Review Paper

Phototherapy Effects on Zinc Level of Neonates With Hyperbilirubinemia: A Systematic Review and Meta-analysis

Diana Sarokhani[1], Amir Adibi[2], Mohsen Abdan[1], Moloud Fakhri[3*]

1. Research Center for Environmental Determinants of Health, School of Public Health, Kermanshah University of Medical Sciences, Kermanshah, Iran.
2. Department of Child and Adolescent Psychiatry, Faculty of Medicine, Ilam University of Medical Sciences, Ilam, Iran.
3. Traditional and Complementary Medicine Research Center, Addiction Institute, Mazandaran University of Medical Sciences, Sari, Iran.

Use your device to scan and read the article online

Citation Sarokhani D, Adibi A, Abdan M, Fakhri M. Phototherapy Effects on Zinc Level of Neonates With Hyperbilirubinemia: A Systematic Review and Meta-analysis. Journal of Pediatrics Review. 2023; 11(2):107-116. http://dx.doi.org/10.32598/jpr.11.2.1047.4

http://dx.doi.org/10.32598/jpr.11.2.1047.4

Article info:
Received: 31 Jan 2023
First Revision: 02 Mar 2023
Accepted: 06 May 2023
Published: 01 Apr 2023

Key Words:
Zinc, Hyperbilirubinemia, Neonatal jaundice, Jaundice, Neonatal, Phototherapy, Light therapy

ABSTRACT

Background: Phototherapy is the most common treatment of neonatal jaundice that affects the zinc level as well as the bilirubin level.

Objectives: The purpose of this study is to investigate the effect of phototherapy on the zinc level of infants with jaundice by a systematic review and meta-analysis.

Methods: In this systematic review and meta-analysis a comprehensive literature search of the databases, including Cochrane Library, Web of Science, PubMed, Scopus, and Google Scholar web browser was conducted using standard keywords. Data analysis of this meta-analysis was performed using STATA software, version 14 and P<0.05 was considered a significant level for tests.

Results: In the five studies reviewed in this article with a sample size of 398 individuals, phototherapy increased the level of zinc [Standardized mean difference (SMD): 0.88 (95% CI: 0.38, 1.38), P<0.001] and decreased bilirubin level [SMD: -7.67 (95% CI: -9.11, -6.23), P<0.001] in infants with jaundice. The effect of phototherapy was on the zinc level of these groups: infants with a birth weight of 3000 to 3300 grams (gr) [SMD: 1.07 (95% CI: 0.42, 1.71), P<0.001] and 3301 to 3600 gr [SMD: 0.40 (95% CI: -0.32, 1.12), P=0.028], three-day-old infants [SMD: 1.05 (95% CI: 0.35, 1.74), P<0.001], four-day-old [SMD: 0.76 (95% CI: 0.26, 1.32)], and 5-day-old ones [SMD: 0.23 (95% CI: -0.01, 0.48)]. In addition, phototherapy affected on zinc level of those whose gestational age (GA) was 37 [SMD: 1.12 (95% CI: 0.06, 2.17), P<0.001] and 38 [SMD: 0.61 (95% CI: 0.15, 1.06), P=0.001] weeks.

Conclusions: Phototherapy by reducing the level of bilirubin increases the level of zinc in infants with jaundice. So, the standardized mean difference of "phototherapy effects on the zinc level of infants with jaundice" decreases with increasing infants' weight, increasing infants' age, and increasing gestational age.

** Corresponding Author:*
Moloud Fakhri, Assistant Professor.
Address: *Traditional and Complementary Medicine Research Center, Addiction Institute, Mazandaran University of Medical Sciences, Sari, Iran.*
Tel: *+98 (911) 1520601*
E-mail: *mmfir@yahoo.com*

Introduction

When the color of the skin, sclera, and mucosal membrane changes to yellow in infants, it is called neonatal jaundice which occurs because of tissue deposition of bilirubin. Jaundice appears when the total serum bilirubin (TSB) becomes 5 mg/dL (86 mcmol/L) and higher [1]. Jaundice incidence is 60% in normal neonates and 80% in premature ones [2]. Infants with severe hyperbilirubinemia are at risk because of the probable accumulation of bilirubin in tissues, especially in the brain that leads to acute bilirubin encephalopathy and chronic complications like cerebral palsy, sensory neural hearing loss, mental problems, or severe growth retardation [3]. There are several treatments for conjugated neonatal hyperbilirubinemia [4]. Phototherapy is the most common intervention used in the treatment and prevention of hyperbilirubinemia since it decreases the total bilirubin concentration and the usage of blood transfusion [5]. However, phototherapy may lead to some complications in neonates including dehydration, skin lesions, eye damage, corneal scar, diarrhea, electrolyte disorders, nervous system complication, hypocalcemia, etc [6, 7].

On the other side, micronutrients level and minerals like zinc, copper, and magnesium can influence the process of protein binding to bilirubin and bilirubin excretion [8, 9]. In addition, bilirubin decreasing by phototherapy may increase the serum zinc level of infants [10]. Thus, in this study we investigate the effect of phototherapy on the zinc level of neonates with jaundice for the first time, using a systematic review and meta-analysis method. Since studies published in this field so far, have presented different results.

Methods

Study design

In this systematic review and meta-analysis, we examine the effect of phototherapy on zinc levels in infants with jaundice. The meta-analysis is carried out based on the preferred reporting items for systematic reviews and meta-analyses (PRISMA 2020) statement for systematic review and meta-analysis studies. The protocol of this meta-analysis was registered on the site of PROSPERO (CRD42022340667).

Outcome measures

Primary outcome

Determining the effect of phototherapy on zinc levels in infants with jaundice.

Secondary outcome

Determining the effect of phototherapy on bilirubin and zinc levels in neonates with jaundice based on neonatal age, neonatal weight, and gestational age.

Search strategy

In this systematic review and meta-analysis, international databases including Cochrane Library, Web of Science, PubMed, Scopus, and Google Scholar web browsers, were searched without time or language restrictions. For papers published in languages other than Persian or English, the full article was translated to extract its data. The search strategy step was performed by standard keywords including "zinc, hyperbilirubinemia, neonatal jaundice, jaundice, neonatal, phototherapy, light therapy." (updated until 03.05.2022). Keyword combinations using Boolean operators "AND" and "OR" were also included in the database search. Additionally, the list of references of all primary studies that remained at the end of the PRISMA flowchart and entered the meta-analysis was screened by manual search. Search strategy in databases: Scopus: (title-abs-key (infant OR neonate) AND title-abs-key (phototherapy) AND title-abs-key (zinc) AND title-abs-key (hyperbilirubinemia OR jaundice)), Web of Science: Infant OR neonate (topic) and phototherapy (topic) and zinc (topic) and hyperbilirubinemia OR jaundice (topic), PubMed: ((Hyperbilirubinemia [title/abstract] OR jaundice [title/abstract]) AND (infant[title/abstract] OR neonate [title/abstract])) AND (phototherapy[title/abstract])) AND (zinc[title/abstract]), Cochrane Library: Infant in title abstract keyword OR neonate in title abstract keyword AND phototherapy in title abstract keyword AND zinc in title abstract keyword AND hyperbilirubinemia OR jaundice in title abstract keyword - in trials (word variations have been searched)

PICO components

Population: Infants with jaundice

Intervention: Phototherapy

Comparison: There is no comparison group and zinc and bilirubin levels of jaundiced babies before and after the intervention have been compared.

Outcome: The effect of phototherapy on infants with jaundice zinc level.

Inclusion criteria

In this meta-analysis, studies are conducted to evaluate the effect of phototherapy on zinc levels in infants with jaundice.

Exclusion criteria

Case report or case series studies, low-quality studies, studies examining the effect of phototherapy and other factors on neonatal zinc level simultaneously, lack of reporting of the required information for data analysis, unavailability of the full-text of articles, and studies that qualitatively reported the effect of phototherapy on neonatal zinc level were excluded.

Quality assessment

The two authors independently evaluated the quality of the studies. The Cochrane checklist was used for randomized clinical trial studies. This Cochrane risk-of-bias tool checklist is divided into seven distinct domains, each assessing a different dimension or type of significant bias in clinical trials. Moreover, each domain in this checklist assigns trials a risk of bias of 'low risk', 'high risk', or 'unclear risk'. After assessing the risk of bias in each study, the discrepancy between the responses in each study was determined and the two evaluators reached a consensus on one response.

For other studies, the STROBE checklist was used [11]. The STROBE checklist has 22 sections that cover different sections of a report. In this checklist, the sum of the scores is decisive, therefore a score of 1-15 indicates low quality, 16-30 indicates average quality and 31-44 indicates excellent quality. The cut-off point in this study was 15 points.

Data extraction

Two researchers independently extracted data from studies to minimize biased reporting and errors in data collection. They entered the extracted data into a checklist containing the name of the author, year of publication, number of girls, number of boys, country, sample size, type of study, type of delivery, neonatal age, neonatal weight, gestational age, the mean and standard deviation of neonatal zinc, and bilirubin levels. A third researcher evaluated the data extracted by the two previous researchers to correct any existing discrepancies.

Statistical analysis

Considering the quantitative nature of the primary outcome in these studies, the effect size of the intervention was calculated. The standardized mean difference (SMD) index, which is a classical effect size index, indicates the strength of the relationship between the intervention and the outcome under study. Usually, the closer SMD is to zero, the weaker the strength of the relationship, and the tendency to the number one or even higher indicates the stronger the relationship. If the SMD confidence interval breaks to zero, then the relationship is not statistically significant, and vice versa (Equation 1).

$$1.\ SMD=\frac{\text{Difference in Mean outcome beetween groups}}{\text{Standard devation (SD) of outcome amang particpants}}$$

The studies were combined considering the sample size, mean, and standard deviation. The heterogeneity of the studies was assessed using the I2 index and Q-Cochrane test. The random-effects model was used in this work to combine the reviewed studies (I2=92%). Data analysis was executed using STATA software, version 14. The significance level was considered $P<0.05$ for all tests. Meta-regression was employed to evaluate the relationship between "The effect of phototherapy on zinc levels in infants with jaundice" and "sample size" and "year of publication."

Results

Study selection

Initially, 285 articles were found in the search in the mentioned databases. After checking the studies' titles, 127 duplicate studies were excluded. The abstracts of 158 articles were explored, and 8 articles whose full texts were not available were excluded. The full texts of the 150 remaining papers were screened, and another 145 articles that met the other exclusion criteria were discarded. Eventually, five high-quality articles entered the meta-analysis process (Figure 1).

In the five reviewed studies with a sample size of 398 individuals, 173 infants were female and 225 were male. The mean infants' weight ranged from 3003 to 3550 and the mean of their age differed from 3.02 to 5.70. Seventy-two percent of neonates were born by cesarian section and the others (28%) were born by vaginal delivery. One of the reviewed studies was conducted

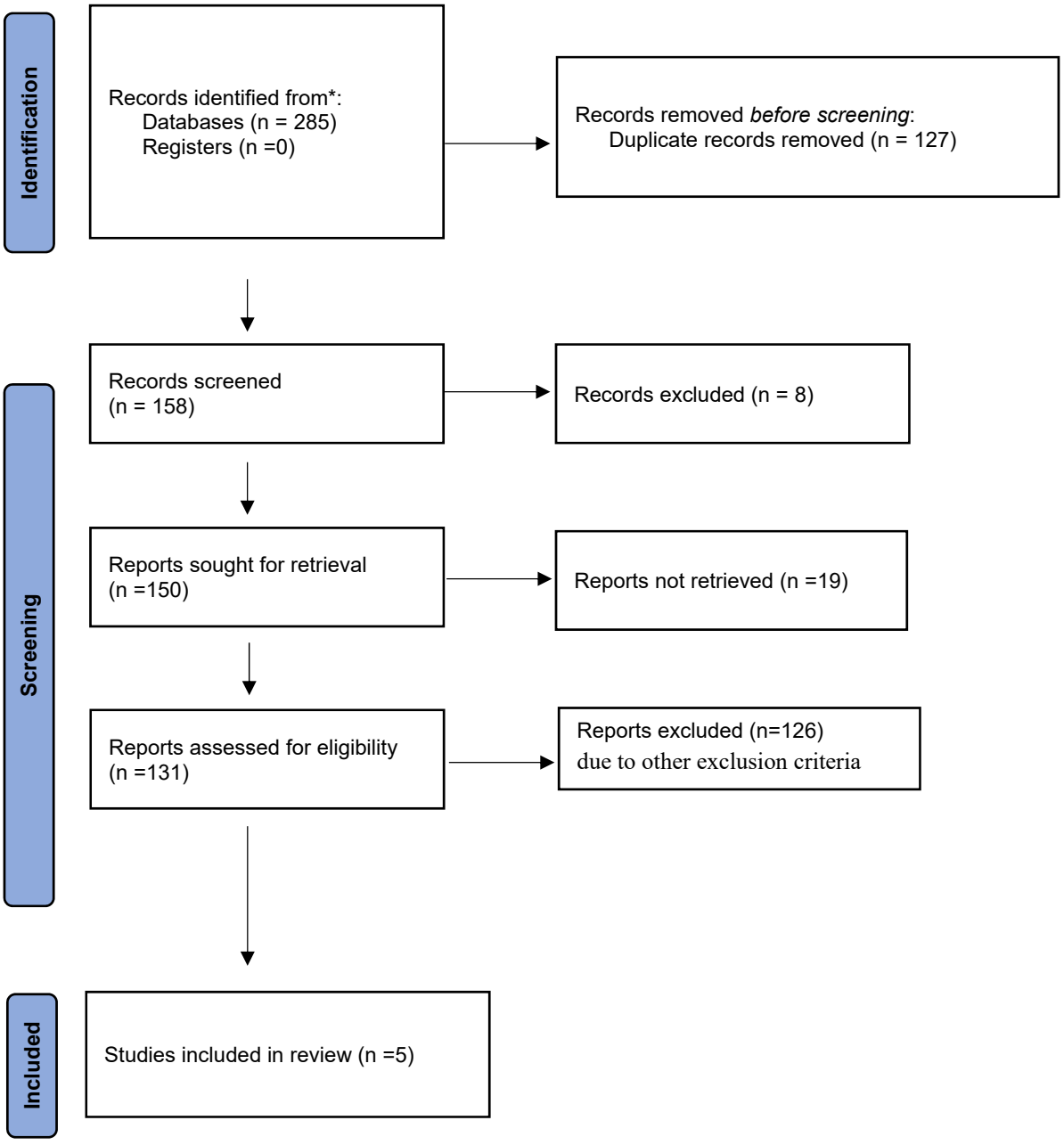


Figure 1. The process of entering the studies into the systematic review and meta-analysis

Journal of Pediatrics Review

in Iran and the other four were from Egypt. The source search phase was done without geographic restrictions, but the articles published in this field were related to these two countries (Table 1).

When we compared the mean of neonatal zinc level with its standard deviation before and after the intervention, we found that the standard measure of phototherapy effect on zinc level of infants with jaundice was [SMD:0.88 (95% CI:0.38, 1.38)]. In other words, phototherapy increased the zinc level of neonates and this relationship was statistically significant (Figure 2).

The effect of phototherapy on infants whose weights were 3000 to 3300 gr was [SMD: 1.07 (95% CI:0.42, 1.71)], and it was [SMD:0.40 (95% CI:-0.32, 1.12)] in those with the weight of 3301 to 3600. Its effect on three-day-old infants was [SMD:1.05 (95% CI:0.35, 1.74)], four-day-old [SMD:0.76 (95% CI: 0.26, 1.32)], and 5-day-old ones [SMD: 0.23 (95% CI:-0.01, 0.48)].

Table 1. Specifications of articles that entered into the meta-analysis process

Authors Name, Year of Publication	Type of Study	Country	Sample Size	No. of Girls	No. of Boys	Gestational Age (Week)	Age Mean (Day)	Cesarean Delivery (%)	Birth Weight (G)	Result of Quality Assessment
Baiomi et al. 2020 [12]	Prospective cross-sectional case-control		150	53	47	38	3.09	84	3003	25
El-Mazary et al. 2017 [13]	Prospective case-control	Egypt	30	13	17	38.2	4.3	---	3550	30
Ali Ahmed Abd El-Magid et al. 2021 [2]	Prospective cohort		50	24	26	37.76	3.4	82	3370	31
Mosayebi et al. 2016 [14]	Prospective cohort	Iran	128	64	64	38.5	5.7	63	3163	36
El-Farrash et al. 2019 [15]	RCT		40	19	21	37.57	3.05	67.5	3040	Low risk
El-Farrash et al. 2019 [15]	RCT	Egypt	40	19	21	37.73	3.04	60	3060	Low risk
El-Farrash et al. 2019 [15]	RCT		40	19	21	37.67	3.02	72.5	3140	Low risk

On the other hand, phototherapy affected on zinc level of those whose gestational age (GA) was 37 [SMD: 1.12 (95% CI:0.06, 2.17)] and 38 [SMD:0.61 (95% CI:0.15, 1.06)] weeks. As mentioned above, in subgroup analysis we found that the effect of phototherapy on the zinc level of infants with jaundice in different weights and gestational ages was significant. In the analysis of different age groups, the phototherapy effect on zinc levels was significant in those whose average ages were 3 and 4 days. But there was not a significant relationship between zinc levels and 5-day-old ones (Table 2).

As shown in Figure 3, phototherapy could decrease the bilirubin level in neonates with jaundice and this relationship was statistically significant.

Meta-regression also showed that the phototherapy effect on zinc levels in infants with jaundice from 2016 to 2021 was not significant based on statistical analysis (P=0.909). It means that we cannot conclude that phototherapy's effect on zinc levels has increased (Figure 4). It is also shown in Figure 5 that the relationship between the phototherapy effect and the sample size of the study was not significant based on statistics (P=0.570).

Table 2. The effect of phototherapy on the zinc level of neonates with jaundice in the studied subgroups

Subgroups		No. of Studies	SMD	SMD Low Limit	SMD Up Limit	I^2 (%)	P
Total		5	0.88	0.38	1.38	92	<0.001
Birth weight (g)	3000-3300	3	1.07	0.42	1.71	93.9	<0.001
	3301-3600	2	0.40	-0.32	1.12	79.2	0.028
Age mean (day)	3	3	1.05	0.35	1.74	93.3	<0.001
	4	1	0.76	0.26	1.32	0	---
	5	1	0.23	-0.01	0.48	0	---
Gestational age (week)	37	2	1.12	0.06	2.17	95	<0.001
	38	3	0.61	0.15	1.06	84.8	0.001

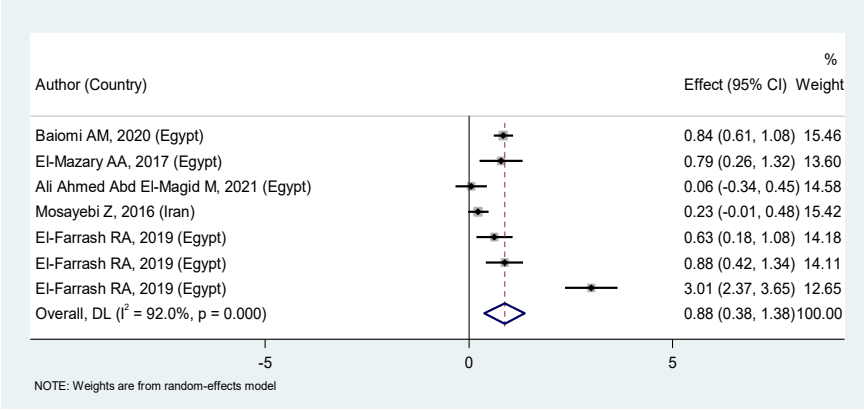


Figure 2. Forest plot showing effect of phototherapy on zinc level of Neonates with Jaundice

Journal of Pediatrics Review

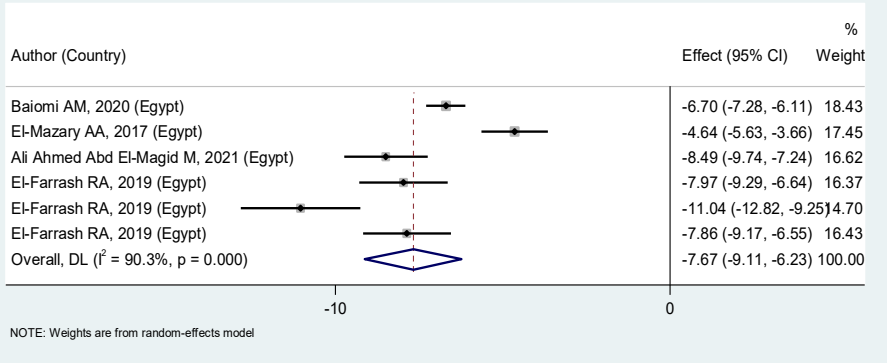
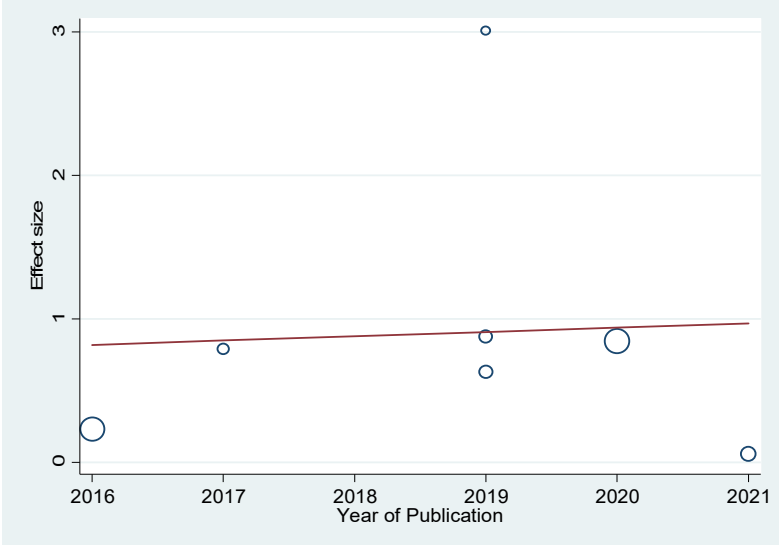


Figure 3. Forest Plot showing effect of phototherapy on bilirubin level of Neonates with Jaundice

Journal of Pediatrics Review



Journal of Pediatrics Review

Figure 4. Meta-regression of the relationship between the effect of phototherapy on the zinc level of Neonates with Jaundice and the year of publication

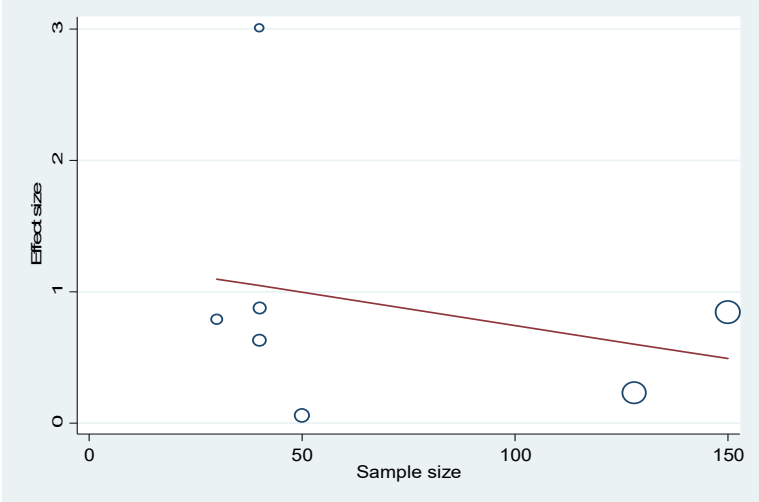


Figure 5. Meta-regression of the relationship between the effect of phototherapy on the zinc level of Neonates with Jaundice and the sample size of studies

Publication bias analysis was done and this relationship was not statistically significant (P=0.248). It shows that the step of the literature search has been done comprehensively and properly so that all studies whether positive results or negative ones have been included (Figure 6).

Discussion

Considering that the level of zinc in infants has a significant impact on the growth of infants and taking into account that the level of zinc in infants with jaundice is lower than that of healthy infants, increasing the level of zinc as a result of phototherapy in infants with jaundice is useful and considered effective. In the five studies reviewed in this article that was published from 2016 to 2021, with a sample size of 398 individuals, phototherapy in infants with jaundice had two outcomes. The first one was the increasing zinc level [SMD: 0.88 (95% CI: 0.38, 1.38)] and the other was decreasing the level of bilirubin in neonates [SMD: -7.67 (95% CI: -9.11, -6.23)]. Phototherapy improved neonatal jaundice status. In previous related studies, three of them reported significant positive effects of phototherapy on neonatal zinc levels [12, 13, 15], while the other two found no significant relationship [2, 14]. Regarding the controversy of previous experiments, the current study was performed by meta-analysis method.

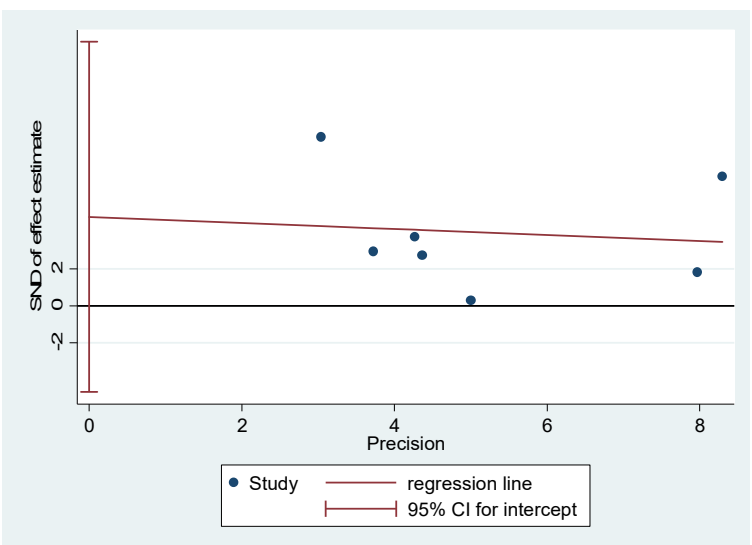


Figure 6. Publication bias

On the other hand, researchers assessed the effect of phototherapy on serum calcium and magnesium level. Gaafar et al. (2020) in Egypt studied the effect of this intervention on serum calcium and magnesium in term and preterm infants with hyperbilirubinemia. Sixty neonates with jaundice were included and 43 of them were term and the other 17 ones were preterm. The results indicated that phototherapy can reduce the jaundice of term and preterm infants significantly [16]. Shahriarpanah et al. (2018) studied the role of phototherapy in calcium, magnesium, and vitamin D serum level changes in the Iranian community, using 50-term infants with jaundice. Based on their study results, phototherapy could reduce calcium and magnesium levels and increase the level of vitamin D [17]. Eghbalian et al. included 160 neonates with jaundice in their study in Iran. The results showed the maximum serum magnesium reduction was in the double phototherapy group (-0.13±-0.42 mg/dL, P=0.018). Decreasing serum magnesium levels in single phototherapy (-0.02±-0.25) and intensive phototherapy (-13.55±2.73) was not significant (P>0.05) [18].

As we discussed above, some of the studies that observed the phototherapy effect on infants' calcium and magnesium level reported increased levels of calcium and magnesium after phototherapy while some of them had opposite results. This conflict is also present in basic studies of the current meta-analysis. One of the reasons for this opposition is the limited number of related studies and the low number of samples in these experiments. Therefore, it is recommended to design studies with a larger sample size.

Conclusion

Phototherapy increased the level of zinc (primary outcome) and decreased the level of bilirubin (secondary outcome) in infants with jaundice, and both relationships were statistically significant. Phototherapy by reducing the level of bilirubin increases the level of zinc in infants with jaundice. So, the SMD of "phototherapy effects on the zinc level of infants with jaundice" decreases with increasing infants' weight, increasing infants, age, and increasing gestational age. Due to the limited number of studies reviewed, we need more studies to comment more confidently about the effect of phototherapy on the zinc level of infants with jaundice.

Limitations

Due to the incomplete information of reviewed studies, we could not analyze the results based on infants' gender, type of child delivery, etc. Other limitations were limited reviewed studies all of them conducted in Iran and Egypt only. In addition, we could not provide an analysis of phototherapy duration because the hours of phototherapy were not mentioned in the articles.

Ethical Considerations

Compliance with ethical guidelines

This article is a meta-analysis with no human or animal sample.

Funding

This research did not receive any grant from funding agencies in the public, commercial, or non-profit sectors.

Authors contributions

Conceptualization, study design, drafting the manuscript and final approval: All authors; Data analysis: Amir Adibi and Moloud Fakhri; The result interpretation: Diana Sarokhani and Mohsen Abdan.

Conflicts of interest

The authors declared no conflict of interest.

References

1. Pan D, Rivas Y. Jaundice: Newborn to age 2 months. Pediatr Rev. 2017; 38(11):499-510. [PMID]

2. Ali Ahmed Abd El-Magid M, Ibrahim El-Samannody M, Mohamed El-Mazahy M, Zaki El-Ghannam M. Effect of phototherapy on zinc status in term neonates with indirect hyperbilirubinemia. Al-Azhar Med J. 2021; 50(1):573-682. [DOI:10.21608/amj.2021.139848]

3. Das S, van Landeghem FKH. Clinicopathological spectrum of bilirubin encephalopathy/kernicterus. Diagnostics. 2019; 9(1):24. [DOI:10.3390/diagnostics9010024] [PMID] [PMCID]

4. Ravichander B, Kundu S. Effect of double surface photo-therapy on serum magnesium levels in term and late preterm neonates. J Evid Based Med Healthc. 2018; 5(4):315-8. [Link]

5. Zhang XR, Zeng CM, Liu J. [Effect and safety of intensive phototherapy in the treatment of neonatal hyperbilirubinemia (Chinese)]. Zhongguo Dang Dai Er Ke Za Zhi. 2016; 18(3):195-200. [PMID]

6. Taksande A, Selvam S. Side effects of phototherapy in neonatal hyperbilirubinemia. Acta Sci Paediatr. 2018; 5(1):24-30. [Link]

7. Mohammadi Pirkashani L, Asghari G, Marofi M, Barekatain B. Effect of chicory extract bath on neonatal bilirubin levels: A randomized clinical trial study. Int J Pediatr. 2017; 5(12):6679-88. [Link]

8. Tan H, Karakelleoğlu C, Akçay F, Akdağ R, Alp H. Serum concentrations of zinc, magnesium, manganese, and copper in neonatal jaundice. Eurasian J Med. 2000; 32(1):9-12. [Link]

9. Sarici SU, Serdar MA, Erdem G, Alpay F. Evaluation of plasma ionized magnesium levels in neonatal hyperbilirubinemia. Pediatr Res. 2004; 55(2):243-7. [DOI:10.1203/01.PDR.0000103874.01584.F3] [PMID]

10. Blindauer CA. Lessons on the critical interplay between zinc binding and protein structure and dynamics. J Inorg Biochem. 2013; 121:145-55. [DOI:10.1016/j.jinorgbio.2013.01.005] [PMID]

11. von Elm E, Altman DG, Egger M, Pocock SJ, Gøtzsche PC, Vandenbroucke JP, et al. The strengthening the reporting of observational studies in epidemiology (STROBE) statement: Guidelines for reporting observational studies. Ann Intern Med. 2007; 147(8):573-7. [DOI:10.7326/0003-4819-147-8-200710160-00010] [PMID]

12. Baiomi AM, Hassan KH, Besher M, Mahmoud M. Effect of phototherapy on serum zinc level in neonatal jaundice. Egypt J Hosp Med. 2020; 81(3):1614-20. [DOI:10.21608/ejhm.2020.116795]

13. El-Mazary A, Abdel Aziz R, Sayed M, Mahmoud R, Saedii A. Effect of intensive phototherapy and exchange transfusion on copper, zinc, and magnesium serum levels in neonates with indirect hyperbilirubinemia. Int J Pediatr. 2017; 5(2):4371-83. [Link]

14. Mosayebi Z, Rahmani M, Behjati Ardakani S, Sheikh M, Shariat M, Rezaeizadeh G. Evaluation of serum zinc levels in hyperbilirubinemia neonates before and after phototherapy. Iran J Pediatr. 2016; 26(3):e4146. [DOI:10.5812/ijp.4146] [PMID] [PMCID]

15. El-Farrash RA, El-Shimy MS, Tawfik S, Nada AS, Salem DAD, M Gallo MS, et al. Effect of phototherapy on oxidant/antioxidant status: A randomized controlled trial. Free Radic Res. 2019; 53(2):179-86. [DOI:10.1080/10715762.2018.1549364] [PMID]

16. Gaafar M, Rasheed E, Abdel Halim S, El Gendi M. Effect of phototherapy on serum level of calcium and magnesium in term and preterm neonates with hyperbilirubinemia. The Egypt J Hosp Med. 2020; 80(1):743-7. [DOI:10.21608/ejhm.2020.97052]

17. Shahriarpanah S, Haji Ebrahim Tehrani F, Davati A, Ansari I. Effect of phototherapy on serum level of calcium, magnesium, and vitamin D in infants with hyperbilirubinemia. Iran J Pathol. 2018; 13(3):357-62. [PMID]

18. Eghbalian F, Shabani S, Faradmal J, Jenabi E. Effects of phototherapy on the serum magnesium level in neonates with indirect hyperbilirubinemia: A prospective cohort study. Int J Pediatr. 2022; 2022:5439630. [DOI:10.1155/2022/5439630] [PMID] [PMCID]

This Page Intentionally Left Blank