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ORIGINAL ARTICLE

Comparison of vitamin D plus phototherapy versus phototherapy alone in the treatment of neonatal jaundice.

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ABSTRACT… Objective: To compare the mean serum total bilirubin levels following the administration of vitamin D plus phototherapy versus phototherapy alone in neonates with jaundice. **Study Design:** Randomized Controlled Trial. **Setting:** Akhtar Saeed Trust Hospital, Lahore. **Period:** November 2023 to April 2024. **Methods:** A total of 60 neonates meeting the inclusion criteria were randomized into two groups. Group A received phototherapy and 1000 IU of vitamin D daily for five days, while Group B received phototherapy alone for up to seven days. Serum bilirubin levels were measured at admission and after treatment. Data were analyzed using SPSS version 20, with an independent sample t-test used to compare groups. Statistical significance was set at $p < 0.05$. **Results:** Baseline bilirubin levels were comparable between groups. Post-treatment, Group A had significantly lower mean bilirubin levels (7.15 ± 0.37 mg/dL) compared to Group B (8.23 ± 0.39 mg/dL, $p < 0.001$). This reduction was consistent across all demographic and clinical variables. **Conclusion:** The addition of vitamin D to phototherapy significantly enhanced bilirubin reduction in neonatal jaundice, supporting its use as an adjuvant therapy to improve treatment outcomes.

Key words: Bilirubin, Neonatal Jaundice, Phototherapy, Randomized Controlled Trial, Vitamin D.

INTRODUCTION

The condition known as neonatal jaundice is one of the most common and potentially fatal conditions that affect newborns. Up to eighty percent of preterm newborns and sixty percent of term infants are affected by jaundice throughout the neonatal period.[1,2]

Numerous factors, including uridine diphosphate glucuronosyltransferase 1A1 (UGT1A1), polymorphism, low birth weight, small for gestational age, neonatal sepsis, haematoma absorption, maternal-fetal ABO blood group incompatibility, metabolic diseases, and liver diseases, are factors that contribute to the development of this disease during the first few days of a baby's life.[3,4]

If it is not treated in a timely manner, it may lead to consequences that are potentially life-threatening and even permanent. These issues include neurological diseases, cerebral palsy, auditory nerve damage, chorea athetoid, and bilirubin encephalopathy. Additionally, it disrupts the emotional contact between the mother and the newborn as well as causes difficulties in nursing.[5,6]

The fat-soluble vitamin known as vitamin D plays a significant role in the body, particularly in the development of teeth and bones in young children and babies.[7] There are two different processes that are responsible for the metabolism of vitamin D and bilirubin; however, during the biosynthesis stage in the liver, these two pathways may interact with one another. The phase of 25-hydroxylation is believed to be a cornerstone step in the production of Vitamin D, which is present in the liver in addition to the phase of bilirubin conjugation.[8]

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Issa et al. (2020) results showed that mean serum bilirubin was significantly declined in neonates of Vitamin D+ Phototherapy group (17.35± 4.6 to 7.9 ± 1.1) compared with neonates of phototherapy alone group (17.45 ± 3.7 to 9.2 ± 1.4) respectively with p-value <0.05 in population of Iraq.[9] While in another similar study, Elfarargy et al. (2019) reported that mean serum bilirubin levels declined from 17.10 ± 2.6 mg/dl to 7.1 ± 1 mg/dl in phototherapy plus vitamin D group whereas it declined from 17.15 ± 2.5 mg/dl to 8.9 ± 0.7 mg/dl in phototherapy alone group in population of Egypt.[10]

Rationale of this study will be to compare the mean bilirubin level following vitamin D plus phototherapy versus phototherapy alone in neonates presenting with neonatal jaundice. The available evidence is limited to only these two studies and there is no other local or international published evidence on the topic. Due to lack of local such published material, the purpose of the current study is to repeat this trial and further confirm the results. If the results of the present study show significantly reduced mean bilirubin level with the addition of vitamin D to standard phototherapy only, it will enable better management of such cases in future practice. The results of this study will identify the magnitude of this problem in local population and will provide local baseline statistical data for future research in this regard.

METHODS

This study aims to compare the mean serum total bilirubin levels following the administration of vitamin D plus phototherapy versus phototherapy alone in neonatal jaundice at a teaching hospital in Punjab. The hypothesis states that there is a difference in the mean serum total bilirubin levels between the two groups.

A randomized controlled trial was conducted in the Department of Paediatric Medicine at Akhtar Saeed Trust Hospital, Lahore, over six months (from November'23 to April'24) after the approval of IRB Committee (Ref No: M-23/ 101 / -Paeds, Date: 18-01-2023) and CPSP. The sample size comprised 60 neonates, divided into two groups of 30 each, and calculated with 80% power of the test and a 95% confidence interval. The expected post-treatment mean serum bilirubin levels were 7.9 ± 1.1 in the Vitamin D plus phototherapy group and 9.2 ± 1.4 in the phototherapy-alone group. A non-probability consecutive sampling technique was used. Written informed consent from parents or legal guardians was required.

Inclusion Criteria

Full-term neonates of both genders, aged more than seven days, with a birth weight greater than 2500 g, and born via caesarean section or normal vaginal delivery were included if they had neonatal jaundice as per the operational definition.

Exclusion Criteria

Newborns with jaundice within the first 24 hours of life, infants of diabetic mothers, neonates with an Apgar score <7 at birth, sepsis, hypocalcaemia, preterm birth, conjugated hyperbilirubinemia, neonatal hypoxia, respiratory distress, or congenital anomalies were excluded.

Following ethical approval, 60 eligible neonates were recruited from the paediatric outpatient department, and informed consent along with detailed histories were obtained. The neonates were randomly assigned to two groups using the lottery method. Group A received phototherapy combined with 10 drops of vitamin D (1000 IU) daily for five days. Group B received only phototherapy for a maximum of seven days, targeting the requisite bilirubin levels as per departmental guidelines. Venous blood samples were collected under aseptic conditions to measure serum bilirubin levels at admission and post-treatment, with all samples analyzed in the hospital's pathology laboratory. Phototherapy was administered as per the operational definition, and neonatal jaundice was diagnosed based on established criteria. All procedures and measurements were standardized, with a single resident conducting sampling and all bilirubin measurements performed by the same medical laboratory to reduce bias. Serum bilirubin levels were reassessed after seven days. Confounding factors were minimized by excluding ineligible neonates.

Data were entered and analyzed using SPSS version 26. Numerical variables, such as age and weight, were reported as mean ± standard deviation (SD). The mean total serum bilirubin levels between the two groups were compared using an independent sample t-test, with statistical significance set at $p < 0.05$. Categorical variables, including gender, residence, and method of delivery, were reported as frequencies and percentages. Data were stratified by age, gender, weight, method of delivery, and residence to account for potential confounding factors, followed by post-stratification analysis using an independent sample t-test, with $p < 0.05$ considered statistically significant.

RESULTS

Group A includes 30 neonates receiving both phototherapy and Vitamin D, and Group B consists of 30 neonates receiving only phototherapy. The majority of neonates in both groups are 15 days old or younger, with Group A having 25 neonates (83.3%) and Group B having 26 neonates (86.7%) in this age category. Only 5 neonates (16.7%) in Group A and 4 neonates (13.3%) in Group B fall within the 16-28 day age range. The mean age of neonates in Group A is 10.00 ± 4.90 days, while in Group B, it is slightly higher at 10.63 ± 6.02 days. In Group A, 19 neonates (63.3%) are male, while 11 (36.7%) are female. Conversely, Group B has a higher percentage of female neonates, with 21 (70%) being female and only 9 (30%) being male.

In this study, the majority of neonates in both groups were born between 37 and 40 weeks of gestation, with 25 neonates (83.3%) in Group A and 27 neonates (90%) in Group B. A smaller number of neonates in both groups were born between 41 and 42 weeks, with 5 neonates (16.7%) in Group A and 3 neonates (10%) in Group B. The mean gestational age of neonates in Group A is 39.20 ± 1.43 weeks, slightly higher than Group B at 38.73 ± 1.23 weeks.

In Group A, 12 neonates (40%) weigh up to 3000 grams, while the remaining 18 neonates (60%) weigh over 3000 grams. In Group B, a slightly higher proportion of neonates (73.3%) weigh more than 3000 grams, while 8 neonates (26.7%) weigh up to 3000 grams. The mean weight of neonates in Group A is 3113.33 ± 177.66 grams, while in Group B, it is 3100.00 ± 129.99 grams.

In Group A, 14 neonates (46.7%) were delivered via cesarean section (C-section), while 16 neonates (53.3%) were delivered vaginally. In contrast, a higher percentage of neonates in Group B were delivered via C-section, with 21 neonates (70%) compared to 9 neonates (30%) delivered vaginally. In Group A, 8 neonates (26.7%) are from rural areas, while the majority, 22 neonates (73.3%), are from urban areas. Group B shows the opposite trend, with 21 neonates (70%) from rural areas and only 9 neonates (30%) from urban areas. This indicates a disparity in the geographical distribution of the participants in the two groups.

Bilirubin levels at baseline and after treatment between the two groups were compared. At baseline, there is no significant difference in bilirubin levels between Group A (Mean = 17.37, SD = 0.12) and Group B (Mean = 17.39, SD = 0.08) with a p-value of 0.337. However, after treatment, there is a significant difference in bilirubin levels, with Group A showing lower bilirubin levels (Mean = 7.15, SD = 0.37) compared to Group B (Mean = 8.23, SD = 0.39) with a highly significant p-value of 0.000.

Table-I compares bilirubin levels at baseline and after treatment in neonates receiving phototherapy with Vitamin D (Group A) versus phototherapy alone (Group B) across various demographic and clinical variables. Baseline bilirubin levels were similar between groups ($p > 0.05$). However, after treatment, Group A consistently showed significantly lower bilirubin levels than Group B across all subgroups, including age, gender, weight, mode of delivery, and residential status ($p \leq 0.013$ for all comparisons). These findings suggest that adding Vitamin D to phototherapy enhances bilirubin reduction in neonates.

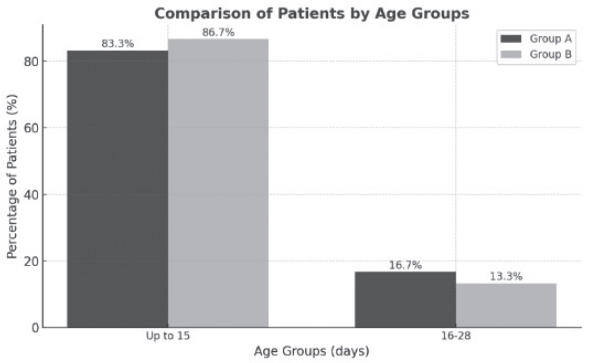

Figure-1. Age distribution (n=60)

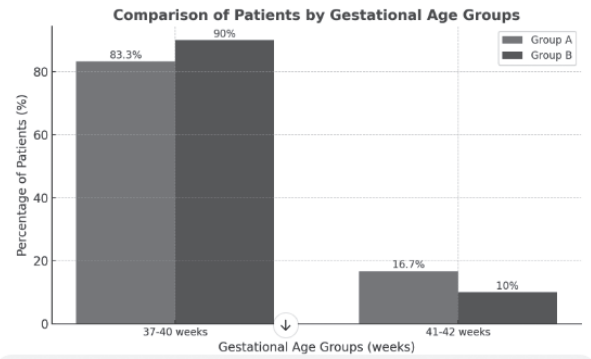

Figure-2. Showing the details of the Gestational age of neonates enrolled in the study (n=60)

DISCUSSION

The present study investigates the comparative efficacy of vitamin D supplementation alongside phototherapy versus phototherapy alone in the management of neonatal jaundice, similar to previous studies exploring adjuvant therapies for pathological neonatal jaundice. Neonatal jaundice, particularly indirect hyperbilirubinemia, is a common condition in newborns and, if left untreated, can lead to severe complications such as bilirubin encephalopathy or kernicterus, resulting in cerebral palsy, mental retardation, deafness, or permanent brain damage.[11]

Our study's findings align with the previous research showing that combining vitamin D with phototherapy significantly reduces serum bilirubin levels compared to phototherapy alone. As seen in our stud, the baseline bilirubin levels in both Group A (phototherapy with vitamin D) and Group B (phototherapy alone) were nearly identical. However, after treatment, Group A showed a significantly greater reduction in bilirubin levels (Mean = 7.15, SD = 0.37) compared to Group B (Mean = 8.23, SD = 0.39), with a p-value of 0.000.

Variables		Bilirubin Levels	Group-A(n=30)		Group-B(n=30)		P-Value
			Mean	SD	Mean	SD	
Age(days)	Upto 15	At Baseline	17.36	0.122	17.38	0.08	0.414
		After treatment	7.12	0.37	8.27	0.40	0.000
	16-28	At Baseline	17.42	0.13	17.48	0.02	0.416
		After treatment	7.30	0.41	8.00	0.12	0.013
Gender	Male	At Baseline	17.36	0.11	17.38	0.10	0.677
		After treatment	7.22	0.39	8.23	0.33	0.000
	Female	At Baseline	17.37	0.15	17.40	0.08	0.502
		After treatment	7.02	0.32	8.23	0.42	0.000
Weight	Upto 3000 grams	At Baseline	17.34	0.13	17.39	0.08	0.30
		After treatment	7.32	0.37	8.15	0.43	0.000
	>3000 grams	At Baseline	17.39	0.12	17.39	0.09	0.821
		After treatment	7.04	0.34	8.26	0.37	0.000
Mode of delivery	Vaginal delivery	At Baseline	17.36	0.15	17.40	0.06	0.224
		After treatment	7.21	0.44	8.19	0.35	0.000
	C. Section	At Baseline	17.38	0.10	17.37	0.11	0.89
		After treatment	7.10	0.31	8.34	0.48	0.000
Residential status	Rural	At Baseline	17.39	0.09	17.42	0.06	0.466
		After treatment	7.14	0.38	8.19	0.38	0.000
	Urban	At Baseline	17.36	0.13	17.34	0.10	0.730
		After treatment	7.15	0.38	8.33	0.41	0.000

Table-I. Comparison of bilirubin levels in both groups (n=60)

This supports the hypothesis that vitamin D plays a crucial role in improving bilirubin metabolism, as indicated in previous studies.[12]

Additionally, in agreement with studies suggesting a strong correlation between vitamin D deficiency and neonatal jaundice, our data revealed that neonates treated with vitamin D had lower post-treatment bilirubin levels compared to those receiving phototherapy alone. This may indicate that vitamin D aids in reducing serum bilirubin levels, likely through its role in liver metabolism. As the liver is essential for both the hydroxylation of vitamin D and bilirubin metabolism, vitamin D supplementation may facilitate the liver's ability to conjugate and excrete bilirubin.[13,14]

Our findings also align with research that identified the importance of vitamin D in liver function. Vitamin D is hydroxylated in the liver, converting cholecalciferol into calcifediol (25-hydroxycholecalciferol), and the liver also plays a central role in synthesizing and conjugating bilirubin. The significant reduction in serum bilirubin levels observed in Group A compared to Group B may suggest that adequate vitamin D levels support the liver's ability to metabolize bilirubin efficiently.[15]

Interestingly, while our findings highlight the positive impact of vitamin D on bilirubin reduction, a few studies have reported conflicting results, stating no association between serum vitamin D levels and neonatal jaundice.[16] These disparities underscore the need for further investigation into the exact mechanisms by which vitamin D influences bilirubin metabolism.

Furthermore, melatonin's role in enhancing liver function and protecting against oxidative stress was evaluated previously, and while our study did not include melatonin, its potential as an adjuvant therapy remains of interest.[17] Melatonin is known to improve hepatic microcirculation and promote adequate liver function, including bilirubin metabolism, by conjugating indirect bilirubin to direct bilirubin. Although our study focused on vitamin D, the antioxidant properties of melatonin might offer another avenue for enhancing the efficacy of phototherapy in the treatment of neonatal jaundice.

Finally, the protective effect of vitamin D in liver function could parallel the antioxidant benefits attributed to melatonin, as both act through mechanisms that support the liver's ability to metabolize bilirubin. This dual impact on liver metabolism, as described in the literature, emphasizes the importance of exploring multiple adjuvant therapies to optimize treatment outcomes for neonatal jaundice.[18,19]

In summary, our study provides further evidence of vitamin D's role in enhancing the efficacy of phototherapy in treating neonatal jaundice. The significant reduction in serum bilirubin levels in the group receiving both vitamin D and phototherapy aligns with prior research, reinforcing the potential of vitamin D as a beneficial adjuvant therapy. Future studies may consider including other agents such as melatonin to explore synergistic effects and improve treatment outcomes.[20,21]

CONCLUSION

In conclusion, the addition of vitamin D to phototherapy significantly enhances the reduction of serum total bilirubin levels in neonates with jaundice compared to phototherapy alone. This study highlights the potential role of vitamin D as a beneficial adjuvant therapy, likely due to its influence on bilirubin metabolism in the liver. Incorporating vitamin D into the management of neonatal jaundice could improve treatment outcomes, reduce the duration of hyperbilirubinemia, and minimize the risk of complications. These findings provide a foundation for further research to establish vitamin D supplementation as a standard adjunct to phototherapy in clinical practice.

RECOMMENDATIONS

Based on the findings, it is recommended that vitamin D supplementation (1000 IU daily) be considered as an adjunct therapy to phototherapy in the management of neonatal jaundice, given its significant role in reducing bilirubin levels. Routine screening for vitamin D deficiency in neonates with jaundice should also be implemented,

as supplementation may enhance bilirubin metabolism and improve outcomes. Pediatric guidelines should integrate vitamin D alongside phototherapy as a standard practice, especially in regions with a high prevalence of vitamin D deficiency. Further research through larger, multicenter trials is necessary to confirm these findings, determine optimal dosing and duration, and evaluate long-term outcomes. Healthcare professionals managing neonatal jaundice should be trained on the potential benefits of vitamin D as an adjuvant to phototherapy, ensuring its effective implementation in clinical practice. Additionally, studies focusing on the cost-effectiveness of this combined approach are recommended to support its widespread adoption. Finally, long-term follow-up studies should assess the sustained impact of vitamin D supplementation on neonatal health and its potential to prevent recurrent jaundice or related complications.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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2	**Muhammad Usman Ajmal:** Data collection, paper writing.
3	**Kinza Fatima:** Discussion writing, review manuscript.
4	**Nida Aslam:** Review of manuscript.
5	**Agha Shabbir Ali:** Data entry, literature review.
6	**Rashid Zia:** Data entry, Literature review.
7	**Muhammad Ahsan:** Data analysis.