



Original Article

Comparison between Oral Zinc and Agar with Phototherapy in the Treatment of Neonatal Jaundice: A Prospective Clinical Trial Study

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Abstract

Background: Neonatal jaundice is a major neonatal health hazard and this calls for the importance of studying effective treatment for it.

Objective: To evaluate the efficacy of phototherapy, oral zinc salts and agar on the treatment of neonatal jaundice in term and late-preterm at-risk neonates.

Methods: This study is a prospective randomized clinical trial study included a total of 75 neonates with indirect hyperbilirubinemia during the period from March 2019 to April 2020 who were allocated randomly to 3 groups (n=25 per each): Group (I) included neonates received phototherapy alone, group (II) that included neonates received phototherapy and oral zinc salts and group (III) that included neonates received phototherapy and oral Agar. Total serum bilirubin (TSB) level was measured on admission, as well as 24, 48, 72 and 84 hours after the intervention. Hospital stay, feeding status, complications and risk factors for neonatal jaundice were assessed.

Results: A significant reduction was recorded in TSB after 24 and 48 hours in all groups and the reduction was more significant in neonates of group (II) who received oral zinc with phototherapy and group (III) who received agar with phototherapy compared to group (I) who received only phototherapy ($p < 0.01$). However after 72 and 84 hours, the total serum bilirubin (TSB) levels were almost similar among all groups, but it still continue to decline. Hospital stay duration was significantly shorter ($p < 0.01$) in the group that received phototherapy and zinc compared to the groups that received phototherapy only and the group that received phototherapy and agar.

Conclusion: Administration of oral zinc or agar besides phototherapy was safe and can be more effective in the treatment of neonatal Jaundice due to indirect hyperbilirubinemia compared to receiving phototherapy alone.

Key words: Oral zinc, Agar; phototherapy; Neonatal jaundice

Introduction

Neonatal hyperbilirubinemia or jaundice is a life threatening disorder and it is one of the most prevalent clinical conditions during the neonatal period as it occurs in up to 85% of all live births [1]. In Egypt, it has been reported that hyperbilirubinemia was found in 54.3% on the neonates in the first 5 days of life [2]. Neonatal jaundice has many types and physiological jaundice is the most abundant which is mainly due to elevated bilirubin production because of increased breakdown of fetal erythrocytes [3].

Phototherapy is one of the most used steps for treatment of jaundice in many cases, it is a safe well-situated method for decreasing bilirubin levels in jaundiced neonates and it lowers the requirement for exchange transfusion but it may be ineffective in some cases because the return of some photobilirubins to their natural isomer and then return to the blood by enterohepatic circulation [1]. Inhibition of enterohepatic circulation is one of the therapies used to prevent neonatal

hyperbilirubinemia and several materials have been utilized for avoiding the absorption of bilirubin such as active charcoal, calcium phosphate, glucuronidase inhibitor, oral agar , etc... but, the obtained results have been conflicting [4].

Zinc (Zn) is a vital element which had great biological importance and it could be used to treat indirect hyperbilirubinemia as some studies reported that zinc salts can decrease serum bilirubin levels by inhibitions of the enterohepatic cycle of indirect bilirubin or by increasing bilirubin excretion [5,6]. Agar is a complex mixture of polysaccharides derived from seaweed, it binds to unconjugated bilirubin (UCB) and thus it could work as a trapping agent for it in the intestinal lumen [7]. The current study attempts to evaluate the efficacy of phototherapy, oral zinc salts and agar on the treatment of hyperbilirubinemia in term and late-preterm at-risk neonates.

Methods

This study is a prospective clinical trial that was performed at Edfu General Hospital (Aswan Governorate) and Al-Azhar University Hospital (Assiut) during the period from March to 2019 to April 2020. The study included a total of 75 neonates (born at ≥ 34 weeks of gestational age) who were allocated randomly to 3 groups (25 neonates per each) as follow:

- Group (I) "Phototherapy alone" included 25 neonates treated by phototherapy alone.
- Group (II) "Phototherapy and oral zinc" included 25 neonates who received phototherapy and oral zinc salts in a dose of 2.5 mL twice daily for zinc salts (20 mg).
- Group (III) "Phototherapy and oral Agar" included 25 neonates who received phototherapy and oral Agar in a dose of 500 mg/kg/day orally in 2 doses for agar for 5 days.

All neonates born at ≥ 34 weeks of gestational age and those who required phototherapy were included while;

exclusion criteria were neonates with Rh incompatibilities and major gross congenital anomalies. and neonates who required exchange blood transfusion. All included cases were subjected to full history taking including personal history and mother's obstetrical history. General, local and physical examinations were done. Regarding laboratory investigations, CBC was determined and the total serum bilirubin level (TSB) was measured at admission, as well as 24, 48, 72 and 84 h after the intervention. Regarding outcome parameters, hospital stay, feeding status, complications and risk factors for neonatal jaundice were assessed.

Ethical approval

The study protocol and all procedures performed involving human participants were in accordance with the ethical standards of the Faculty of Medicine, Al-Azhar University (Assiut), Egypt. Informed consent was obtained from all patients before the beginning of the study.

Statistical analysis

Statistical analyses were performed using Statistical Package for Social Science (SPSS) version 20 [8]. Results are expressed as mean \pm SD for quantitative data and by No. (%) for qualitative data. Analyses were done for parametric quantitative variables using one way ANOVA test followed by post-Hoc Tukey's correction for the comparison among the three groups and Paired T-test was used to compare between different periods compared to on admission value regarding TSB. However, Chi-square test or Fisher Exact test were used for qualitative data. Probability level (P. value) was assumed significant if < 0.05 and highly significant if < 0.01 , while, it was considered non-significant if it was ≥ 0.05 .

Results

No significant differences were found among groups regarding sex ($p=0.95$), gestational age ($p=0.28$), neonatal age ($p=0.33$), birth weight ($p=0.39$), mothers age ($p=0.58$), parity ($p=0.61$), mode of

delivery ($p=1.00$), length of neonates ($p=0.16$) and head circumference ($p=0.26$). Also, the three groups were comparable regarding WBCs ($p=0.94$), Hb % ($p=0.40$), HCT % ($p=0.09$) and platelet count ($p=0.54$), (Table, 1). No significant differences were found among groups in TSB at admission ($p=0.63$) however, a significant reduction in TSB was noticed after 24 hrs. in the three groups and the reduction was more significant in group II (that received Phototherapy and oral zinc) and group III (that received Phototherapy and oral Agar) compared to group I (that received Phototherapy alone), it was 15.5 ± 1.67 (mg/dL) in group (I), 13.4 ± 1.11 (mg/dL) in group (II) and 13.9 ± 1.85 (mg/dL) in group (III). Also, a similar trend of results was found after 48 hours, (group II and III had a significant reduction in TSB compared to group I). However after 72 hrs, TSB concentration almost was similar among the three groups (it was higher in group III due to the small sample size, 3 cases only), but

it still continue to decline in the three groups. Also, similar results were noticed after 84 hrs (Table, 2), (Figure, 1). Hospital stay duration was significantly shorter in the group that received Phototherapy and oral zinc (51.9 ± 10.8 hrs.) compared to the group that received Phototherapy only (58.6 ± 13.0) and the group that received Phototherapy and oral agar (60.2 ± 11.2) while, no significant differences were recorded among the three groups as regards feeding status, the occurrence of complications (Table, 3 & Figure, 3) and all risk factors in terms of the male sex, gestational age, neonatal age, prime parity, CS delivery and bottle feeding.

Discussion

Neonatal hyperbilirubinemia or jaundice poses a major neonatal health burden facing both the families and governments and requires hospitalization and medical attention and several modalities exist for treatment of it. This study aimed to evaluate the efficacy of phototherapy, oral zinc salts and agar on the

treatment of hyperbilirubinemia in term and late-preterm at-risk neonates. To the best of our knowledge, many studies investigated the efficacy of zinc salts (alone or combined with phototherapy) on treatment of hyperbilirubinemia and few "old" studies investigated the effect of oral agar (alone or combined with phototherapy) on treatment of hyperbilirubinemia. But, there were no studies compared the phototherapy, zinc and agar. The results showed that there were no significant differences were noticed among groups regarding demographic and baseline data. This non-significant difference is important to ensure the homogenization of the studied groups to get accurate results from the comparison between groups which are similar to our findings.

The main findings of this study indicated that no significant differences were found among groups in TSB at admission however, a significant reduction in TSB was noticed after 24 hrs in the three groups and the reduction was more

significant in the group that received phototherapy and oral zinc and the group that received Phototherapy and oral agar compared to the group that received phototherapy alone. Also, a similar trend of results was found after 48 hrs. In addition, the duration of hospital stay was significantly shorter in the group that received phototherapy and agar compared to the group that received phototherapy only and the group that received phototherapy and zinc. These results agreed with those of Eldesoky *et al.* [9] who found that the administration of oral zinc sulphate (in a dose of 5 mg twice daily) combined with phototherapy recorded a significant reduction in TSB after 12 hours, 24 hrs of treatment and at discharge compared with phototherapy alone and in addition, the treatment markedly decreased the duration of phototherapy. Similarly, Hashemian *et al.* [10] reported that oral zinc sulfate (single dose of 10 mg/day) decreased significantly both TSB level and duration of phototherapy. Furthermore, Maamouri

et al. [6] and Faal *et al.* [11] found similar results. These results may be explained by that supplementation of oral zinc enhanced the action of phototherapy with a subsequent decline in its duration also it has the ability to suppress bilirubin entero-hepatic circulation [12]. In addition, it has been reported that zinc salts inhibit the hemoxygenase enzymes and this consequently may prevent jaundice [13].

Also, our results agreed with those of a recent Egyptian study by Safwat *et al.* [14] who evaluated the effect of oral agar administration (600 mg/kg/day) combined with phototherapy on TSB levels of jaundiced neonates in comparison with control ones who received phototherapy alone.

They found that this treatment resulted in a significant decrease in TSB level and as compared to phototherapy alone. Also, Ahmed *et al.* [15] found typical results. These results may be explained by that agar can bind bilirubin in the intestine and this results in decreasing bilirubin

enterohepatic circulation and consequently decreasing TSB levels and in addition it has been reported that agar acts as a trapping agent for the unconjugated bilirubin in the intestinal lumen [16].

Shortening phototherapy duration is important because it led to more contact between the mother and her infant, lowering hospitalization and consequently lowering the risk of nosocomial infections and decreasing the economic burden and the adverse effects of phototherapy.

Regarding occurrence of complications, no significant differences were recorded among the three groups in this study. Similarly, Eldesoky *et al.* [9] and Faal *et al.* [11] found that there was no significant difference between groups that received oral zinc plus phototherapy and that received phototherapy alone regarding adverse effects. Also, many authors reported similar findings regarding agar [14, 15].

Conclusions

Administration of oral zinc or Agar besides phototherapy could be more effective in the treatment of neonatal Jaundice due to indirect hyperbilirubinemia compared to receiving phototherapy alone and both were safe and could augment the efficacy of phototherapy in decreasing TSB level, besides they could be considered as a cost-effective modality. Oral zinc besides phototherapy significantly shortened the hospital stay period. Further studies with larger sample sizes, different dosages and formulations of zinc and agar, longer duration of follow-up, and more precise laboratory studies are recommended to confirm our findings.

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Author's contributions

All of authors shared equally in this work and have seen and agreed to the submitted version of the manuscript.

Conflict of interest

The authors declare that they have no competing interests

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Table (1): Comparison among the three studied groups regarding demographic and baseline data.

Variable	Group (I) Phototherapy alone (n=25)	Group (II) Phototherapy & Zinc (n=25)	Group (III) Phototherapy & Agar (n=25)	P. value
Sex (Male/Female)	12/13	13/12	13/12	0.95 ^{NS}
Gestational age (week)	37.5 ± 1.2	38.0 ± 1.2	37.6 ± 1.1	0.28 ^{NS}
Neonatal age (day)	3.3 ± 0.48	3.5 ± 0.51	3.5 ± 0.51	0.33 ^{NS}
Birth weight (gm)	2852 ± 177	2934 ± 202	2884 ± 246	0.39 ^{NS}
Mother age (year)	29.3 ± 6.2	28.0 ± 4.0	29.5 ± 5.9	0.58 ^{NS}
Parity (Prime/Multi)	11/14	8/17	11/14	0.61 ^{NS}
Mode of delivery (CS/NVD)	16/9	16/9	16/9	1.0 ^{NS}
Length (cm)	45.0 ± 3.8	46.8 ± 2.7	45.7 ± 3.4	0.16 ^{NS}
Head circumference (cm)	33.7 ± 0.48	33.8 ± 0.46	33.9 ± 0.33	0.26 ^{NS}
WBCs (10⁹/L)	11.16 ± 2.37	11.02 ± 2.45	11.26 ± 2.36	0.94 ^{NS}
Hb (%)	16.28 ± 2.28	15.45 ± 3.04	15.36 ± 2.46	0.40 ^{NS}
HCT (%)	46.1 ± 4.66	46.5 ± 5.30	48.9 ± 4.46	0.09 ^{NS}
Platelets (10⁹/L)	251 ± 83.81	248.9 ± 62.90	282.3 ± 97.80	0.54 ^{NS}

Quantitative data were presented as mean ± SD. Qualitative data were presented as No. (%).

ANOVA and Chi-square test were used to compare among groups.

NS Not significant.

Table (2): Comparison among the three groups and different periods as regards total serum bilirubin.

Total serum bilirubin (mg/dL)		Group (I) Phototherapy alone (n=25)	Group (II) Phototherapy & Zinc (n=25)	Group (III) Phototherapy & Agar (n=25)	P. value
At admission		17.1 ± 0.92	16.84 ± 0.83	17.01 ± 1.12	0.63 ^{NS}
After 24 hrs.		15.5 ^{a#} ± 1.67	13.4 ^{b#} ± 1.11	13.9 ^{b#} ± 1.85	<0.01**
After 48 hrs.		12.0 ^{a#} ± 1.81	10.7 ^{b#} ± 1.17	10.2 ^{b#} ± 2.37	<0.01**
After 72 hrs.	No. of cases	(n = 11)	(n = 15)	(n = 3)	
	Mean ± SD	9.27 ^{ab#} ± 2.15	8.87 ^{b#} ± 0.64	11.33 ^{a#} ± 2.08	0.04*
After 84 hrs.	No. of cases	(n = 5)	(n = 1#)	(n = 2)	
	Mean ± SD	8.20 [#] ± 0.45	7.0	8.50 [#] ± 0.71	0.51 ^{NS}

ANOVA test was used to compare among groups and Paired T-test was used to compare between different periods compared to at admission value. *Significant (p<0.05). **Significant (p<0.01).

a, b Means with different superscript letters in the same row are significantly different (Post Hoc- Tukey test).

significant difference as compared to (on admission) value

Table (3): Comparison among the three groups regarding outcome.

Variable	Group (I) Phototherapy alone (n=25)	Group (II) Phototherapy & Zinc (n=25)	Group (III) Phototherapy & Agar (n=25)	P. value
Hospital stays duration (hrs.)	58.6 ^a ± 13.0	51.9 ^b ± 10.8	60.2 ^a ± 11.2	0.03*
Feeding status	Breastfeeding	14 (56.0%)	13 (52.0%)	0.50 ^{NS}
	Bottle	11 (44.0%)	12 (48.0%)	
Complications	Non-complicated	22 (88.0%)	23 (92.0%)	0.91 ^{NS}
	Complicated	3 (12.0%)	2 (8.0%)	

* Significant (p<0.05).

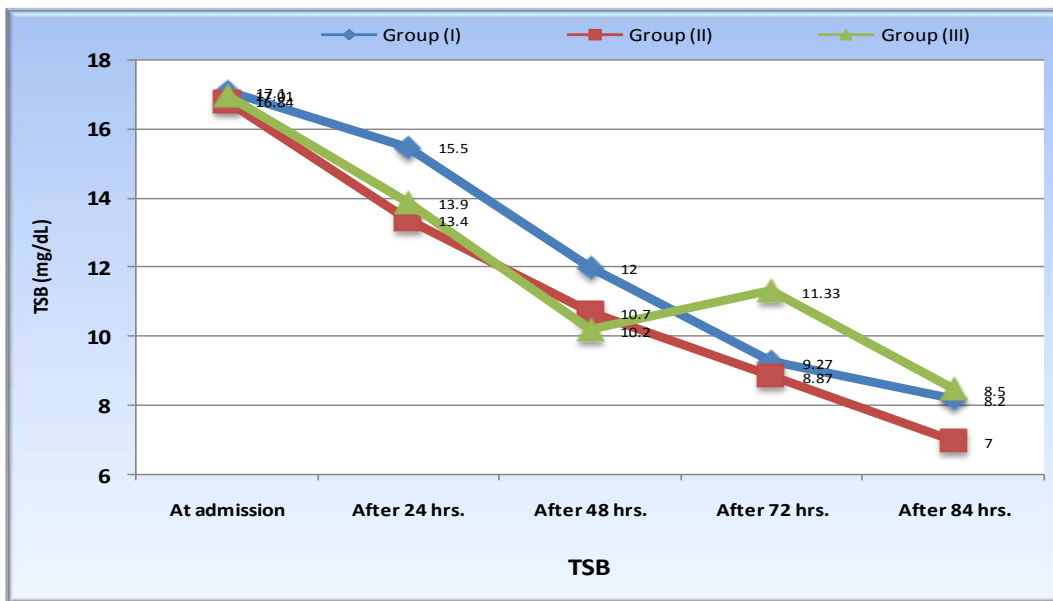


Figure (1): TSB levels among groups at different follow up periods.

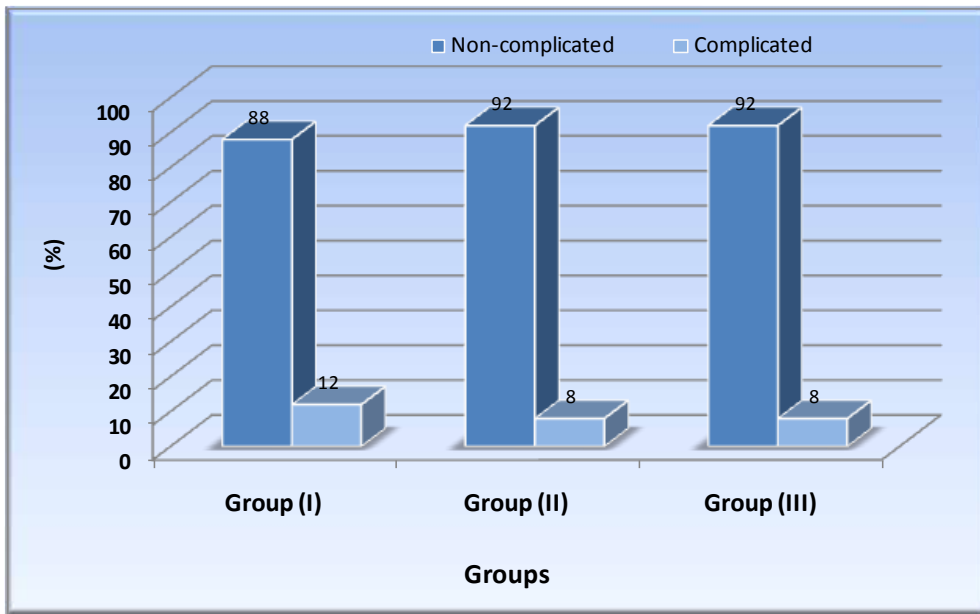


Figure (2): Complications among groups.

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