Probiotics for the management of Neonatal hyperbilirubinemia

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Abstract

Background In recent years, the tendency to use drugs has been increasing in the treatment of neonatal jaundice. Several drugs have been used since then, but the effect of probiotics on serum bilirubin level (SBL) is not so clear. This study was conducted to evaluate the effect of probiotics on SBL and the duration of phototherapy in term neonates with hyperbilirubinemia. Objective/ the aim of the work: To evaluate and assess the therapeutic effects of the probiotic substance on neonatal jaundice. Subjects and Methodes: - In this Experimental Randomized clinical trial study we studied (400) newborns with jaundice hospitalized for phototherapy in kenayate Hospital in zagazig during 5/2017 to 5/2018 - Eligible neonates were Randomly divided into two groups: 1) Intervention (n = 200) 2) control (n= 200) Both groups receive standard conventional phototherapy but the intervention group received 250mg lactobacillus powder with milk as a probiotic substance until hospital discharge. The out come variable were. TSB and the duration of phototherapy.- the data were analyzed by (SPSS version 20.0) and p value was at (< 0.05) for significant, (< 0.01) for high significant. Results - TSB (out)/on discharge after hospitalization of intervention group was a mean: 9.39 ± 1.35 and of control group was a mean: 9.89 ± 0.9, (TSB) was highly significant lower in intervention group / on discharge with aprobiotic substance than the control Group/ on discharge without aprobiotic substance. Duration of hospitalized days needed to stay under the phototherapy treatment are of intervention group is a mean of : 4.84 ± 0.62 and of control group is a mean of 5.785 ±0.801 , Conclusion: Probiotics lowered the serum bilirubin levels of neonates with jaundice and decrease the duration of hospitalized days under phototherapy treatment Recommendation: This study recommended that we can use a probiotic substance within a plane of management of neonatal hyperbilirubinemia. Key words: total serum bilirubin, phototherapy, probiotics.

الملخص العربي

تمثل نسبة حالات الصفراء في الدم في الأطفال حديثي الولادة حوالي 65% منهم وتزداد النسبة في الأطفال ناقصي النمو والعمر الجنيني وناقصي الوزن.

فمن الناحية الوظيفية: تعرف صفراء الدم بأنها زيادة في نسبة مادة البيليروبين في الدم والتي تنتج عن:

ثانيا: نقص في عملية ارتباط البيلروبين مثل حالات الصفراء الفسيولوجية وبعض المتلازمات المرضية.

تحتوى أمعاء الطفل علي بكتيريا تقوي مناعته ضد البكتيريا الضارة تسمي (بروبيوتيك).

- وفكرة الدراسة في هذا البحث هو إدخال مادة خارجية تسمي (البروبيوتيك) وهي متواجدة فعلا في أمعاء الطفل ولكن بنسبة قليلة أو غير ناضجة نتيجة نقص العمر الجنيني للطفل، أو نقص الوزن الحاد، مما تؤدي هذه المادة(بروبيوتيك) إلي تقليل نسبة صفراء الدم عن طريق عدة طرق إكلينيكية ستوضح في العمل بالتفصيل.

= قد اشتملت هذه الدراسة علي (400) طفل حديثي الولادة مصابا بالصفراء مقسمين إلي مجموعتين:

(1) المجموعة الضابطة: مكونة من (200) طفل مصابا بالصفراء تخضع للعلاج بالأشعة الضوئية ( الفوتوثيرابي) فقط

(2) المجموعة التداخلية: مكونة من (200) طفل مصابا بالصفراء تخضع للعلاج بالأشعة الضوئية (الفوتوثيرابي) بالإضافة إلي مادة (البروبيوتيك) تضاف مع رضعات اللبن الصناعي للطفل

= قد تم قياس مستوى صفراء الدم لكل طفل مع بداية دخوله في المحضن وكل ثاني يوم أو كل يوم حسب شدة حالته.

= تم عمل جداول إحصائية لهذه القياسيات وبعد التحليل الإحصائي باستخدام برنامج كمبيوتر 1س بي اس اس 2012 وتبين منها الآتي:

(1) يوجد انخفاض ملحوظ في نسبة صفراء الدم لأطفال المجموعة التداخلية الذين خضعوا للعلاج بمادة (البروبيوتيك) بنسبة انخفاض أعلي من أطفال المجموعة القابضة الغير خاضعة للعلاج بمادة (البروبيوتك).

الهدف من العمل:

إن الهدف من هذا العمل هو: تأثير مادة البروبيوتيك على صفراء الدم للأطفال.

الخلاصة في الدراسة

تستخلص من الدراسة أنه يمكن استخدام مادة ( البروبيوتيك) في علاج صفراء الأطفال حديثي الولادة والوقاية منها في أيام عمرهم الأولي.

التوصيات:

توصي الدراسة بإمكانية استخدام مادة ( البروبيوتيك) لعلاج صفراء الأطفال حديثي الولادة بدون مضاعفات كعلاج مساعد مع العلاج بالأشعة الضوئية وكوقاية للأطفال في أيام عمرهم الأولي من الإصابة بالصفراء.

Introduction:

\* Infantile microbiota :

- The mature GIT contains a large quantity of microbiota. that play a role in protecting infant and promoting health functionality.

- The normal development of the human GIT depends on the presence of complex gastro intestinal microbiota.

-Probiotic : It's a living friendly bacteria or micro - organism in the intestine.

- Have health Benefit on the host.

- It's a normal intestinal flora.

- Controlls the growth of harmfull bacteria.

which, when administered in adequate amounts, confer a health benefit on the host, (Bjarnasdn I, MacPherson A, Hollander1995 )

- Most commonly available probiotic supplements contain Lactobacillus and/or Bifidobacterium, which are part of the normal human microbiotic. (Bertini G, Dani C. Neonatol.; 2012)

Current recommendations for the management of hyperbilirubinemia in preterm infants have focused on determining age - specific bilirubin levels for initiating phototherapy.

(Maisels MJ, Watchko JF, Bhutani VK, Stevenson DK.2012)

However, there is concern regarding Potential adverse effects. of aggressive phototherapy in preterm infants.)

Besides blue light phototherapy, and drugs, probiotics have also been used to enhance immunity mainly by regulating bacterial colonies. They can form a biological barrier by specifically binding intestinal epithelial cells through teichoic acid. Therefore, particular attention has-been paid to the use of probiotics in treating neonatal jaundice. (Tyson JE, Pedroza C, Langer J, et al.2012)

Probiotic microorganisms are typically members of the genera Lactobacillus, Bifidobacterium, anAstreptococcus. However, yeast such as Saccharomyces boulardii is also a probiotic microorganism.

Methods

- This study was carried out in the Neonatal intensive care unit of kenayat- hospital in zagazig for all the cases of two groups

- Laboratory investigations were done in clinical pathology department in the same hospital.

- It was held in between May 2017 and May 2018.

\* subjects included in the study:

(400) of Jaundiced newborn cases included both full – term and pre – term.

Age: Ranges between 1st day of life the to the 7th day.

Sex: both males and females.

- The studied neonates were classified into (2) groups.

Group (1) intervention Group: included 200 neonates of high total serum bilirubin level which necessitated phototherapy treatment.

Group (2) Control Group: included 200 neonates of high total serum bilirubin level which necessitated phototherapy treatment.

- Clinically significant indirect hyperbilirubinemia was defined according to data blotted on the chart of guidelines for phototherapy in hospitalized infants obtained from American Academy of pediatrics.

Subcomitte on hyperbilirubinemia.

3- Routine laboratory investigations:

- Completes blood count (CBC) before and after treatment by automated cell counter (cell dyne 1700).

- ABO, RH grouping for neonates and mothers.

(Dacie and lewis, 2012).

- Reticulocyte count (Dacie and lewis, 2012)

- Comb's test (Dacie and lewis, 2012)

- C- reactive protein (CRP) (Sonntag and scholer 2001)

Special laboratory investigation:

- Total and direct bilirubin levels.

- on admission: before exposure to treatment

- every 2 days: during treatment

- before discharge: after treatment

Analysis procedure:

- Venous blood (3ml) were drawn from the newborn to detect serum bilirubin levels, After centrifugation at 3000 rlminutes for 10 minutes. The serum was collected and detected

Automated by auto analyzer. (COBAS 6000)

Automated by Bio chemical Analyzer with the oxidation method.

(Salinas M, et al,2012) (Wolff M., et al, 2012)

- Comparison between the two groups was done according to:-

(1) Rate of decline TSB

(2) Duration of exposure to.

Phototherapy and hospitalized duration.

\* Intervention:

All infants were fed with an initial dose of 70 ml/kg/day milk reaching to 150 ml/kg/ day breast or artificial milk.

- Parenteral nutrition was gradually tapered as enteral feeding volume was in creased.

- The infants were randomly allocated into the probiotic intervention and controlled group, infants in the probiotic group received a supplementation of sterilized probiotic supplementation a safe for VLBW infants in the short term.

- All infants in both groups are investigated by blood sample to detect the percentage of total and direct serum bilirubin, in the 1st , 3rd, 5th, 7th, days in the incubator.

Result

Table1: Age distribution between groups

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
|  | Intervention group(N=200) | Control group(N=200) | t | P  |
| Age  | 3.24±1.1 | 3.33±1.08 | -0.812 | 0.411 |

There was no significant difference between groups regard as age distributed 3.24±1.1 and 3.33±1.08 respectively

Table2: Gestational age distribution between groups

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
|  | Intervention group(N=200) | Control group(N=200) | t | P  |
| GA | 36.85±2.18 | 37.01±2.54 | -1.904 | 0.061 |

There was no significant difference between groups regard GA P = 0.061 as groups distributed as 36.85±2.18 and 37.01±2.54 respectively

Table3: weight distribution between groups

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
|  | Intervention group(N=200) | Control group(N=200) | t | P  |
| Weight | 3239.5±456.07 | 3306.0±463.18 | -1.447 | 0.149 |

There was no significant difference between groups regard weightP= 0.149 as groups distributed as 3239.5±456.07 and 3306±463.18 respectively

Table 4: Total bilirubin distribution between groups

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
|  | Intervention group(N=200) | Control group(N=200) | t | P  |
| Tbilirubinout | 9.39±1.35 | 9.82±0.91 | -3.685 | 0.00\*\* |
| Tbilirubinin | 17.97±2.31 | 18.28±4.74 | -1.718 | 0.075 |

Total bilirubin were high significantly lower in intervention group out ONLY, P =0.00 as distributed were 9.39±1.35 and 9.82±0.91 respectively, but no significant regard T bilirubin in P= 0.075 as distributed were 17.97±2.31and 18.28±4.74 respectively

Table 5:Change assessment in each group

|  |  |  |  |
| --- | --- | --- | --- |
| Group | Mean ±SD | Paired t | P  |
| Control group |  | T\_bilirubinin | 18.28±4.74 | 25.114 | 0.00\*\* |
| Tbilirubinout | 9.82±0.91 |
| Intervention group |  | T\_bilirubinin | 17.97±2.31 | 57.378 | 0.00\*\* |
| Tbilirubinout | 9.39±1.35 |

Both groups significantly decreased but more in intervention group

Table 6: Day before discharge distribution between groups

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
|  | Intervention group(N=200) | Control group(N=200) | t | P  |
| Days  | 4.84±0.62 | 5.785±0.801 | -13.115 | 0.00\*\* |

Days needed highly significantly lower in intervention group P= 0.00 as day distributed as 4.84±0.62 and 5.785±0.801 respectively

Table7: Correlations

|  |  |  |  |
| --- | --- | --- | --- |
| Group | Tbilirubinin | Tbilirubinout | Day |
| Control group | Tbilirubinin | r | 1 | .014 | -.076- |
| P  |  | .847 | .286 |
| Day | r | -.076- | -.081- | 1 |
| P  | .286 | .256 |  |
| GA | r | .266\*\* | .070 | -.423-\*\* |
| P  | .000 | .328 | .000 |
| WT | r | .201\*\* | .149\* | -.458-\*\* |
| P  | .004 | .035 | .000 |
| Intervention group | Tbilirubinin | r | 1 | .529\*\* | -.121- |
| P  |  | .000 | .087 |
| Day | r | -.121- | -.079- | 1 |
| P  | .087 | .267 |  |
| GA | r | .558\*\* | .404\*\* | -.233-\*\* |
| P  | .000 | .000 | .001 |
| WT | r | .540\*\* | .400\*\* | -.247-\*\* |
| P  | .000 | .000 | .000 |

\*\* significant + or – positive or negative correlation

In control group there were significant positive correlation between T bilirubin in and GA and weight also between T bilirubin out and weight, and there were significant negative correlation between days needed and GA and weight. Regard intervention group there were significant positive correlation between T bilirubin in and out with GA and weight also between T bilirubin out and in, there were significant negative correlation between days needed and GA and weight

Table 8:Type distribution between groups

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
|  | Group | Total | X2 | P  |
| Control group | intervention group |
| Type | Hemolytic  | N  | 33 | 43 | 76 | 1.8 | 0.4 |
| %  | 16.5% | 21.5% | 19.0% |
| Infectious  | N  | 35 | 36 | 71 |
| %  | 17.5% | 18.0% | 17.8% |
| Physiological  | N  | 132 | 121 | 253 |
| %  | 66.0% | 60.5% | 63.2% |
| Total | N  | 200 | 200 | 400 |  |  |
| %  | 100.0% | 100.0% | 100.0% |  |  |

No significant difference between groups

Table 9: Comparison among types in control group

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
| Group | N | Mean | SD | Minimum | Maximum | F | P  |
| Control group | Day | Hemolytic  | 33 | 5.7273 | .83937 | 5.00 | 7.00 | 1.981 | 0.141 |
| Infectious  | 35 | 6.0286 | .98476 | 5.00 | 8.00 |
| Physiological  | 132 | 5.7348 | .72953 | 5.00 | 8.00 |
| Tbilirubinout | Hemolytic  | 33 | 9.9788 | .89294 | 8.00 | 12.00 | 4.214 | 0.023\* |
| Infectious  | 35 | 9.6571 | .93755 | 7.00 | 11.00 |
| Physiological  | 132 | 9.4485 | .91205 | 8.00 | 11.00 |
| Tbilirubinin | Hemolytic  | 33 | 19.1515 | 1.69781 | 16.00 | 22.00 | 1.403 | 0.248 |
| Infectious  | 35 | 17.2857 | 1.67282 | 14.00 | 22.00 |
| Physiological  | 132 | 18.2848 | 5.68712 | 15.00 | 81.00 |

Bilirubin out significantly lower in physiological than other two groups and infection lower than hemolytic type as distribution was 9.44±0.91, 9.65±0.93and 9.97±0.89 respectively

Table 10: Comparison among types in intervention group

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
| Group | N | Mean | SD | Minimum | Maximum | F | P  |
| intervention group | Day | Hemolytic  | 43 | 4.8837 | .54377 | 4.00 | 6.00 | 0.790 | 0.455 |
| Infectious  | 36 | 4.7222 | .70147 | 4.00 | 7.00 |
| Physiological  | 121 | 4.8595 | .63647 | 4.00 | 6.00 |
| Tbilirubinout | Hemolytic  | 43 | 9.6279 | 1.44788 | 7.00 | 12.00 | 6.512 | 0.004\* |
| Infectious  | 36 | 9.1556 | 1.45297 | 6.00 | 10.00 |
| Physiological  | 121 | 8.6132 | 1.27586 | 6.00 | 10.00 |
| Tbilirubinin | Hemolytic  | 43 | 19.1256 | 2.11256 | 11.00 | 22.00 | 1.581 | 0.189 |
| Infectious  | 36 | 17.7222 | 2.64695 | 11.00 | 22.00 |
| Physiological  | 121 | 17.8231 | 2.18513 | 12.00 | 22.00 |

Bilirubin out significantly lower in physiological than other two groups and infection lower than hemolytic type as distribution was 8.61±1.2, 9.15±1.4 and9.62±1.44 respectively

Table 11: Total bilirubin distribution between groups in hemolytic

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
|  | Intervention group(N=200) | Control group(N=200) | t | P  |
| Tbilirubinout | 9.62±1.44 | 9.97±0.8 | -2.685 | 0.02\* |
| Tbilirubinin | 19.1±2.11 | 19.15±1.6 | -1.018 | 0.234 |

Total bilirubin were high significantly lower in intervention group out ONLY, P =0.02\* as distributed were 9.62±1.44 and 9.97±0.8 respectively, but no significant regard T bilirubin in P= 0.234 as distributed were 19.1±2.11and 19.15±1.6 respectively

Table 4: Total bilirubin distribution between groups in infection

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
|  | Intervention group(N=200) | Control group(N=200) | t | P  |
| Tbilirubinout | 9.15±1.45 | 9.65±0.93 | -3.878 | 0.00\*\* |
| Tbilirubinin | 17.72±2.6 | 17.28±1.6 | -1.754 | 0.068 |

Total bilirubin were high significantly lower in intervention group out ONLY, P =0.00 as distributed were 9.15±1.45 and 9.65±0.93 respectively, but no significant regard T bilirubin in P= 0.068 as distributed were 17.72±2.6 and 17.28±1.6 respectively

Table 4: Total bilirubin distribution between groups in physiological

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
|  | Intervention group(N=200) | Control group(N=200) | t | P  |
| Tbilirubinout | 8.61±1.27 | 9.44±0.91 | -4.547 | 0.00\*\* |
| Tbilirubinin | 17.82±2.18 | 18.28±5.68 | -1.841 | 0.061 |

Total bilirubin were high significantly lower in intervention group out ONLY, P =0.00 as distributed were 9.44±0.91 and 8.61±1.27 respectively, but no significant regard T bilirubin in P= 0.061 as distributed were 17.82±2.18and 18.28±5.68 respectively.

DISCUSSION

Neonatal hyperbilirubinemia is diagnosed when the total serum bilirubin is higher than accepted with respect to weight and age of the newborn. (American Academy of pediatics, 2004)

- Neonatal Jaundice, which is comnon in clinical practice, can mainly be classified as physiological and pathological ones. The former does not need special treatment but the later which originates from vaxious factors, easily lead to bilirubin encephalopathy and even brain damage or death. (Maisels et al 2012)

- The lack of bacteria in the gut during the newborn period has an impact on the enterohepatic circulation of conjugated bilirubin.

- The low bacterial load during this first week of life results in decresed conversion of conjugated bilirubin to stercobilin.

- The resultant high levels of conjugated bilirubin get converted to un conjugated bilirubin in the intestine by the enzyme beta – glucoronidase.

- The resultant high levels of un conjugated bilirubin gets absorbed and reaches the Blood stream resulting in un conjugated hyperbilirubinemia during this period.

- Neonatal Jaundice is caused by enhanced intestinal – hepatic circulation of bilirubin owing to high content and activity of B- glucuronidase (B- GD). ( Raju TN, 2012)

- B- GD can hydrolyze the bound bilirubin into unbound one and glucuronide, and the unbound bilirubin boost intestinal hepatic circulation after being absorbed by intestinal cells. (wang x 2006)

- Enteral feeding is often delayed in preterm neonates which may limit intestinal flow and bacterial colonization resulting in further enhancement of the enterohepatic circulation and increase in serum bilirubin level. (partner LMJ perinat al 2011)

- Very high total serum bifirubin (TSB) levels can injure the newborn central nervous system,

- For this reason, TSB levels in Jaundiced newborns are followed and treated with either photo therapy or exchange transfusion when they are at risk of rising or to have reached potentially dangerous level. (Newman et al 2012)

- In this study neonatal jaundice was treated by using lactobacilus that are normal microorganisms in the human intestinal tract.

(Wang et al 2006)

- After being orally talken, they grew in the intestinal tract to produce vitamins and to help the proliferation of normal bacterial colonies.

- Accordingly, lactobacillus (delbrueki, fermentum), 10 billons units accelerated jaundice fading by rapidly lowering the bilirubin level, by facilitating the growth of normal bacterial colonies in the intestinal tract of neonates and the resulting metabolites effectively corrected the slightly alkaline environment thus weakening the activity of B- GD and preventing it from binding and hydrolyzing bilirubin. (Maldonado et al, 2012)

Furthermore, the activities of liver enzymes were also enhanced, which benefited the excretion of and binding of bilirubin.

- The Roles of probiotics in human body have been explained by different pharma cological mechanisms, for example, they can rapidly increase the number of anaerobic bactenal colonies promotes the recovery of intestinal microflora balance, and resist infection in some cases, on the other hand, intestinal probiotics affect the amount of bilirubin in the enteroheptic circullation by reducing the degradation of bound bilirubin, Meanwhile they are able to stimulate intestinal peristalsis, which also benefits the elimination of bilirubin, it has been reported that oral administration of probiotics showed markedly better effects than those of routine blue light photo therapy.

- probiotic enhance the healthy microbiota of the gastrointestinal tract of the new born. (Raju, TN, 2012, Wang x 2006)

- They produce lactic, acetic, and other acids that lower the PH in these environments, thus impeding the growth of bacterial pathogenes on mucosal surfaces of the intestine. (Wang x, chowdhury JR 2006)

- probiotics used also to enhance immunity by regulating bacterial colonies, they can form a biological barrier by specifically binding intestinal epithelial cells through techoic acid.

(LiG et al 2012)

- probiotics are thought to work synergistically with the host immune system to stimulate specific lymphocytes cytokines and IgG and IgA antibodies to fight infection.

(Chen CH 2011) (LiG et al 2012)

- probiotic also appear to stimulate the production of numerous substances that work together to improve healthy microflora and displace harmful Bacteria. (Wangx, chowdhury JR 2006)

- These substances inclued vitamins, bacteriocins, and enzymes that alter the surface tension and reduce pathogen adherence to the mucosa. (Zheng sf 2012) ( LIG et al 2012)

- In our study we aimed to assess the therapeutic effects of probiotic substances on neonatal (Jundic to reduce the need and duration of phototherapy and hospitalization duration.

- In our study we have (400) neonates having a jaundice classified into (2) groups.

Group (1): intervention group: (200) cases who received intensive phototherapy with getting oral probiotic substance as lactobacillus powder with milk feeding as 250 mg/day (one sachet) divided in (2) doses.

Group (2): Control group: (200) cases who received intensive phototherapy only.

|  |  |
| --- | --- |
| Group (1)Intervention Group  | Group (2)Control Group  |
| Hemolytic cases (43) | (33) Cases |
| Infectious cases (36) | (35) Cases |
| Physiological cases (121) | (132) Cases |

- In our study we have (400) cases of jaundiced newborns Males and females, Males were 58% and females were 42%, Here, percentage of Males is greater than females,

This is supported by the study of Paul et al (2010) , where jaundiced Males were significantly higher than females and was in agreement with (Abdel fatah et al, 2014) who had studied two groups with severe neonatal jaundice and found that malas were 58.8%.

- In our study the Ages of the newborn varies between (1 day to 7 days), Mean Age in days of admission of intervention group was 3.24 ± 1.1 and in control group was 3.33 ± 1.08 and we found that, there was no significant difference between groups regards Age as (P = 0.411)

- This was higher than mean age of admission in sivanandan et al (2009) study who reported the average postnatal age of jaundiced new borns beginning phototherapy was 2.7± 1.03 and 3.04 ± 1.83 days in groups.

But less than reported in Abdel fattah et al (2014) study, who, reported that the average age was 4.7 ± 2.7 and 5± 3.1 days in groups

In our study:

Mean Gestational age of cases of intervention group was 36.85 ± 2.18, of control group was 37.01± 2.54, we found that, there was no significant difference between groups regard GA as ( P = 0.061).

Because we did not select between neonates having a jaundice to put them in any group.

This agree with Abd el fattah et al (2014) study who reported that Mean GA was 36.12 ± 1.04 and 37.09 ± 8.92.

In our study:

Mean weight in groups was in intervention group was 3239.5±456.07, in control group was 3306 ± 463.18, we found that, there was no significant difference between groups regard weight as (P = 0.149).

That was similar to reported in Abdel fattah et al (2014) study, who found Mean weight at time was 2989 ± 395 and 2967 ± 417. statistical analysis revealed that all of the pre – treatment parameters were well balanced between the two groups of jaundiced neonates,

There were no significant differences between groups regarding their gender, Age, gestational age, weight, days of admission and family history of other jaundiced sibling.

- In our study, there was no significant differences between groups regarding laboratory parameters as hematological indices, reticulo cytic count, blood group and Rh of the Baby and mother and (TSB) levels at the time of application.

This was in agreement with Abdel Fattah et al (2014) who found no significant differences between studied groups regarding laboratory parameters.

- In our study about 30% of included neonates had appositive family history of other jaundiced siblings, that was higher than reported in (Abdel fattah et al, 2014) Study who found that 20% of included neonates with appositive history of other Jaundiced siblings this may be due to difference in numbers of first babies in the two studies.

- In our study, the most common cause for hyperbilirubinemia is physiologic (4.8595/5.7348) more than (hemolytic) mean (4.8837 /5.7273) and (infectious) mean (4.7222 / 6.0289) this was similar with Begum et al (2012) study who performed that the physiological jaundice was 50%, ABO, Rh in compatibility was 30% and infections was 20%. and we found that the most common cause for hemolytic jaundice was ABO, Rh in compatibilities,

- This agree with Annagur et al (2014) who found that the most common cause was ABO, Rh in compatibilities.

- In our study, TSB (out) of intervention Group was 9.39 ± 1.35 of control Group was 9.82 ± 0.91. we found that (TSB) were highly significant lower in intervention group out only as (P = 0.00) this was agree with demirel et al (2013) who reported that the good impact of probiotic on the course of indirect hyperbilirubinemia and phototherapy duration in full term and very law birth weight infant through his study in reducing (TSB) level. and liu et al (2015) who reported that the good therapeutic effect on neonatal Jaundice through his study to reduce (TSB) level.

- In our study, (TSB) out was decreased in Both groups by the effect of phototherapy but more derease in intervention group. This agree with jia Hy (2015) through his study of effect of oral probiotics on treatment of jaundiced neonates by its influence on Immune function and suganthi et al (2016) who reported through his study the important role of probiotic in reduction of neonatal hyperbilirubinemia and Mu – xue et al (2003) who reported that (TSB) in intervention group was 33.33% while it was 57.14% in the control group when given aprobiotic as aprophylactic treatment and this was against (Zahed et al 2017) who reported by his study that: oral probiotics in neonates with jaundice have no significant effect on (TSB) and the duration of phototherapy. As follows:

The mean (TSB) before intervention in the intervention and control groups was 16± 1.9 and 16.9 ± 1.9 mg l dl Respectively as (P > 0.05), and on Exit after 72 hours it decreased to 10.25 ± 1.32 in intervention group 09.09 ± 1.38 in control group with no significance as (P > 0.05).

- In our study:

The days needes to stay under the phototherapy treatment in the ICU are:

Mean of intervention group: 4.84 ± 0.62 and of control group: 5.785 ± 0.801

We found that the days needed are highly significantly lower in intervention group as (P = 0.00).

This agree with Demirel et al (2013) who reported from his study that: the median duration of phototherapy in the intervention group was (18 hrs) and that of control group was (24 hrs) was significant as (P = 0.027) with probiotic therapy.

- and agree with wenbin et al (2015) who reported from his study that in the treatment group, the probiotic therapy exerted effects on (1.0 ± 0.5) days and jaundice faded on (3.8 ± 1.7) days.

Which were (2.6 ± 0.6) day and (5.3 ± 2.1) days respectively in the control group as (P < 0.05) in addition, the two groups had significantly different numbers and times of phototherapy as (P < 0.05).

But this was against with yadallah zahed posha et al (2017)

Who reported from his study that the duration of phototherapy in the intervention group and the control group was. 3.61 ± 1.17 days and 3.72 ± 1.18 day respectively with probiotic therapy.

- This means that there in no significant difference between (TSB) in both groups after exposure to probiotic therapy.

- This was agree with demirel et al (2013) who reported that in his study the effect of probiotic therapy to reduce the duration of phototherapy in very low birth weight (VLBW) newborns of GA ≤ 32 weeks and also Suganth et al (2016) who reported that significant differences in (TSB) levels between intervention group and control group in full- term and pre – term newborns treated with probiotic for the first few days of life.

- In our study:

(TSB) out was significantly lower in the intervention group in physiological cases than other two hemolytic and infection cases and infection lower than hemolytic cases as distribution was 8.61± 1.2, 9.15± 1.4 and 9.62 ± 1.44 respectively and in the control group as 9.44± 0.91, 9.65± 0.93 and 9.97± 0.89 respectively,

This was agree with

Tewari et al (2015) who reported in his study that the proper effect of Bacillus clausii probiotic for prevention and treatment of late onset sepsis in preterm infant.

and agree with Zheng et al (2012) who reported that the proper effect of probiotic treatment in neonatal necrotizing enterocolitis and LiG et al (2018) who reported that the propr effect of bifid triple viable on immune function of newborn of with infection.

- But against zahed pasha et al (2017) who reported that he could not evaluate the neonates for colonization of probiotic bacteria and not a significant difference in (TSB) in the two groups may be associated with this fact that the selected probiotics may not colonize the neonates intestine.

In our study:

- In control group there were significant positive correlation between (TSB) IN and GA and weight also between T. bilirubin OUT and weight and there were significant negative correlation between days needed and G.A and weight.

- Regard intervention group there were significant positive correlation between (TSB) IN and OUT with GA and weight also between, (TSB) IN and OUT there were significant negative correlation between days needed and GA and weight.

Summary

- Neonatal Jaundice or hyperbilirubinaemia is a common neonatal problem in a bout 60% of fulf – term and 80% inpre- term in fants in the first week of life. (Rennie at al 2011).

- Extreme neonatal jaundice occurs in frequently but carries a high risk of permanent sequelae (Kernictrus)

- Rapid therapeutic intervention has the potential to reduce this Risk in some infants, like phototherapy and exchange transfusion:

 (Hansen, 2011) (American Academy of ped. 2014)

- The aim of this study was to assess the effectiveness of the probiotic substance as lactobacillus in reducing the total serum bilirubin level, reducing the number of days needed for phototherapy treatment to decrease its common side effects and to reduce the need of exchange transfusion with its complication.

(Alizadeh et al 2014), (Uatlah, et al 2016)

- The study was carried out during one year from 5/2017 to 5/2018 in the ICU incubator department in kenayat-hospital in Zagazig.

- In our study Neonatal Jaundie was treated by using probiotic substances by orally – taking with milk to reduce the number of days under the phototherapy in the incubator.

- This study included (2) groups.

(1) Intervention Group: (200 cases)

Of jaundiced neonates of different gestational ages, weights, sexes, and total serum bilirubin levels.

The cases were given the probiotic (lactobacillus)with milk during the photo therapy management

(2) Control group (200 cases)

- Also with different Gestational ages, weights, sexes and total serum bilirubin levels.

After blood sample analysis for bilirubin level and using statistical methods we found that.

- Total serum bilirubin were highly significantly lower in intervention group out more than in control group out by the effect of probiotic lactobacillus and the duration of phototherapy was shorter in the intervention group.

- Feeding intolerance was significantly lower in the intervention Group than in the control group.

- The dose of 250mg/daily of lactobacillus is safe and effective for full – term and pre – term including VLBW neonates in the short term. (Demirel et al 2013)

- The effect of probiotic (lactobacillus) was through:

\* improving the feeding intolerance.

\* suppressing the reabsorption and degradation of bound bilirubin into the enterohepatic circulation. (LIG et al 2012) (LIG et al 2017)

\* facilitating the growth of normal bacterial colonies and vitamins in the intestinal tract of neontes. (Maldonado it al 2012)

\* Forming metabolites corrected the alkaline environment thus weakening the activity of B-GA ( B- glucuronidase) and preventing it form binding and hydrolyzing biliubin.

(Ratu TN 2012) (Suganthi et al 2016)

\* forming acids that lower the PH in the intestine thus/ Impeding the growth of bacterial pathogens.

(Wang et al 2006) (Tewarivv, et al 2006)

\* Enhancing the Immunity by forming a biological barrier in the intestinal epithelial calls and stimulate specific lymphocytes cytokines and IgG and IgA antibodies to fight infection.

- Improving a healthy micro flora and displace a harmful bacteria.

 (Wang et al 2006) (Zheng Sf, et al 2012)

- Stimulating intestinal peristalsis to eliminate bilirubin from Reducing the enterohepatic circulation.

(LIG et al 2012) (Jia Hy, 2015)

Conclusion

Probiotics were able to treat and lowered the serum bilirubin levels of neonates with jaundice, Rapidly, safely, and significantly,

Without discernible side effect and a ccelerated jaundice fading as on well. Thous reducing both need and duration of phototherapy with its burden related issues:

Hence, this method is worthy of application in clinical practice.

Recommendation

- This study recommended that that we can use aprobitic substances within a plane of management of neonatal hyperbilirubinemia.

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