Proceedings S.Z.M.C. Vol: 38(4): pp. 305-309, 2024. PSZMC-960-38-4-2024

Vitamin D Supplementation as Adjuvant with Phototherapy Is Beneficial in Neonatal Jaundice

[1]Zeeshan Afzal, [1]Muhammad Tayyab, [1]Wajiha Rizwan

ABSTRACT

Introduction: Jaundice is common among neonates especially during the initial week of life and poses significant risks for neonatal morbidity and mortality. Phototherapy is the standard management for neonatal hyperbilirubinemia, but its potential side effects have led to exploration of adjunct therapies like vitamin D.

Aims and Objective: This study aimed to determine the efficacy of vitamin D supplementation in combination with phototherapy versus phototherapy alone in reducing total serum bilirubin (TSB) levels in neonates with jaundice.

Place and Duration of Study: Nursery Department, The Children's Hospital, Lahore (CHL) over six months from 10-05-2022 to 09-11-2022

Materials and Methods: It was a randomized controlled trial including one hundred neonates diagnosed with unconjugated hyperbilirubinemia (14-20 mg/dl). Patients were randomized into groups A and B. Group A received phototherapy with vitamin D (800 IU daily), while Group B received phototherapy alone. The primary outcome was the reduction in TSB levels after a maximum of five days of treatment. SPSS version 22 was used for data analysis with independent t-tests comparing post-treatment TSB levels between the two groups.

Results: The study included 64 males (64%) and 36 females (36%). Mean pre-treatment TSB levels were similar between Group A (18.14 ± 2.6 mg/dL) and Group B (18.15 ± 2.4 mg/dL). Post-treatment TSB levels were significantly lower in Group A (6.99 ± 0.457 mg/dL) compared to Group B (8.94 ± 0.884 mg/dL), with a p-value < 0.001. Stratified analysis showed consistent TSB reductions across gender, gestational age, and socioeconomic factors.

Conclusion: Vitamin D supplementation in combination with phototherapy resulted in a significantly greater reduction in TSB levels in neonates with jaundice as compared to phototherapy alone. These findings suggest that vitamin D may enhance the efficacy of phototherapy in treating neonatal jaundice.

Keywords: Neonatal Jaundice, Phototherapy, Vitamin D therapy, Bilirubin.

INTRODUCTION

Neonatal jaundice frequently occurs during initial week of life, affecting around 60% and 80% of term and preterm neonate respectively and poses a significant risk for newborn illness and death.[1] It is a leading cause of neonatal hospital admissions and readmissions.[1,2]Jaundice occurs when elevated bilirubin accumulates in the skin and tissues. Jaundice is visible in skin and eyes of newborns when TSB concentration is more than 5 mg/dl.[3]Bilirubin, a byproduct of red blood cell breakdown, must be conjugated in the liver for excretion. Hyperbilirubinemia can stem from pre-hepatic, hepatic, or post-hepatic causes. Unconjugated hyperbilirubinemia mainly occurs due to pre-hepatic causes, most commonly including prematurity, sepsis, G6PD deficiency, blood group incompatibilities, breast milk and breastfeeding jaundice, and a large number of cases are idiopathic.[4,5] Unconjugated bilirubin may enter the brain, leading to potential damage and conditions like bilirubin encephalopathy or kernicterus and hence in severe cases it is usually managed with either phototherapy and/or exchange transfusion.[3,4,6] Phototherapy is the primary treatment for unconjugated hyperbilirubinemia in neonates, irrespective of cause.[6] It is most effective with maximum body exposure at blue light wavelengths (450 ± 20 nm) and positioned closely, typically within 30 cm. It breaks down bilirubin and helps in its excretion. Guidelines relate total serum bilirubin thresholds to the newborn's gestational age, postnatal age, and risk factors for bilirubin neurotoxicity.[6,7] Phototherapy is generally considered safe but can lead to few complications including skin rashes, hyperthermia, diarrhea, dehydration, hypocalcaemia, retinal damage and reopening of the patent ductus arteriosus in low birth weight neonates.[8] Hence, adjunct therapies can be beneficial in reducing duration of phototherapy

[1]University of Child Health Sciences, Children's Hospital Lahore

Correspondence:
Dr. Zeeshan Afzal, *Registrar, Pediatric Medicine Department*
University of Child Health Sciences, Children's Hospital Lahore
E-mail: afzal.zeeshan93@outlook.com

Submission Date:8th October2024
1st Revision Date:23rd November 2024
Acceptance Date: 07th Dec,2024

treatment to minimize unwanted side effects. Vitamin D, fat-soluble vitamin, is being recently used in neonatal jaundice as an adjunct therapy. Few studies suggest that healthy newborns with hyperbilirubinemia outside the physiological range have notably reduced serum vitamin D levels. This deficiency is inversely associated with neonatal hyperbilirubinemia, suggesting that low vitamin D levels could be a potential risk factor for jaundice among neonates.[9] Whereas, another similar study was conducted to assess the relationship between neonatal idiopathic hyperbilirubinemia and serum vitamin D levels in newborns admitted in a hospital of Iran. The mean serum 25-hydroxyvitamin D levels were 14.88 ± 11.38 ng/dl in the control group and 10.76 ± 8.6 ng/dl in the case group with no significant difference (p= 0.11). These variable findings suggest further research is needed to confirm vitamin D's role in the condition's pathogenesis.[10]The connection between vitamin D and neonatal hepatitis is not well understood but may involve several factors. Vitamin D may reduce erythropoietin levels, leading to decreased red blood cell lysis and bilirubin production. It may also alleviate oxidative stress, preventing bilirubin accumulation from red blood cell damage. Given that both vitamin D and bilirubin undergo metabolism in the liver, their processes may interact. Additionally, vitamin D's role in neurotrophic regulation suggests that its deficiency could be linked to bilirubin encephalopathy in severe neonatal hepatitis.[11]A study by Elfarargy et al. in Egypt reported that the mean TSB levels in neonates receiving both phototherapy and vitamin D decreased from 17.10 ± 2.6 mg/dl to 7.1 ± 1 mg/dl. In contrast, those treated with phototherapy alone experienced a reduction from 17.15 ± 2.5 mg/dl to 8.9 ± 0.7 mg/dl.[12] Due to the dearth of data on the topic, by comparing the outcomes of neonates receiving both vitamin D and phototherapy versus those receiving phototherapy alone, this study aims to determine whether vitamin D can effectively reduce the duration of hyperbilirubinemia, potentially minimizing the need for prolonged phototherapy and reducing the associated complications in our local population.

MATERIALS AND METHODS

We conducted our randomized controlled trial in the nursery unit of CHL, over a six-month period from May 10, 2022, to November 9, 2022 following IRB Clearance vide CPSP/REU/PED-2019-075-5341.One hundred neonates having jaundice neonatorum were included in the study, with fifty in each treatment group. The sample size calculation was based on an anticipated post-treatment mean TSB of 7.1 ± 1 mg/dL for the vitamin D plus phototherapy group and 8.9 ± 0.7 mg/dL for the phototherapy-only group[12], with a statistical power of 80% at a 95% confidence interval. Neonates were eligible if they were admitted on or after 3rd day of birth, had indirect hyperbilirubinemia with TSB levels between 14-20 mg/dL, were born via either cesarean or vaginal delivery, and had a birth weight greater than 2500 grams. Exclusion criteria included prior phototherapy treatment, preterm birth, direct hyperbilirubinemia, hypoxia (SpO2 < 95%), severe respiratory distress or failure, neonatal sepsis and congenital anomalies. Informed consent was obtained from the parents, and demographic data, including gestational age, mode of delivery, ABO and Rh incompatibility, gender, and weight, were recorded. Participants were randomly assigned to two groups using a draw method, where parents selected sealed envelopes marked with either "A" or "B." Neonates in group A received phototherapy combined with vitamin D supplementation (vitamin D, 2 drops i.e., 800 IU daily for 5 days), while those in group B received phototherapy alone for a maximum of 5 days, following hospital protocols. Phototherapy was given to all patients using Blue LED at 30 microW/cm2/nm (wavelength490nm) at a distance of 18 cm from baby. Blood samples were collected before treatment initiation and after 5 days for serum bilirubin level assessment, conducted by a senior pathologist with over five years of experience. Data were systematically collected and documented in a specially designed proforma.

Data Analysis: Statistical analysis program (SPSS version 22) was used to analyze data. Qualitative variables like gender, residential status, mode of delivery etc. were calculated as frequencies and percentages. Mean ±SD were calculated for quantitative variables like gestational age and TSB levels. Post treatment TSB levels in Group A and B were compared using SS independent sample t test. Effect modifiers like gestational age, birth weight, gender, mode of delivery, ABO and RH incompatibility and residential status were controlled by stratification. An independent sample t-test was conducted post-stratification, with a p-value of ≤0.05 considered statistically significant.

RESULTS

Our study comprised of a total of 100 neonates full filling inclusion and exclusion criteria. Among these 100 neonates, 64 (64.0 %) were male patients while 36 (36.0 %) were females (Figure 1). Majority of

participants i.e., 53 (53.0 %) were term i.e., up to 39 weeks. Whereas, 36 (36.0 %) belonged to rural and 64 (64.0 %) were from urban areas. Poor socioeconomic status was documented in 47 (47.0%) while 53 (53.0%) were from middle income family. Mode of delivery was vaginal in 75 (75.0%) while 25 (25 %) were born through cesarean section. ABO incompatibility was noted in 10 (10.0%) and Rh incompatibility was noted in 14 (14 %). (Table 1)

Table 1. Demographic data of participants (n=100)

	Group A		Group B	
	n	%	n	%
Gender				
Male n = 64 (64%)	31	62.0	33	66.0
Female n= 36 (36 %)	19	38.0	17	34.0
Total(n=100)	50	100	50	100
Age groups (In Weeks)				
Up to 38: n= 53 (53.0 %)	26	52.0	27	54.0
More than 38: n= 47 (47.0 %)	24	48.0	23	46.0
Total(n=100)	50	100	50	100
Residential status				
Ruraln = 36 (36.0 %)	17	34.0	19	38.0
Urbann= 64 (64.0 %)	33	66.0	31	62.0
Total(n=100)	50	100	50	100
Socioeconomic status				
Poorn = 47 (47.0 %)	25	50.0	22	44.0
Middle incomen= 53 (53.0 %)	25	50.0	28	56.0
Total(n=100)	50	100	50	100
Mode of delivery				
Vaginaln = 75 (75.0%)	38	76.0	37	74.0
Cesarean sectionn= 25 (25.0 %)	12	24.0	13	26.0
Total	50	100	50	100
ABO incompatibility				
Yesn = 10 (10.0 %)	04	8.0	06	12.0
Non= 90 (90.0 %)	46	92.0	44	88.0
Total(n=100)	50	100	50	100
Rh Incompatibility				
Yesn = 14 (14.0 %)	07	14.0	07	14.0
Non= 86 (86.0 %)	43	86.0	43	86.0
Total(n=100)	50	100	50	100

Mean total serum bilirubin level before treatment was 18.14 ± 2.6 mg/dl in group A while 18.15 ± 2.4 mg/dl in group B which dropped to 6.99 ± 0.457 mg/dl in group A while 8.94± 0.884 mg/dl in group B (p value< 0.001). (Table 2).

Table 2: Distribution of post treatment TSB levels among study case (n=100)

Total Serum bilirubin levels(TSB)(n=100)	Group A		Group B	
	Mean	SD	Mean	SD
Post treatment serum bilirubin levels	6.99	0.457	8.94	0.884
***P value**	< 0.001			

*Independent sample t test

Mean total serum bilirubin levels (Post treatment) in both groups were stratified with regards to gestational age, residential and socioeconomic status, gender mode of delivery, ABO incompatibility and Rh incompatibility (Table 3).

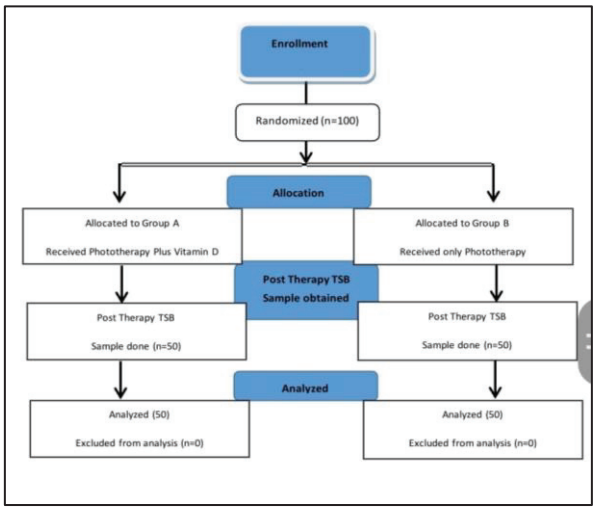
Table 3: Stratification of study variables with regards to post treatment TSB levels in both groups (n = 100)

Variable	Groups	Total serum bilirubin levels		*P – value
		Mean	SD	
Gender				
Male (n=64)	Group A (n=31)	6.98	0.46	0.001
	Group B (n=33)	8.91	0.78	
Female (n=36)	Group A (n=19)	7.01	0.45	0.001
	Group B (n=17)	8.96	0.85	
Gestational age				
Up to 38 weeks (n=53)	Group A (n=26)	6.97	0.47	0.001
	Group B (n=27)	8.93	0.77	
More than 38 weeks	Group A (n=24)	7.02	0.48	0.001
	Group B (n=23)	8.97	0.84	
Residential status				
Rural (n=36)	Group A (n=17)	6.95	0.47	0.001
	Group B (n=19)	8.89	0.86	
Urban (n=64)	Group A (n=33)	7.08	0.49	0.001
	Group B (n=31)	8.99	0.88	
Socioeconomic status				
Poor (n=47)	Group A (n=25)	6.97	0.47	0.001
	Group B (n=22)	8.92	0.79	
Middle Income (n=53)	Group A (n=25)	7.02	0.46	0.001
	Group B (n=28)	8.97	0.86	
Mode of delivery				
Vaginal (n=75)	Group A (n=38)	6.96	0.45	0.001
	Group B (n=37)	8.90	0.79	
Cesarean section (n=25)	Group A (n=12)	6.99	0.40	0.001
	Group B (n=13)	8.98	0.81	
ABO incompatibility				
Yes (n=10)	Group A (n=04)	7.02	0.47	0.001
	Group B (n=06)	8.93	0.79	
No (n=90)	Group A (n=46)	6.98	0.43	0.001
	Group B (n=44)	8.91	0.82	
Rh incompatibility				
Yes (n=14)	Group A (n=07)	7.02	0.47	0.001
	Group B (n=07)	8.96	0.76	
No (n=86)	Group A (n=43)	6.98	0.43	0.001
	Group B (n=43)	8.99	0.84	

*Independent sample t test

The findings indicate that post-treatment total serum bilirubin (TSB) levels were significantly lower in Group A across all stratified variables, including gender, gestational age, residential and socioeconomic status, mode of delivery, and ABO/Rh incompatibility (p = 0.001). This suggests that vitamin D plus phototherapy used in Group A was consistently more effective in reducing bilirubin levels, regardless of these factors as compared to phototherapy alone (Group B).

Figure 1: Consort flow Chart



DISCUSSION

Neonatal jaundice, or hyperbilirubinemia, is a widespread and critical issue affecting newborns worldwide. While phototherapy remains the standard treatment, investigating additional supportive therapies can provide further benefits[13]. Vitamin D may benefit neonatal hyperbilirubinemia by reducing red blood cell breakdown, lowering bilirubin production, and alleviating oxidative stress. Its liver metabolism and neuroprotective role also suggests that it could aid in preventing bilirubin accumulation and encephalopathy, making it a useful adjunct therapy alongside phototherapy[11]. Our study included 100 neonates, of which 64 (64%) were boys and 36 (36%) were girls. The predominance of jaundice in male newborns has also been noted in several other studies. For instance, a study conducted by Gamal ledin et al[14] in Egypt reported that 54.2% of boys had hyperbilirubinemia, which aligns with the findings of our research. A study done in Rawanda, including 210 newborns also found male gender (60.5%) as significant risk factor for neonatal jaundice (p=0.004)[15]. Mean gestational age of our participants was 38.88 ± 1.82 weeks years (minimum age= 37 weeks while maximum age= 41 weeks). Majority of our patients i.e. 53 (53.0 %) were term, aged up to 39 weeks. Similar findings have been reported by Murekatete C et al. [15] where 87.2% of newborns diagnosed as having neonatal jaundice were term.

Out of 100 cases, in 36 (36.0 %) mode of delivery was vaginal in 75 (75.0%) while 25 (25 %) were born through cesarean section. ABO incompatibility was noted in 10 (10.0%) and Rh incompatibility was noted in 14 (14 %). Gamaleldin et al.[14] reported a 74% rate of vaginal deliveries, which is consistent with the findings in our study. Whereas, Murekatete C et al. study had 49.5% neonatal jaundice patients born through SVD and 50.5% through C-section[15].

Mean total serum bilirubin level before treatment was 18.14 ± 2.6 mg/dl in group A while18.15 ± 2.4 mg/dl in group B which dropped to 6.99 ± 0.457 mg/dl in group A while 8.94± 0.884 mg/dl in group B. An Egyptian study carried out by Elfarargy et al. [12] reported mean serum bilirubin levels dropped from 17.10 ± 2.6 mg/dl to 7.1 ± 1 mg/dl in neonates treated with phototherapy and Vitamin D while it dropped from 17.15 ± 2.5 mg/dl to 8.9 ± 0.7 mg/dl in neonates treated with phototherapy only. These findings are similar to our observations. A comparable study conducted by Das G et al. aimed to evaluate the effects of vitamin D supplementation as an adjunct to phototherapy for managing neonatal hyperbilirubinemia. This research took place at a tertiary care hospital of India over 2 years. In that study, 70 newborns with neonatal jaundice were split into two groups: one group received phototherapy along with vitamin D supplementation, while the other group received phototherapy alone. Bilirubin levels were measured and compared at baseline, as well as at 48, 96, and 120 hours between the groups. The p-values at these intervals were 0.077, 0.339, and 0.237, respectively, showing no statistically significant differences between the groups. This study, contrary to our study concluded that vitamin D supplementation did not significantly reduced the bilirubin levels or the duration of phototherapy[13].Moreover our findings indicate that post-treatment TSB levels were significantly lower in Group A (phototherapy plus vitamin D) compared to Group B (Phototherapy alone) across all stratified variables, including gender, gestational age, residential and socioeconomic status, mode of delivery, and ABO/Rh incompatibility (p=0.001). Such stratification was not in previous researches conducted by Elfarargy et al.[12] and Das G et al.[13] and hence add to the strengths of our study. Few limitations of our study include being a single-center study and a relatively small sample size. Moreover, we did not evaluate the total duration of phototherapy required, which could have provided additional insights into the overall efficacy of vitamin D supplementation in the management of neonatal jaundice. Lastly, we did not measure the baseline vitamin D status of the mothers which may have influenced the outcomes. Future research should explore phototherapy duration and vitamin D levels of mothers with larger trials to confirm vitamin D's role in neonatal jaundice management.

CONCLUSION

In our study, vitamin D supplementation in combination with phototherapy resulted in a significantly greater reduction in TSB levels in neonates with jaundice compared to phototherapy alone. These findings suggest that vitamin D may enhance the efficacy of phototherapy in treating neonatal jaundice.

REFERENCES

1. Bizuneh AD, Alemnew B, Getie A, Wondmieneh A, GedefawGJBpo. Determinants of neonatal jaundice among neonates admitted to five referral hospitals in Amhara region, Northern Ethiopia: an unmatched case-control study. 2020;4(1). Doi: 10.1136/bmjpo-2020-000830
2. Huang J, Zhao Q, Li J, Meng J, Li S, Yan W, Wang J, Ren C. Correlation between neonatal hyperbilirubinemia and vitamin D levels: A meta-analysis. PloS One. 2021 May 27;16(5):e0251584. Doi:10.1371/journal.pone.0251584
3. Greco C, Arnolda G, Boo N-Y, et al. Neonatal jaundice in low-and middle-income countries: lessons and future directions from the 2015 Don Ostrow Trieste Yellow Retreat. 2016;110(3):172-180. Doi:10.1159/000445708
4. Anderson CM, Kandasamy Y, Kilcullen M. The efficacy of home phototherapy for physiological and non-physiological neonatal jaundice: A systematic review. Journal of Neonatal Nursing. 2022 Oct 1;28(5):312-26. Doi:10.1016/j.jnn.2021.08.010
5. Anderson NB, Calkins KL. Neonatal indirect hyperbilirubinemia. Neo reviews. 2020 Nov 1;21(11):e749-60.doi:10.1542/neo.21-11-e749
6. Woodgate P, Jardine LAJBce. Neonatal jaundice: phototherapy. 2015;2015. PMID: 25998618; PMCID: PMC4440981.
7. Gidi NW, Siebeck M. Neonatal hyperbilirubinemia treatment by locally made low-cost phototherapy units. Ethiopian Journal of Health Sciences. 2021 Jan 1;31(1). Doi:10.4314/ejhs.v31i1.7
8. Rajesh KC, Kanodia P. Phototherapy induced hypocalcaemia in neonates with jaundice. Journal of Nepalgunj Medical College. 2020;18(2):1-3. Doi:10.3126/jngmc.v18i2.38829
9. Bhat JA, Sheikh SA, Ara R. Correlation of 25-hydroxy vitamin D level with neonatal hyperbilirubinemia in term healthy newborn: A prospective hospital-based observation study. International Journal of Pediatrics and Adolescent Medicine. 2021 Mar 1;8(1):5-9. Doi:10.1016/j.ijpam.2019.10.001
10. Mehrpisheh S, Memarian A, Mahyar A, Valiahdi NS. Correlation between serum vitamin D level and neonatal indirect hyperbilirubinemia. BMC pediatrics. 2018 Dec;18:1-7. Doi:10.1186/s12887-018-1140-9
11. Zhou W, Wang P, Bai Y, Zhang Y, Shu J, Liu Y. Vitamin D metabolic pathway genes polymorphisms and vitamin D levels in association with neonatal hyperbilirubinemia in China: a single-center retrospective cohort study. BMC pediatrics. 2023 May 31;23(1):275. Doi:10.1186/s12887-023-04086-y
12. Elfarargy MS, Ali DA, Al-Ashmawy GMJPR. Study of Vitamin D and melatonin supplementation as adjuvant therapies in neonatal jaundice. Curr. 2019;23:101-105. url=https://api.semanticscholar.org/CorpusID:198306860
13. Das G, Jain A, Gupta V, Shukla D. The Effect of Vitamin D Supplementation as Adjuvant to Phototherapy versus Phototherapy Alone on Neonatal Jaundice: A Randomised Controlled Trial. Journal of Clinical & Diagnostic Research. 2024 Mar 1;18(3).doi:10.7860/JCDR/2024/64646.19181
14. Gamaleldin R, Iskander I, Seoud I, et al. Risk factors for neurotoxicity in newborns with severe neonatal hyperbilirubinemia. 2011;128(4):e925-e931. Doi: 10.1542/peds.2011-0206
15. Murekatete C, Muteteli C, Nsengiyumva R, Chironda G. Neonatal jaundice risk factors at a district hospital in Rwanda. Rwanda journal of medicine and health sciences. 2020 Sep 7;3(2):204-13. Doi:10.4314/rjmhs.v3i2.10

The Authors:

Dr. Zeeshan Afzal
Registrar,
Pediatric Medicine Department
University of Child Health Sciences, Children's Hospital Lahore

Dr. Muhammad Tayyab
Registrar,
Pediatric Medicine Department
University of Child Health Sciences, Children's Hospital Lahore

Dr. Wajiha Rizwan
Associate Professor,
Pediatric Medicine Department
University of Child Health Sciences, Children's Hospital Lahore

Authorship:

ZA: Literature research, Initial draft writing, Data collection, Statistical work

MT: Data collection, Statistical work

WR: Original draft, Critical Revision, Final Approval