bacterial flora in the intestines of neonates increases the intestinal of bilirubin compared to older children. Hyperbilirubinemia is also attributed to excessive beta-glucuronidase activity in a sterile gut. Dysbiosis is one of the most important causes in the development or exacerbation of neonatal jaundice. The gut microbiome did not evolve at birth and is developing from prenatal to about three years of age.

Prebiotics are human indigestible foods that can be consumed by microorganisms in the gut and stimulate the selective growth of a limited number of beneficial intestinal bacteria and provide beneficial conditions for the host. Probiotics are living organisms that, when administered, bring health to the host. All probiotics are isolated from humans, which are administered orally, and increase the specific species of microbes in the gastrointestinal tract that are beneficial to humans. Symbiotics are a synergistic combination of probiotics (living organisms that, when prescribed, bring health to the host) and prebiotics (indigestible foods by humans that can be consumed by microorganisms) used to enhance modifying gastrointestinal bacterial colonies. The role of probiotics in the human body has been described by several pharmacological mechanisms.

Prebiotics and probiotics have been observed to have a beneficial effect on the enteropathic cycle, including better gastrointestinal motility and improved stool viscosity. Prophylactic or therapeutic effects of prebiotic or probiotics had been revealed in numerous previous studies.

Despite the different gut microbiota in full-term and preterm infants, the present study compares the process of bilirubin reduction with pedilact administration along with phototherapy.

Methodology

The study populations are term and pre-term neonates admitted due to jaundice. Inclusion criteria included Age 3-14 days, bilirubin between 22 and 15, exclusive breastfeeding, no risk factor for hemolysis. Exclusion criteria included Sepsis and underlying disease, hematoma, ABO, RH dissatisfaction, G6PDD, transfer to intensive care unit, diabetic mother, evidence of bleeding, polycythemia, phenobarbital treatment, Down syndrome, Family history of immunodeficiency, blood transfusions, antibiotic therapy, evidence of hemolysis and serum administration. 97 neonates were enrolled in the study after obtaining the approval of the Ethics and Parental Consent Committee. This study was approved with the code of ethics number IR.GUMS.REC.1397.196 and with the IRCT code number IRCT2018.228.38895N1 on clinical trials.

All infants were given 5 drops of pedilact once daily until the day of discharge before breastfeeding along with phototherapy. Pedilact drops made by Iran Bio-fermentation Company and containing three types of probiotics (Lactobacillus ruten, Lactobacillus romanus and Bifidobacterium infantis at 109 coloni count per ml and also the fructooligosaccharide as prebiotic. The pedilact drop was stored in the refrigerator and removed from the refrigerator ten minutes before...
administration. Phototherapy conditions were the same in both groups. Infants with bilirubin above 18 received rotational phototherapy and those with bilirubin between 15 and 18 received four-lamp phototherapy. The standard of phototherapy treatment was according to the guidelines of the American Academy of Pediatrics. Neonates discharged with bilirubin below 11. Neonates were divided into two groups: full-term and pre-term, as well as three subgroups (under 37 weeks, between 37 to 39 weeks and above 39 weeks) and were compared in terms of serum bilirubin reduction during hospitalization. The variables of sex, gestational age, and daily bilirubin level until the day of discharge were recorded and entered SPSS software. Bilirubin reduction process was compared in the two groups and also in three subgroups.

**Results**

21 neonates (21.6%) were pre-term and 77 neonates (78.3%) were full-term. 21.6% of infants were < 37 weeks, 65% between 37 and 39 weeks and 11% > 39 weeks. Of the total neonates, 51 were male and 46 were female, with no statistical difference in terms of gender (p = 0.41). The minimum and the maximum gestational age of the neonates were 35 and 41 weeks respectively.

| Table 1. Comparison of bilirubin reduction during hospitalization between two groups |
|---------------------------------|---------------------------------|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|
| Term/preterm                   | Mean, median and standard deviation of bilirubin reduction from first day of admission until discharge | P               | Mean            | 7.91            | P = 0.451       | Standard deviation | 1.24            |
| Term                           | Mean                          |                | Median          | 8:00            |                | Median          | 8.53            |
| Preterm                        | Mean                          |                | Median          | 8:00            |                | Median          | 8:00            |

Repeated ANOVA test method

According to Table 2, there was no difference between median, mean and standard deviation of bilirubin reduction during hospitalization days between 2 groups (P = 0.451).

| Table 2. Comparison of bilirubin reduction during hospitalization according to gestational age status |
|-----------------------------------------------------------------------------------------------------|---------------------------------|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|
| Gestational age (week)                                                                           | bilirubin reduction during hospitalization | P               | Mean            | 7.91            | P = 0.473       | Standard deviation | 1.24            |
| <37 weeks                                                                                         | Mean                          |                | Median          | 8.00            |                | Median          | 8.63            |
| 37-39 weeks                                                                                       | Mean                          |                | Median          | 8.20            |                | Median          | 2.30            |
| >39 weeks                                                                                        | Mean                          |                | Median          | 7.92            |                | Median          | 7.8             |

Repeated ANOVA test method

According to the findings of Table 3 mean, median and standard deviation of bilirubin reduction during hospitalization days, did not show a statistically significant difference in different gestational ages (p = 0.473).

**Discussion**

The role of probiotics in the human body has been described by several pharmacological mechanisms. Probiotics can improve the balance of intestinal microbiota, which will definitely affect the enteropathic cycle. On the other hand, by improving intestinal peristalsis, they cause better excretion of bilirubin. Microbiological preparations, including probiotics, can reduce enterohepatic circulation by altering the normal intestinal flora and inhibiting beta-glucuronidase activity. So far, many studies have been performed to prove the effectiveness of probiotics or prebiotics on the development or treatment of
neonatal jaundice, most of them achieved positive results. Therefore, in this study, we did not consider a control group without receiving probiotics. Some bacteria, such as Bifidobacteria, can directly hydrolyze bilirubin. The human digestive system has 100 trillion organisms, which is about 10 times the total number of cells in the body. Of these, about 99% are anaerobic. Studies revealed that the diversity of digestive microbes varies from person to person.

Previous studies have shown that the mother's uterus is a sterile environment and that the first gastrointestinal microbiomes enter the neonatal gastrointestinal tract during the first minutes after birth. Recent studies have concluded that bacterial colonization begins through placenta from intrauterine life. The gastrointestinal microbiome is constantly developing and will look exactly like an adult by about 3 years of age.

In the first 48 hours after birth, aerobic microbes such as Enterobacteriaceae and then gradually anaerobes such as Clostridium and Bifidobacterium and Bactoid enter the digestive system and during the first 4 weeks Streptococcus lactobacilli are added. In full-term infants, the intestines of newborns are generally colonized within 10 days, but in pre-term infants this time is longer and even this time is considered up to 3 weeks longer. Lactobacillus, Bifidobacterium and bacteroids deficiency is present in pre-term infants. In full-term infants at 7 days of age, bifidobacterium colonization occurs, but in pre-term infants it does not occur. On the other hand, there is more Enterobacteriaceae and Staphylococcus aureus in premature infant's gut. Prebiotics in pedilact drop themselves stimulate the growth of Lactobacillus and Bifidobacterium and increase intestinal motility. On the other hand, even consuming small amounts of a pre or probiotic containing formula along with breast milk might to microbial shift. Knowing the above, in the present study, infants who were fed formula or combined breastfeeding and formula were not enrolled in the present study. Considering the effect of antibiotics on the intestinal microbiome of infants, receiving any antibiotics was one of the exclusion criteria in this study. In 2015, Liu and et al studied the effects of probiotics in the treatment of jaundice in term infants, but did not include premature infants. Jamayaca and Bisglasi and et al investigated the prophylactic effect of Bacillus clausii on the development of jaundice in full-term and full-term infants, but did not compare the difference in response between term and preterm neonates. Armanian and et al investigated prophylactic effect of probiotics on premature infants and revealed positive results but term neonates excluded from study. Premature infants, even if not hospitalized and treated with antibiotics, have a different bacterial flora than full-term infants due to lack of bowel development and reduced bowel movements and higher risk of cesarean section. Alternatively, they are at risk of growing pathogenic bacteria.

The current study revealed no significant difference in bilirubin reduction rate during hospitalization in term infants compared to preterm and both groups experienced a similar decreasing trend. Also, in the present study, we did not find any difference in the rate of serum bilirubin reduction with pedilact administration in the subgroups of gestational age (under 37 weeks, between 37 to 39 weeks and above 39 weeks) and the decreasing trend of bilirubin was similar in sub groups.

In the present study, we expected that due to the poverty and differences of intestinal microbiota in all neonates and the fact that this issue is more pronounced in preterm infants, symbiotic administration reveal more beneficial effects in the preterm group compared to full-term infants along with beneficial adjuvant effects on both groups. Perhaps the reason for this result is the type and dose of prescribed synbiotic. The method of delivery affects the microbiota in first months of life, which we did not consider and was the limitation of the present study. Neonates born by NVD are colonized with germs from the mother's vagina such as Lactobacillus and Provatella, but neonates born by cesarean section are more likely to be colonized by epithelial germs such as Clostridium, Staphylococcus, Propionobacterium, and Corynebacterium.

Breastfed neonates are more likely to be colonized by Enterobacteriaceae, Bifidobacterium, Lactobacillus, and Bacteroids. Due to difference in oligosaccharide added to formula from breast milk, the microbial flora of formula fed neonates are mostly Ecoli, Clostridium difficile and provatella.

On the other hand, due to serum therapy and antibiotic initiation, most of the preterm neonates excluded from the study, the minimum age of the neonates was 35 weeks. The lack of significant differences in terms of gestational age in the full-term and full-term neonates enrolled in the present study may be the reason for these results.
**Conclusion**

Despite the difference in gut microbiota, pre-term neonates did not show a different therapeutic response to pedilact compared to full-term neonates, and the decreasing trend of bilirubin was similar in both groups. **Limitation:** In our study, we did not consider the type of fecal basal microbes before and after synbiotic administration due to cost and laboratory limitations. On the other hand, we did not consider the type of delivery and receiving the mother’s antibiotics. **Recommendation:** It is suggested that in similar studies, the larger sample size, the greater the difference in gestational age range, and the effects of type of delivery should be considered by researchers.

**Acknowledgment**

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**Conflict of Interest:** The authors declare that there are no conflict of interest regarding the publication of this manuscript.
مقایسه پاسخ نوزادان ترم و پرترم ایکتیک تحت درمان با فتوتراپی به تجوز پدیلاکت

مرجعه: زرکی، سیده آزاده حسینی نوری، یلدا نوبی، مینی تبریزی، احسان کاظم نژاد. رشت، ایران

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تاریخ دریافت: 1401/04/29

چکیده

هبوبیپیلی روی‌پیدا، مشکل شایع نوزادان فلور ناهنجاری‌های بدن متحف و پره‌داری با کمک آزمایش‌های بیماری‌شناسیی قابل شناسایی و در صورت احتمال ناهنجاری‌های متغیر فلور ناهنجاری‌های بدن متجه و پره‌داری با کمک آزمایش‌های بیماری‌شناسیی قابل شناسایی و پنهان شهره است. تحقیقات مربوط به اثرات آنژیئیک بر روی سایر سیستم‌های زنده در نوزادان فلور ناهنجاری‌های بدن متجه و پره داری با کمک آزمایش‌های بیماری‌شناسیی قابل شناسایی و پنهان شهره است. تحقیقات مربوط به اثرات آنژیئیک بر روی سایر سیستم‌های زنده در نوزادان مراجعه شده است. این تحقیق نشان می‌دهد که در نوزادان ترم و پرترم با فتوتراپی، معامله‌های حاضر متناسب با کاهش درمان پرورشی به روش می‌باشد. 

کلیدواژه‌ها: نوزاد ترم، سیب‌پرپونه، هبوبیپیلی، پرترم، فتوتراپی
ملاحظات اخلاقی
پس از توضیحات کافی در مورد طرح از ویژگیهای مطالعه، رضایت‌مانه کننده‌ای از نظر احترام به احترام، این مطالعه در کتاب "علم پزشکی گیلان" شماره 1377 موسسه بررسی روش‌های مفید برای درمان اختلالات عمومی نوزادان، از جمله اختلالات اضطرابی، از گروه تجربی بسته شد.

مقاله حاضر به مطالعه کارآمدی پایین‌ترین در یک پژوهش زمینه مطالعه، رضایت‌مانه کننده‌ای از نظر احترام به احترام، این مطالعه در کتاب "علم پزشکی گیلان" شماره 1377 موسسه بررسی روش‌های مفید برای درمان اختلالات عمومی نوزادان، از جمله اختلالات اضطرابی، از گروه تجربی بسته شد.
مقایسه پایه‌بندی نوزادان ترم و پرترم ایکتیکی

中心یت ایلاتی قابلیتی با شماره 95/4818۲۸۳۸۸۹۲۸ مورخ ۱۳۹۲/۴/۲۸ رسید.

داده‌ها وارد نرم‌افزار SPSS ورژن ۲۱ شدن و به‌وسیله آماره‌های توصیفی تعداد، میانگین و انحراف معیار گزارش شدند.

نمایی‌بخش داده‌ها وارد نرم‌افزار SPSS ورژن ۲۱ شدن و به‌وسیله آماره‌های توصیفی تعداد، میانگین و انحراف معیار گزارش شدند.

بی‌توجه ممکن است استفاده در زبان‌هایی‌ستند نورمال بیلی‌روبی در جزئیاتی استفاده شده.

در صورت نورمال بیلی‌روبی در جزئیاتی استفاده شده.

جدول ۳. مقایسه کاهش بیلی‌روبی دروز ترخیص برحسب وضعیت ترم ایکتیکی ترم وا یا پرترم بودن

<table>
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<th>ضعیت سن حاملگ</th>
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</tr>
</tbody>
</table>

Mean

Standard deviation

Median

P

451

Standard deviation

Median

P

451

Repeated ANOVA test method

طبق جدول ۲ از سن حاملگ، میانگین و انحراف معیار، میزان کاهش بیلی‌روبی دروز ترخیص برحسب وضعیت ترم ایکتیکی ترم وا یا پرترم بودن، تفاوتی در پاسخ بپیداگفت از نظر کاهش بیلی‌روبی حاصل نشد.

جدول ۴. مقایسه کاهش بیلی‌روبی دروز ترخیص برحسب وضعیت سن دیفرانسیال

<table>
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<td>پرترم</td>
<td>۸/۵۷</td>
</tr>
</tbody>
</table>

Mean

Standard deviation

Median

P

451

باین بیوتیک درکنار فتوتراپی نیز از نظر ترم و پرترم بودن، تفاوتی در پاسخ بپیداگفت از نظر کاهش بیلی‌روبی حاصل نشد.
کمتر بود [6]. وی برخلاف مطالعه حاضر، نوزادان پرترم سالم نکته آن که هنوز ایکتیک نشانه وارده مطالعه کرد و تأثیرات پروفیلاکتیک مثبت را نشان داد. تکرم و همکاران نیز نوزاد تمرا که تحت درمان کمکی با پروبیوتیک قرار دادند و مطالعه آنها روی کاهش بیلی و بیشتر و سریع‌تر را نشان داد ولی در این مطالعه نیز نوزادان پرترم وارد مطالعه نشدند [22].

این نتایج می‌تواند به منشأ درآمده باشد که بروز ویروس در کمترین مدت دوره زمانی و همچنین در اکثر نوزادان پرترم بروز بیماری آن است. 

این نتایج می‌تواند به منشأ درآمده باشد که بروز ویروس در کمترین مدت دوره زمانی و همچنین در اکثر نوزادان پرترم بروز بیماری آن است. 

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<tr>
<td>0.473</td>
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</tr>
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<td>0.782</td>
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</tr>
</tbody>
</table>

جدول 1. بررسی تفاوت در بیلی در دو گروه نوزادان ترم و پرترم.

به‌طور آماری مثبت را نشان داد. ترکمن و همکاران نیز درمانی به محصولات پروبیوتیک بپردازد نکردند. بیلی بیشتر و سریع‌تر در گروه پروبیوتیک به همراه فتوتراپی (پدیکس) درمانی به میزان بالاتری در نوزادان ترم و پرترم مشاهده شد. به طور قابل توجهی در گروه پروبیوتیک با پروبیوتیک برای همکاران در مطالعه حاضر مشاهده نشد. این مطالعه نیز نشان داد که بروز ویروس در کمترین مدت دوره زمانی و همچنین در اکثر نوزادان پرترم بروز بیماری آن است. 

این نتایج می‌تواند به منشأ درآمده باشد که بروز ویروس در کمترین مدت دوره زمانی و همچنین در اکثر نوزادان پرترم بروز بیماری آن است.
مطالعه هال و شارما در مطالعه حاضر به دلیل محدودیت‌های آزمایشگاهی امکان تحلیل بررسی میکروب‌های مصرف‌پذیر دارد. و یکی از مهم‌ترین محدودیت‌های مورد راه‌حل کننده از این منظر به خوبی اعمال می‌شود.

روش زایمان و مصرف آنتی‌بیوتیک‌ها تأثیر نیز بر فلور مصرف‌پذیر دارد. نوزادان تا حدی تسلیح های مصرف‌پذیر می‌شود و بر روی تولید آنتی‌بیوتیک‌ها می‌تواند اثر نسبی داشته باشد. و نیز در مطالعه حاضر به خوبی اعمال می‌شود.

روش زایمان به دلیل فلور مصرف‌پذیر در نوزادان تأثیر نیز بر فلور مصرف‌پذیر دارد. و نیز در مطالعه حاضر به خوبی اعمال می‌شود.

روش زایمان به دلیل فلور مصرف‌پذیر در نوزادان تأثیر نیز بر فلور مصرف‌پذیر دارد. و نیز در مطالعه حاضر به خوبی اعمال می‌شود.
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