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Is Oral Agar Combined with Phototherapy Superior than Phototherapy in Treatment of Neonatal Indirect Hyperbilirubinemia

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ABSTRACT

Background: Neonatal jaundice is the commonest condition encountered during daily practice of neonatologists. Phototherapy remains the main-stay in the treatment. However, its safety and efficacy still questioned. Agar was proposed as an adjuvant therapy to improve the effectiveness and safety profile of bilirubin. However, the evidence is still building up. The current work aimed to address the value of agar as an adjuvant to phototherapy for neonatal hyperbilirubinemia of full-term neonates.

Methods: The study was a randomized double-blind comparable clinical trial. Full term neonates with indirect hyperbilirubinemia within their first week of life at the level of phototherapy were included. Patients were randomly assigned into two equal groups. The phototherapy alone group, where newborns received 10 ml of distilled water by bottle every 12 hours. The second group, where neonates received 300 mg/kg of agar orally by bottle every 12 h before feedings in 10 ml of distilled water. The collected data for comparison included patient demographics and serial measurements of total serum bilirubin (TSB). Treatment was stopped when TSB levels falls to 2 mg/dl below the phototherapy initiation threshold.

Results: Both groups were comparable regarding patient demographics, mode of delivery and gestation age at delivery. TSB levels showed significant progressive reduction after the first, at the third and the fifth days of therapy among agar and comparable groups. The percentage of reduction in TSB levels was significantly higher in phototherapy-Agar combination group than the other group at third day of therapy (- 38.92 versus - 28.66%, p=0.0001). Finally, the length of hospital stay duration was significantly shortened with agar than the other group (3.34±0.70 vs 3.7 ±0.74, p=0.014).

Conclusion: Adding oral agar to phototherapy improves the effectiveness and safety among full-term neonates with indirect hyperbilirubinemia.

Keywords: Full-term; Jaundice; Bilirubin; Indirect.

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INTRODUCTION

Hyperbilirubinemia is the commonest abnormal neonatal finding faced in everyday neonatal medicine practice. About 60% of full-term and 80% of pre-term neonates will develop jaundice during their first week of life [1]. Mild hyperbilirubinemia peaks at the third to fifth days and returns back to normal in the next weeks. However, some infants will need treatment for severe hyperbilirubinemia aiming to prevent acute bilirubin encephalopathy and kernicterus [2]. Phototherapy remains the primary treatment option used to keep the maximal total serum bilirubin (TSB) below the pathologic levels [3]. It has been shown that 0.5–4% of full-term and late-preterm neonates receive phototherapy in nursery and about 5.0% of those neonates were readmitted for photo-therapy [4].

Phototherapy is an effective therapeutic option for neonatal hyperbilirubinemia. However, it is associated with short-term adverse effects (e.g., transient skin rashes, diarrhea, hyperthermia, and dehydration) [5]. In addition, its long-term effects are reported and included induction of apoptosis as well as damage of the DNA in full-term infants' peripheral blood [6-7].

Agar is a polysaccharide obtained by extraction from red seaweeds of the genera of *Gelidium spp*. and *Gracilaria* spp. [8]. It is a non-absorbable substance that may be attached to bilirubin in the intestine or reduce the enterohepatic cycle with subsequent reduction of the bilirubin absorption and its serum build up [9].

In Egypt, serious hyperbilirubinemia is still being reported for a significant number of neonates and cannot be ignored. For example, a considerable number of acute bilirubin encephalopathy was recorded in Cairo University few years ago [10].

Because of the higher prevalence of physiological jaundice among Egyptian neonates [11], the current study was conducted to determine the efficacy of oral agar administration in reducing the levels of TSB and shortening the length of hospital stay in full-term neonates admitted for phototherapy in order to overcome overcrowding and reducing the costs of therapy.

METHODOLOGY

The study was a randomized double-blind comparable clinical trial. It was held from April 2020 till October 2020 at the neonatal intensive care unit (NICU) of Al-Azhar University Hospital (New Damietta). Full term neonates with indirect hyperbilirubinemia within their first week of their life at the level of phototherapy were included. Any newborn who had other pathological condition (respiratory distress, sepsis, asphyxia, etc...), or required exchange transfusion was excluded from the study. Informed consent was obtained from parents of the studied newborns or legal guardian for participation in the study. Approval of the Institutional Review Board (IRB) was obtained after revision and approval of the study protocol. The sample size was calculated using open-epi online calculator. The following data were assumed: two-sided significance level (1-alpha) of 95, power (1-beta) is 80, percent of unexposed group with outcome to be 30%, and percent of exposed with outcome as 70%. After insertion of these data, the total sample size was calculated as total number of 58 newborns, being 29 newborns in each group.

Neonates were randomly assigned into two equal groups (each included 30 neonates). The phototherapy alone group (first group) where newborns received 10 ml of distilled water by bottle every 12 hours as a placebo. The second group (combination group), where neonates received 300 mg/kg of oral agar by the bottle every 12 h before feedings in 10 ml of distilled water [11].

Both evaluating physician and neonates care-givers were blinded to the neonatal group. The amount of food was equal for all neonates in each group and calculated by caloric needs per day. Agar was purchased as sachets (E.S. Reg. No. 1131/2008) from a local pharmaceutical company (Med Care, IBM Pharma, Egypt). The phototherapy unit had four white-light fluorescent-lamps (TL 18 W/MB; Philips Co. Holland) and three blue-light lamps (ii 20 W/03T; Philips Co. Holland). Phototherapy sensitivity was set at 30 $\mu W/cm^2$ per nanometer (nm). The distance between the source of light (white or blue) and the neonate was 20 cm.

During the session of phototherapy, the neonate's eyes and gonads were protected by fitted eye patches and diapering respectively. The data bout the clinical examinations, patient demographics, body weight, serial TSB measurements were documented. The serial measurements of TSB were set at start and every other day. In addition, the frequency of stools/day and adverse effects associated with the treatment were recorded. Treatment was discontinued when bilirubin falls 2 mg/dl below the phototherapy initiation threshold.

Statistical analysis: The recorded data were fed to personal computer and analyzed using SPSS 20 (IBM®SPSS® Inc, Chicago, Armonk, USA). Data was tested for normal distribution by appropriate tests. Then, summarized by relative frequencies with percentages for qualitative variables. Otherwise, quantitative data were presented by their mean and standard deviation (SD). The comparison between the two groups was performed by the independent samples (*t*). However, the categorical variables compared by the Chi square (X^2) test. For all tests, P value < 0.05 was considered significant [12].

RESULTS

First group (or group 1) in the results section refer to the group of neonates received phototherapy alone, while the second group (or group 2) assigned for the group for combination therapy (oral Agar plus phototherapy). There was no significant difference between both groups as regard age, sex, mode of delivery, gestational age, weight at admission and hemoglobin level. Men, for example represented 57% and 50% of the first and second groups respectively and all neonates were full-term. (Table 1). The levels of the total serum bilirubin (TSB) were significantly decreased after 24 h, at 3rd and fifth days of therapy among combination group (oral Agar plus phototherapy) the phototherapy alone group (p =0.001, p=0.0001 and p=.00001 respectively). The percentage of reduction in TSB levels was significantly higher in photo-therapy-Agar combination group the first group at third day of therapy (- 38.92 versus - 28.66%, p=0.0001). Finally, the length of hospital stay duration was significantly decreased among the second than the first group (p=0.014) as shown in table (2).

Table (1): General characteristics, mode of delivery, gestational age and hemoglobin levels among study groups

		Phototherapy (n=30)	Phototherapy- Agar combination (n=30)	P value
Age (days)		3.6 ± 1.2	3.9 ± 1.4	0.38
Sex	Male Female	17 (57%) 13 (43%)	15 (50%) 15 (50%)	0.79
Mode of delivery	Normal Cesarean	11 (37%) 19 (63%)	8 (30%) 22 (73%)	0.58
Gestational age (weeks) at delivery		38.1±0.6	38.3±0.5	0.16
Weight (Kg)		3.62±0.66	3.54±0.53	0.61
Hemoglobin (g/dl)		13.8±2.4	14.1±2.8	0.66

Table (2): Serum bilirubin and length of hospitalization among studied cases

	Phototherapy (n=30)	Phototherapy- Agar combination (n=30)	P value
TSB on admission (mg/dl)	17.20 ± 1.27	16.70 ± 1.58	0.182
TSB at the end of first day of therapy (mg/dl)	14.70 ± 1.58	13.33 ± 1.54	0.001*
Changes (%)	- 14.53%	- 20.18%	0.061
TSB at the end of the third day of therapy (mg/dl)	12.27 ± 1.44	10.20 ± 1.56	0.0001*
Changes (%)	- 28.66%	- 38.92%	0.0001*
TSB at the end of the fifth day of therapy (mg/dl)	9.70 ± 1.63	7.4 ± 1.44	0.0001*
Changes (%)	- 21.39%	- 30.45%	0.007*
Daily stool frequency	4.00 ± 1.36	4.78 ± 1.36	0.005*
Length of hospital stay (days)	3.34±0.70	3.7 ±0.74	0.014*

* = significant

DISCUSSION

Neonatal hyperbilirubinemia is imitated with by the enhanced excretion of bilirubin through enterohepatic circulation [13]. Previously, various treatment policies have been applied to counteract enterohepatic circulation with inconsistent results, regarding the jaundice prevalence and severity [14]. These are - at the best - used as an adjuvant to the established treatment options like phototherapy [15]. Therefore, enterohepatic circulation takes part in, at least, prolongation of physiological jaundice, though the suggested role for it as a major etiology of the neonatal hyperbilirubinemia is debated [13]. Thus, any substance binds to, or increases the break of bilirubin in the intestine may reduce the severity or the overall duration of hyperbilirubinemia [16]. Accordingly, the current work rationale and aim was to assess the potential role of oral agar, as an adjuvant in augmentation of the phototherapy effects by reducing serum bilirubin.

In the present study, oral agar in a dose of 600 mg/kg/day resulted in a statistically significant reduction in TSB levels in healthy full-term neonates admitted for phototherapy compared to the phototherapy-along group. Thus, the effectiveness of phototherapy in reducing bilirubin levels were improved with the use of oral agar. Oral Agar is marked as a cheap and simple technique for the neonatal jaundice treatment. There were many studies that evaluated the efficacy of oral agar in the neonatal jaundice treatment. For example, Poland *et al.* [17] initially registered high in-vitro affinity of bilirubin to agar. Subsequent researches demonstrated either beneficial effects [18,19] or no effects [20] of agar treatment on the reduction of unconjugated bilirubin levels or reduction of the total phototherapy duration.

During the past decade, Bahman *et al.* [21] conducted a double-blind clinical trial of 50 term neonates divided into two equal groups (Agar-supplemented and a placebo groups). TSB levels showed marked increase in both the groups, but this increase was significantly lower in Agar than placebo group. Also, the need for phototherapy was significantly reduced in the oral agar group. More recently, Abdel-Aziz *et al.* [11] investigated 160 full-term neonates with TSB of 10–19 mg/dl at first week of age. Neonates were divided on the basis of TSB values into outpatient group (n=100) with TSB values 10–15 mg/dl, and the admission (phototherapy) group (n=60) with TSB more than 15–19 mg/dl). The introduction of Agar was more effective in the TSB reduction in neonates of the outpatient group. However, TSB percentage of change was not significantly reduced in agar-fed admitted group compared to the outpatient group after 24 hours and 7 days. But, Agar feeding reduced the time required to decrease the TSB and increased stool frequency.

Our results also showed that agar oral administration not only improved the phototherapy effectiveness but also shortened the total time of phototherapy for the treatment of neonatal hyperbilirubinemia. Reducing the duration of phototherapy treatment is of a great value, as it led to more contact between the mother and her neonate, shorter duration of hospitalization and reduce in the cost and phototherapy side effects. Moreover, the efficacy of

phototherapy might be reduced due to the reversion of some photo-bilirubin's to their equivalent natural isomers and return to the blood by entero-hepatic circulation [11]. Mean daily frequency of stooling was significantly higher in oral agar group compared with the phototherapy alone group. This may be part of its mechanism of action as the result of increased enterohepatic circulation. However, photo-therapy is known to increase stool frequency with salt and water secretion into the GIT as a result of intralumenal concentration of unconjugated bilirubin [18].

Conclusion: Our results indicated that administration of oral agar is effective in reducing the length of hospital stay for full-term neonates through reduction of the TSB levels and the overall duration of phototherapy. Further large-scale trials are required to confirm and validate the oral agar potential on the course of hyperbilirubinemia specifically in the preterm neonates regardless of the justification of the sample size, as it is considered as a small, and prevents generalization of the results.

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