IMPACT OF PROBIOTICS ON NEONATAL HYPERBILIRUBINEMIA

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ABSTRACT

***Background**: Jaundice is one of the most common conditions requires medical care in neonates. The yellow colour of the skin and the sclera in neonates is the result of the accumulation of bilirubin, the most common natural consequence of the first week of life as indicated by Bhutani Hour-specific bilirubin nomogram, Bilirubin encephalopathy is a devastating brain injury, which can cause permanent neurodevelopmental handicaps, so prevention& treatment of neonatal hyperbilirubinemia is very important .*

***Objectives**: The aim of this study was to evaluate the efficacy and safety of probiotics on neonatal hyper bilirubinemia.*

***Methods:** It is randomized controlled clinical trial; it included 100Full term neonates who were admitted immediately or shortly after birth due to pathological Hyperbilirubinemia as indicated by Bhutani Hour-specific bilirubin nomogram. To NICU of Al-AZHAR university hospitals the cases dived into Group (A) 50 cases treated by phototherapy in combination with probiotics and group (B) 50 as control treated by Phototherapy only. The serum bilirubin levels were done before and the1st, 4th, 7th days after treatment with probiotics (lactobacillus 5 billion/ sachets) divided into 3 doses daily for 7 days).*

The time when therapy showed effects and jaundice faded, Clinical outcomes as well as adverse reactions were recorded.

***Results:** Serum bilirubin levels of the two groups were similar before treatment. The levels significantly decreased at the 4th and 7th days after treatment of probiotics in group(A)($P<0.05$), but there was no significant different after the 1st day of treatment with probiotics ($P>0.05$) between the two groups, In group (A) the therapy exerted effects after (2.7±0.8) day and jaundice faded after (4.8±0.9) day) while in group (B)) the therapy exerted effects after (3.9±1.7) day and jaundice faded after (5.9±1.8) day, the effective rate of decrease in group (A) significantly exceeded that in group (B), ($P=0.007, 0.002$).*

***Conclusion:** The use of probiotics is an important adjuvant to phototherapy during management of neonatal hyper bilirubinemia this combination reduce the side effects*

of phototherapy and the duration of hospital stay for cases of neonatal hyper bilirubinemia.

Key Words: *Full term Neonate, Neonatal hyperbilirubinemia, phototherapy, Probiotics.*

INTRODUCTION

Neonatal jaundice is the yellowish discoloration of the sclera and skin caused by hyperbilirubinemia it is one of the most common conditions confronting neonatologists daily the incidences, About 60% of term and 80% of preterm infants develop jaundice in the first week of life **(Rennie et al., 2010)**.

Phototherapy plays a significant role in the treatment and prevention of hyperbilirubinemia in neonates. It lowers the serum bilirubin by transforming bilirubin into water-soluble isomers that can be eliminated without conjugation in the liver **(Stokowski, 2006)** fortunately, photo therapy a noninvasive and easily available treatment in degrading unconjugated bilirubin **(Hansen, 2010)**.

The goals of phototherapy are to prevent the already elevated serum bilirubin level from rising and this will prevent the occurrence of kernicterus **(Bell et al., 2006)**.

Phototherapy has been widely adopted as the initial therapy of choice of Hyperbilirubinemia. When comparing blue, blue-green, green, and white light, researchers found that blue light was the most effective in degrading bilirubin **(Maisels and McDonagh, 2008)**.

Some phototherapy side effect as a significant increase in the infant's body temperatures through increasing in Trans epidermal water loss during phototherapy **(Pezzati et al., 2002)** Also phototherapy necessarily separates the neonate from the mother and may interfere with the process of establishing lactation **(Grunhagen et al., 2002)**.

Most of probiotics are bacteria similar to those naturally found in humans gut, especially in those of breastfed infants, probiotic microorganisms are members of genera lactobacillus and Bifidobacterium, within each group there are different species (Lactobacillus acidophilus, Lactobacillus case, Bifidobacteriumbifid us),Few probiotics such as Saccharomyces

boulardii, are yeasts which are different from bacteria **(Alvarez-Olmos et al., 2005)**.

Probiotic microorganisms produce antimicrobial compounds and compete for nutrients and sites of attachment in gut lining, thereby preventing colonization by pathogen **(Boyle et al., 2006)**.

In recent years, probiotics has been used in the treatment of jaundice, suggested that Bifidobacterium species may protect against breast milk jaundice and probiotics may be protective against hyperbilirubinemia by affecting intestinal motility and intestinal microbial flora **(Funda et al., 2013)**.

Ethical consideration:

- Written Parent consent for the study was obtained before the study.
- Approval of the local ethical committee in the pediatrics department, college and university were obtained before the study.
- The author's declared no potential conflict of interest with respect to the research & publication of this article.
- All the data of the patient & results of the study are confidential & the patient has the right to keep it.
- The authors received no financial support for the research & publications of the article.

PATIENT AND METHODS

This study included one hundred (100) neonates who were admitted immediately or shortly after birth due to presences of pathological hyperbilirubinemia as indicated by Bhutani Hour-specific bilirubin nomogram to neonatal intensive care unit (NICU) of Al Hussein and Bab- El Sharyia university hospitals from May 2017 to September 2017.

The cases were randomized into the study by a random number table sequence (i.e. patients 1, 3, 5.etc to phototherapy in combination with probiotics (group A) and alternatively patients 2, 4, 6.etc to only with Phototherapy only (group B).

Inclusion criteria:

- Full term and oral feeding.
- Neonates with hyperbilirubinemia requiring management with phototherapy according to Bhutani Hour – Specific bilirubin.

Exclusion Criteria:

- Full term baby with mixed hyperbilirubinemia.

- Pre mature with neonatal hyperbilirubinemia.
- Full term babies with neonatal hyperbilirubinemia and on I.V fluid or Total parenteral nutrition.

All the neonates included in the study were subjected to the following:

I- Full history taking:

With special emphasis on:

1. Perinatal history: Maternal Blood group & RH and medical disorders during pregnancy especially preeclampsia, diabetes mellitus, Antenatal corticosteroids, Gestational age.
2. Natal history: Blood group &RH of the baby, Mode of delivery, perinatal asphyxia, Meconium aspiration.
3. Postnatal history: Birth weight, Resuscitation data and delivery room interventions, Apgar score at 1 and 5 minutes resuscitation.

II- Clinical Examination with Estimation of the following:

- Estimation of gestational age using modified Ballard score (Meherban, e t al., 2015).
- Vital Signs: heart rate, respiratory rate and core temperature.
- Measurement of birth weight, length and head circumference at birth and plotted on growth charts (WHO et al., 2006)
- Color of the baby as jaundice, pallor and cyanosis, plethoric or meconium stained.
- Assessment of all system (Cardio Vascular &Pulmonology & Central Nervous and Gastroenterology).

III- Laboratory investigations including:

Venous bloods (3ml) was drawn before and after 1st, 4th and 7th day to detect Total serum bilirubin levels for all cases, Also Blood Group, CRP and CBC, liver function done for all cases before phototherapy and probiotics administration.

IV - Intervention:

This includes:

- Oral administration of probiotics (lactobacillus 5 billion/CFU sachets divided into 3 doses daily for 7 days) (group A) only.
- Phototherapy for both groups (A, B).

RESULTS

Table (1): Demographic characteristics of the studied cases

Variable		Cases (Group A) N=50 %	Control (Group B) N=50 %	P value
Postnatal Age(days)	2 days	3 (6%)	5 (10%)	0.922
	3 days	24 (48%)	19 (38%)	
	4 days	11 (22%)	16 (32%)	
	5 days	7 (14%)	5 (10%)	
	6 days	4 (8%)	3 (6%)	
	7 days	1 (2%)	2 (4%)	
Sex	Male	33 (66%)	27 (54%)	0.221
	female	17 (34%)	23 (46%)	
Consanguinity	Negative	38 (76%)	43 (86%)	0.205
	positive	12 (24%)	7 (14%)	
Mode of Delivery	CS	34 (68%)	32 (64%)	0.673
	vaginal	16 (32%)	18 (36%)	

This table shows no significant difference between cases and control group in age, sex, consanguinity and mode of delivery.

Table (2): Neonatal clinical evaluation

Variable	Cases N=50	Controls N=50	P value
	Mean(±SD)	**Mean (±SD)**	
Gestational age (weeks)	37(±0.5)	36.9 (±0.4)	0.553
Onset of treatment (days)	3.7(±1.15)	3.7 (±1.2)	0.922
Wight (kg)	3.4(±0.4)	3.3 (±0.5)	9.228
Length (CMs)	48.1(±2.1)	48.5 (±1.8)	0.304
Head Circumference (CMs)	34.7(±0.8)	34.9 (±0.7)	0.107

This table shows no significant difference between cases and control group (Gestational age, onset of treatment, Weight, Length and Head Circumference of Neonates).

Table (3): Total bilirubin before and after treatment with probiotics

Total serum bilirubin		Cases N=50	Control N=50	T test	P value
➢ Before probiotics	M ± SD	20.2± 3.9	21.1± 4.2	0.36	>0.05
➢ After Probiotics 1st day	M ± SD	18.8± 2.1	18.4± 3.6	0.87	<0.05
4th day	M± SD	9.06± 2.3	11.7± 1.6	2.74	<0.05
7th day	M± SD	4.7± 1.4	6.3± 2.2	5.91	<0.05

This table shows the level of serum bilirubin before treatment, Where There is no significant difference between both groups but after treatment at 1st, 4th, 7th days there is a significant reduction in total serum bilirubin level.

p >0.05 *Significant difference

Table (4): Change in clinical indices

Group	Time of exerting effect (d)	Time of jaundice fading (d)	Time of phototherapy (h)
Cases n=50	2.7±0.8	4.8±0.9	39.7
Control n=50	3.9±1.7	5.9±1.8	53.1
t	2.04	1.774	3.059
P	0.007	0.002	0.004

This table shows that the case group underwent more significant decreases on the 4th and 7th days than the control group. In group(A) the therapy exerted effects on (2.7±0.8) days and jaundice faded on (4.8±0.9) days, while in the control group the therapy exerted effects on (3.9±1.7) days and jaundice faded on (5.9±1.8) days respectively.(P=0.007, 0.002) respectively.

Table (5): Clinical outcomes of cases

	Marked effective	effective	Ineffective	Effective rate%
Cases	36	10	6	92%
Control	28	12	10	80%
X^2				3.404
P				0.002

This table shows the effective rate in group (A) is significantly exceeded that of group (B) (P=0.002). In group (A) underwent more significant decreases on the 4th and 7th days than the group (B) with significant difference p >0.002.

$$\text{N.B : Effective rate \%} = \frac{\text{Marked Effective + Effective}}{\text{Total numbers (50)}} \times 100$$

DISCUSSION

Neonatal jaundice is one of the most common conditions need medical care and affects approximately 2.4–15% of newborn babies during the first 2 weeks of life.

Our study carried out on One hundred (100) neonates with hyperbilirubinemia divided into a case group (A) (n=50) and a control group (B) (n=50) randomly selected from Al-Hussain & Bab-El Sharyia University Hospitals from May 2017 to September 2017, group (A) treated with phototherapy in combination with probiotics (lactobacillus 5 billion sachets divided in 3 dose) after 7 days and group (B) treated with phototherapy only. The serum bilirubin levels were measured before and at 1st, 4th and 7th days after treatment.

In this study: before probiotic& phototherapy treatment, there is no significant difference between both groups in total bilirubin level.

While after probiotic & phototherapy treatment at 1st, 4th and 7th days there is a significant reduction in total bilirubin level in group (A) compared to group (B).

The group (A) underwent more significant decreases on the 4th and 7th days than the group (B). In the group (A) the therapy exerted

effects on (2.7±0.8) days and jaundice faded on (4.8±0.9) days while group (B) the therapy exerted effects on (3.9±1.7) day and jaundice faded on (5.9±1.8) day respectively with signifecant difference between both gourps (Table 4).

We detected 92% effective rate in group (A) versus 80% effective rate in group (B) within a significant differences between both groups (Table 5)

(Liu et al., 2015) study our results coincide with where he noticed that using probiotics and phototherapy are effective than phototherapy only.

(Gamze et al., 2013) Study which evaluated probiotics and phototherapy versus Phototherapy only, they reported that probiotics supplementation is safe for full-term baby in the short term and effective in reducing the duration of phototherapy in full-term baby due to improving the feeding intolerance and suppressing the reabsorption of bilirubin into the enterohepatic circulation.

We are in disagreement with **(Ozge et al., 2015)** that compared probiotics and phototherapy versus Phototherapy only. They suggested that probiotics did not influence the clinical course of hyperbilirubinemia significantly.

(Armanian et al., 2016) Studied Probiotics and Phototherapy versus Phototherapy only, they found Probiotics increase stool frequency, improve feeding tolerance and reducing bilirubin level in preterm neonates and can be effective for the management of neonatal hyperbilirubinemia.

(Cen et al., 2015) they concluded that Probiotics decreased the serum bilirubin level of healthy neonate with jaundice safely and significantly without any adverse reaction.

(Deshmukh et al., 2017) recently metanalysis of Nine studies (prophylactic: six trials, therapeutic: three trials) shows probiotic supplementation reduce duration of phototherapy. Serum Total Bilirubin Level reduces at 4th days, 7th days after probiotic treatment. Prophylactic probiotics did not reduce the incidence of jaundice significantly.

With all previous results; we could provide evidence that the combination of phototherapy with probiotics supplementation therapy had an obvious increase of efficacy rate in neonatal jaundice through restoring normal bowel flora and inhibit growth of harmful bacteria, simulate local immunity and promotes water

reabsorption in colon, increase feeding and increase frequent of stool.

Moreover, it is not only significantly improved neonatal jaundice by reducing total bilirubin level, time of jaundice fading, decreased the duration of phototherapy and hospitalization, but our

Results indicate that probiotics supplementation therapy is an effective and safe therapy option for the treatment of pathological neonatal jaundice without any serious adverse reaction.

CONCLUSION

The use of probiotics is an important adjuvant to phototherapy during management neonatal hyper bilirubinemia this combination reduced the side effects of phototherapy and the hospital stay for cases of neonatal hyper bilirubinemia.

RECOMMENDATIONS

We recommend using of probiotics in addition to phototherapy in the treatment of neonatal hyperbilirubinemia, where this combination gives results better than phototherapy alone.

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تأ ثير البروبيوتك على اليرقان الوليدى

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اليرقان الوليدي هو أحد أكثر الحالات شيوعاً التي تتطلب عناية طبية عند الأطفال حديثي الولادة ومعدل حدوثه حوالي 60 ٪ من الرضع مكتملي النمو و 80 ٪ من الرضع ناقصى النمو (الخدج) وينتج اللون الأصفر للجلد والعين عند الأطفال حديثي الولادة عن تراكم البيليروبين وهو أكثر اكتشافا في الأسبوع الأول من الحياه.

زياده نسبه البيليروبين المفرطه يؤدى الى اعتلال دماغي مدمر يمكن أن يتسبب في إعاقة عصبية دائمة اذا لم يعالج و يلعب العلاج الضوئي دوراً هاماً في علاج ومنع فرط بيليروبين الدم عند الرضع ويقلل العلاج الشائع نسبيا مستوى البيليروبين في الدم عن طريق تحويل البيليروبين إلى أيزومرات قابلة للذوبان في الماء يمكن التخلص منها دون الاقتران في الكبد.

معظم البروبيوتيك هي بكتيريا مشابهة لتلك الموجودة بشكل طبيعي في أمعاء البشر ، وخاصة في الأمهات اللواتي يرضعن من الثدي.

الهدف من هذه الدراسة:

كان الهدف من هذه الدراسة هو تقييم فاعليه وسلامة البروبايوتكس على فرط البيليروبين في الدم حديثي الولادة مضافا الى العلاج الضوئى . فى الاطفال

المرضي وطرق البحث:

اشتملت الدراسه علي مائه حاله من حديثي الولاده كاملى النمو الذين يعانون من فرط اليرقان الوليدى وتم حجزهم بوحدة العنايه المركزه لحديثي الولاده بمستشفيات جامعه الازهر(الحسين وباب الشعريه الجامعى) وقد تم تشخيصهم علي اساس اكلينيكى و معملى عن طريق قياس معدلات البليروبين فى الدم ولقد تم استثناء الحالات الاتيه من البحث.

معايير الاستبعاد:

1- حديثي الولاده ناقصى النمو (الخدج) مع فرط بيليروبين الدم.

2- طفل كامل النمو مع فرط بيليروبين الدم المختلطة.

3- طفل كامل النمو حديثي الولادة مع فرط بيليروبين الدم وعلى محاليل ورديه او محاليل خاصه تحتوى على بروتينات للتغذيه.

ولقد خضعت جميع الحالات للعلاج الضوئى ونضيفهم للعلاج بالبروبيوتكس بدون تحيز 1&2&3 &0000 وهكذا لمده اسبوع بالفم.

وقد خضع جميع المرضي في هذه الدراسه الي :

اخد التاريخ الكامل للام من ناحيه فصيله الدم والحمل وطريقه الولاده وتاريخ اخر دوره شهريه وكذالك الطفل ثم فحصه كاملا وعمل فصيله الدم له ونسبه الصفراء قبل وبعد العلاج بيوم وأربعه وسبعه بعد العلاج.

وبعد مقارنه مجموعات الدراسة تم التواصل الى تحسن ذو دلالة احصائية في المجموعة المستخدمة للدواء مع العلاج الضوئى وذلك في انخفاض نسبه البليروبين وفترة الاقامة بالمستشفي عن المجموعه المستخدمه للعلاج الضوئى فقط.

وهذا ادى الى ان نوصى باستخدام البروبيوتكس لحالات فرط نسبه البيليروبين بالدم للحالات ذو الخصائص السابق ذكرها فى البحث.