Evaluation of using agar combined with phototherapy in management of neonatal unconjugated hyperbilirubinemia

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Background: Neonatal hyperbilirubinemia is a common problem in neonates.Phototherapy is an efficient way to decrease the accumulation of bilirubin, although it involves hospitalization, and can force the baby to stop eating due to the breast separation. In certain cases of infant jaundice, the hepatic circulation of bilirubin plays a major role

Objectives: The purpose of the study was todetermine the value of oral agar ingestion combined with phototherapy in management of neonatal unconjugated hyperbilirubinemia and to compare it with the use of phototherapy alone in the management.

Patients and methods: This was a randomized controlled study conducted at Neonatal intensive care units in Qena university hospital and Qena general hospital. They were divided into: Case group (neonates received oral agar with phototherapy).Control group (neonates received phototherapy alone). The duration of this study was 6 months.

Results: The study included 517 neonates,314 neonates (60.74%) treated with phototherapy alone and 203 neonates (39.26%) treated with phototherapy combined with agar .There was a significant decrease in total serum bilirubin (TSB) in both subgroups, but the decrease was more significant in term male babies and in group that received agar with phototherapy than the group received phototherapy alone.

Conclusion: Our results show that the administration of oral agar in full-term neonates was safe to decrease total serum bilirubin (TSB) concentrations and to shorten the length of phototherapy in hyperbilirubinemic neonates. As a supplementary treatment for neonates with hyperbilirubinemia, our results indicated that agar may benefit in minimizing the length of hospitalization.

Keywords: Phototherapy, Neonatal, Jaundice, Hyperbilirubinemia, Agar, Kernicterus.

Introduction:

Neonatal hyperbilirubinemia is a common problem in neonates with an incidence of about 60% in term babies and 80% in preterm babies. It is the most common cause of admission to the hospitals in the neonatal period **(Mostafaet al.,2019).**

Neonatal jaundice refers to the yellowish discolouration of the skin and sclera of newborn babies that result from accumulation of bilirubin in the skin and mucous membranes. Clinically it becomes apparent when the serum bilirubin exceeds 7 mg/dl **(Aliand Tomar ,2015).**

Phototherapy is an efficient way to decrease accumulation of bilirubin, although it involves hospitalization, and can force the baby to stop eating due to the breast separation. In certain cases of infant jaundice, the hepatic circulation of bilirubin played a major role **(Gilbersenet al., 1962).**

So the effect of phototherapy can be increased by the way of sequestration of bilirubin from entering hepatic circulation. Agar

has been revealed to bind bilirubin in the gut and thus decreases re-entry to hepatic circulation of bilirubin **(Polandet al., 1971).**

Patient and Methods

This was Randomized controlled study conducted on 517 neonates with neonatal jaundice .It was designed on all newborn babies attending neonatal intensive care unit at Qena university hospital and Qena general hospital discovered to have unconjugated hyperbilirubinemia at the beginning of December 2019 to the end of May 2020.

Study subjects: Two groups composed of neonates received oral agar with phototherapy and others received phototherapy alone.

a. Inclusion criteria: all newborn babies attending neonatal intensive care unit at Qena university hospital and Qena general hospital discovered to have unconjugated hyperbilirubinemia

(1) Case group (neonates received oral agar with phototherapy).(2) Control group (neonates receivedphototherapy alone).

b. Exclusion criteria: (1) Neonates developed conjugated hyperbilirubinemia. (2) Neonates who needed exchange transfusion.

Sample Size Calculation: all newborn babies admitted for neonatal jaundice during 6 month period starting from 1/12/2019 to 31/5/2020.

Methods

After admission to the neonatal intensive care unit, the patient had been randomly assigned to receive either phototherapy alone or phototherapy combined with agar.

All studied neonates were subjected to:

- **Full history taking antenatal, natal and postnatal**
- **Nutrition history.**
- **Examination: included the followings:**

1-General examination: General appearance of child, General examination of systems to associated medical conditions.

2-Vital signs: Heart rate, respiratory rate, temperature, blood pressure.

3-Complete cardiac examination: Inspection, palpation, percussion and auscultation, to detect any complication.

4-Abdominal examination: For hepatomegaly or splenomegaly**.**

5-Anthropometric measures which included: Weight, length, head circumference, mid upper arm circumference and body mass index (BMI).
Laboratory investigations including: Total serum bilirubin at admission and after 5 days**.** CBC with reticulocyte, Blood groups and Rh of the neonate and the mother, Liver function tests ,C-reactive protein in specific cases and Transcutaneous bilirubin follow up every other day till discharge

Outcome measures: (1) Primary outcome: rate of decline of total serum bilirubin in 5 days. (2) Secondary outcomes: Duration of stay in the neonatal intensive care unit. Other complications as sepsis, kernicterus

Administrative considerations: An official permission was obtained from the pediatric department, Approval from ethical committee in Qena Faculty the faculty of medicine (Institutional Research Board IRB)

Ethical consideration: Written informed consent was taken from parents for participation in the study. After being informed about the aims and process of the study as well as applicable objectives.

Data management and Statistical Analysis: Data entry, processing and statistical analysis was carried out using Statistical package for social sciences (IBM-SPSS), version 24 (May 2016); IBM-Chicago, USA will be used for statistical data

analysis. Data were presented and suitable analysis was done according to the type of data (parametric and non-parametric) obtained for each variable. P-values less than 0.05 (5%) was considered to be statistically significant.

Results

Table 1. Demographic data distribution of the two studied groups

Variable		**Phototherapy** (n=314)		**Combined é agar** (n=203)		χ^2	**P**
		N	**%**	**N**	**%**		
Age	1 – 3 days	137	43.6	67	33	**7.21**	**.027**
	4 – 7 days	148	47.1	120	59.1		
	7 – 10 days	29	9.2	16	7.9		
Sex	Male	189	60.2	103	50.7	**4.48**	**.034**
	Female	125	39.8	100	49.3		
Delivery	Vaginal delivery (VD)	69	22	51	25.1	.686	.408
	Cesarean section (CS)	245	78	152	74.9		
Gestational age (GA)	<30	5	1.6	0		3.41	.181
	30-35	73	23.2	51	25.1		
	36-40	236	75.2	152	74.9		

There is a significant difference between the two studied groups as regard age and sex.

Table 2. Complications distribution of the two studied groups

	Phototherapy (n=314)		**Combined é agar** (n=203)		χ^2	**P**
	N	**%**	**N**	**%**		
No complication	313	99.7	203	100	.648	.421
Intracranial hemorrhage (ICH)	1	0.3	0			

There is no significant difference between the two studied groups as regard complications.

Table 3. Total serum bilirubin and direct bilirubin of the two studied groups.

Variable	**Phototherapy** (n=314)	**Combined é agar** (n=203)	**t**	**P**
Total serum bilirubin (TSB) at admission Mean ± SD	17.28 ± 4.15	15.23 ± 2.03	**7.46**	**.000**
TSB after 5 day Mean ± SD	13.85 ± 6.29	6.74 ± 2.83	**10.2**	**.000**
Direct bilirubin Mean ± SD	2.02 ± 0.297	2.11 ± 0.404	**4.54**	**.000**
Direct bilirubin after 5 day Mean ± SD	0.511 ± 0.267	0.662 ± 0.491	**3.15**	**.002**

There is a significant difference between the two groups regarding total serum bilirubin (TSB) at admission and follow up and direct bilirubin. Also, there is a significant decrease in TSB and direct bilirubin in both groups.

Table 4. Therapy response between the two groups

	Paired Differences		t	Sig. (2-tailed)
	Mean ±SD	95% Confidence Interval of the Difference		
Phototherapy combined with agar group				
Total serum bilirubin (TSB)	5.49 ± 2.08	5.728 - 5.267	**46.87**	**.000**
Direct bilirubin	1.51 ± 0.273	1.535 - 1.475	**97.73**	**.000**
Transcutaneous bilirubin (TCB)	2.28 ± 1.82	2.074 – 2.478	**22.15**	**.000**
Phototherapy only group				
TSB	3.43 ± 2.82	3.819 – 3.038	**17.31**	**.000**
Direct bilirubin	1.44 ± 0.339	1.492 – 1.398	**60.64**	**.000**
TCB	4.92 ± 4.32	4.318 – 5.513	**16.22**	**.000**

There is a significant decrease in bilirubin in both groups. Thus, response is more significance in neonates who managed by phototherapy combined with agar than neonates who managed by phototherapy only.

Table 5. Total serum bilirubin and direct bilirubin of the two studied groups.

Variable	Phototherapy (n=314)	Combined é agar (n=203)	t	P
Time for TSB decrement (hours)Mean ± SD	83.76 ± 6.44	66.52 ± 7.94	**7.86**	**.000**

There is a significant difference between the two groups regarding time for total serum bilirubin (TSB) decrement

Table 6. Response in TSB between term and preterm babies in phototherapy combined with agar group

Phototherapy Combined with agar group	Paired Differences		T	Sig. (2-tailed)
	Mean ±SD	95% Confidence Interval of the Difference		
Term	3.49 ± 2.88	3.952 - 3.03	**14.9**	**.000**
Preterm	3.24 ± 2.67	3.993 - 2.489	**8.66**	**.000**

There is a significant decrease in TSB in both subgroups, but the decrease is more significant in term babies.

Discussion

Despite the common uses of phototherapy, there are therapies that increased its action and decreased phototherapy duration and side effects. Considering that enhancing enterohepatic circulation is main causes of neonatal jaundice, factors that increased elimination of meconium from infant's intestines or binding to bilirubin that found in the gut and inhibited its absorption could decreased serum bilirubin levels **(Viteket al., 2005).**

Various substances had been used for bilirubin binding in intestine to resist its absorption as oral agar and laxatives. Oral zinc salts at normal body pH deposit UCB and so curbs total serum bilirubin (TSB). Agar is a gelatinous substance that gets from seaweed. Agar is low cost, and easily fed; it can bind bilirubin in intestine, decreasing its enterohepatic circulation, thereby decreasing TSB levels. In 1970s, Poland et al. reported that UCB combined with dried agar and so agar act as a trapping agent for UCB in intestinal lumen **(Ranaet al., 2011).**

The results of agar in hyperbilirubinemic neonates, however, were conflicting. Consequently, although oral agar appeared to be free from side effects in these studies, its effectiveness still unproven. In Egypt, serious hyperbilirubinemia is still being detailed in numbers that cannot be ignored. All data available about neonatal hyperbilirubinemia were hospital-based and did not presenting the general population. A research from Cairo University Children's Hospital revealed that more than 10 cases of confirmed kernicterus in a 1-year period **(Iskanderet al., 2014).**

There was a significant difference between the two studied groups as regard age, sex and body weight.Our results were in contrary with study of **Odellet al. (1983),**as they reported that there was no significant difference between the two studied groups as regard age, sex and body weight.

In the study in our hands, there was no significant difference between the two studied groups as regard complications.

The present studies showed that there was a significant difference between the two groups regarding total serum bilirubin (TSB) at admission and follow up and direct bilirubin. Also, there is a significant decrease in TSB and direct bilirubin in both groups. There is a highly significant difference between the two groups regarding transcutaneous bilirubin (TCB) at admission and follow up. Also, there was a significant decrease in TCB in both groups. There was a significant decrease in bilirubin in both groups. Thus, response was more significance in neonates who managed by phototherapy combined with agar than neonates who managed by phototherapy only. There was a significant difference between the two groups regarding time for TSB decrement.

Our results were supported by study conducted by **Abdel-Aziz et al.(2020),**Their findings showed that the oral using of agar not just enhance the phototherapy effectiveness but also decreased the time required for phototherapy to treat hyperbilirubinemic neonates.

Short phototherapy time is relevant because it has contributed to better interaction with the mother-infant, low hospitality and reducing money and phototherapy side effects and can also minimize the risk of nosocomial infection as a result of long-term hospitalization. phototherapy has been commonly used For the treatment of neonatal Hyperbilirubinemia,. The potency of such photobilirubin reversions to their natural isomer could therefore decrease and then by enterohepatic circulation back to the blood. Since flat agar has been shown to bind bilirubin in the gut and to decrease enterohepatic bilirubin circulation.

The current study showed that there was a significant decrease in TSB in both subgroups, but the decrease was more significant in term babies.

Our results were supported by study conducted by **Abdel-Aziz et al.(2020),**as treating with oral agar in 600 mg/kg/day in conjunction with the placebo-administered community has been shown to lead to substantial reductions in TSB level in stable full-term neonates with TSB levels of 10–15 mg/dl within the first week of life. The deterioration was also observed clinically .In addition; the findings of this research have shown that the use of oral agar in conjunction with phototherapy was greatly reduced in the TSB relative to the community

treated only with phototherapy. The effectiveness of phototherapy may be improved by using oral agar to lower serum bilirubin levels in neonatal hyperbilirubinemia.

In this study, oral agar was set in a dose of 600 mg/kg/day. In this detail **Caglayan et al.(1993),**used agar with a dose of 500 mg/kg each 6 h as certain investigators had stated that low dosages of agar (<1.5 g/d) might reduce its efficacy, in a dosage of 2 g/day and **Romagnoli et al.(1975),** in a dosage of 600–700 mg/kg/day.

Conclusion

Our results showed that oral agar administration is safe for full-term neonates in minimizing TSB levels and effective in minimizing the phototherapy duration in hyperbilirubinemic neonates. We recommend that agar may be helpful in minimizing the length of hospitalization.

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