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Original Article

Paediatrics Section

The Effect of Vitamin D Supplementation as Adjuvant to Phototherapy versus Phototherapy Alone on Neonatal Jaundice: A Randomised Controlled Trial

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ABSTRACT

Introduction: Neonatal jaundice, or neonatal hyperbilirubinaemia, is a common and significant concern among newborns globally. Given that phototherapy is the primary treatment for neonatal jaundice, exploring alternative adjunctive treatments is beneficial.

Aim: To observe the impact of vitamin D supplementation as an adjuvant therapy alongside phototherapy in managing neonatal jaundice.

Materials and Methods: A hospital-based double-blinded randomised controlled trial was conducted at the Special Newborn Care Unit (SNCU) in Department of Paediatrics, G.R. Medical College, Gwalior, Madhya Pradesh, a tertiary care neonatal centre in North India, over a two-year period (April 2020 to March 2022). The study included 70 newborns with neonatal jaundice, divided into two groups: one receiving phototherapy and vitamin D (Group 1), and the other receiving phototherapy alone (Group 2). The average levels of bilirubin were compared at baseline, 48 hours, 96 hours, and 120 hours in the two groups. Statistical analysis was performed using Statistical Package for Social Sciences (SPSS) 22.0, calculating frequency, percentage, mean, Standard Deviation (SD), and applying the independent t-test for comparison. A p-value less than 0.05 was considered statistically significant.

Results: The mean total serum bilirubin at admission in Group 1 was 18.58±1.76 mg/dL, and in Group 2 was 17.77±2.01 mg/dL, with a p-value of 0.077. At 48 hours, the levels in Group 1 were 15.11±1.99 mg/dL, and in Group 2 were 14.69±1.53 mg/dL, with a p-value of 0.339. At 96 hours, the levels in Group 1 were 14.75±5.62 mg/dL, and in Group 2 were 13.16±1.49 mg/dL, with a p-value of 0.237. At 120 hours, the levels in Group 1 were 8.90±4.66 mg/dL, and no patients were observed in Group 2. The study found that vitamin D as an adjuvant to phototherapy did not significantly impact the rate of decline of serum bilirubin, and the duration of phototherapy was not affected significantly.

Conclusion: The study concludes that vitamin D, as an adjuvant to phototherapy, does not significantly affect the rate of decline of serum bilirubin, and it does not alter the duration of phototherapy when comparing both groups.

Keywords: Full-term, Hyperbilirubinaemia, Neonates

INTRODUCTION

Neonatal hyperbilirubinaemia is a prevalent condition worldwide and is considered one of the most critical issues in neonates, particularly when levels of indirect bilirubin increase to a point where they could cross the blood-brain barrier, leading to bilirubin encephalopathy or kernicterus if not promptly treated [1]. Pathological jaundice can be influenced by various factors such as gestational age, birth weight, premature rupture of membranes, maternal infection, and other conditions during pregnancy [2]. Vitamin D activation occurs through 25-hydroxylation in hepatocytes followed by 1-hydroxylation in the kidneys. Despite vitamin D being synthesised in the liver, it also plays a role in metabolising indirect bilirubin to direct bilirubin. The metabolisms of vitamin D and bilirubin occur in two distinct pathways, but they may influence each other during the biosynthesis stage in the liver [3].

Although, the present study was conducted at a tertiary care centre, the results can provide valuable insights for primary healthcare physicians regarding the role of vitamin D in treating neonatal jaundice. Exploring any treatment modality that could reduce the need for phototherapy, shorten hospital stays, and decrease serum bilirubin levels is essential. Thus, the present study was designed to assess the additional role of vitamin D alongside phototherapy for the treatment of neonatal jaundice. The objective of the study was to evaluate the role of vitamin D supplementation as adjuvant therapy with phototherapy in managing neonatal jaundice.

The present study was conducted with the null hypothesis that vitamin D supplementation as adjuvant therapy with phototherapy has no effect on the management of neonatal jaundice. As an alternative hypothesis, it was hypothesised that vitamin D supplementation as adjuvant therapy with phototherapy is more effective in managing neonatal jaundice.

MATERIALS AND METHODS

This hospital-based double-blinded randomised controlled trial was conducted at the SNCU Department of Paediatrics, G.R. Medical College, Gwalior, Madhya Pradesh, India, over a two-year period (April 2020 to March 2022), following ethical clearance from the institutional ethical committee (IEC number: 488/IEC-GRMC/2019).

Sample size calculation: The study involved a total of 70 newborns, with the sample size calculated using the formula [4]:

$$n=\left(\frac{r+1}{r}\right)*(s^2)*\left(\frac{\left(Z_{\frac{\alpha}{2}}+Z_{1-\beta}\right)^2}{(d^2)}\right)$$

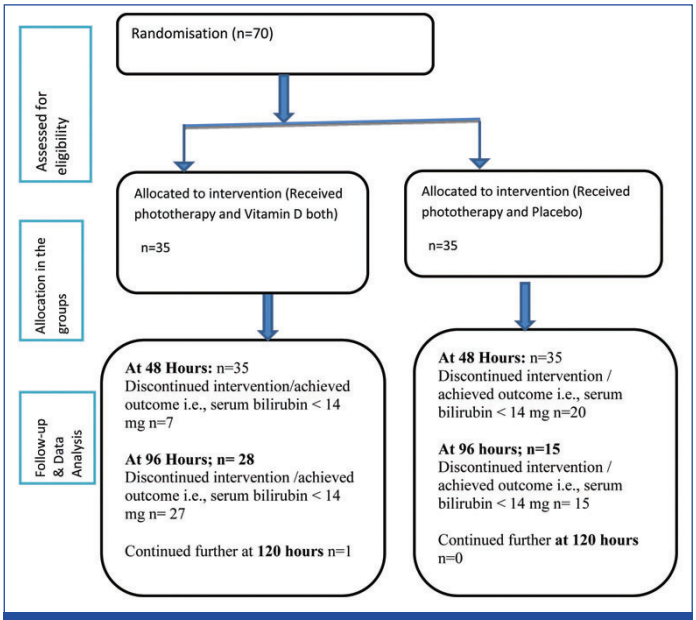
at a 5% level of significance and 80% power of the test, assuming a 1.8 effect size with a standard deviation of 2.6 in the vitamin D group and a standard deviation of 2.7 in the control group based on the pilot study.

The obtained sample size was 34 in each group, approximated to 35 in each group, i.e., Group 1 (allocated to intervention-received phototherapy and vitamin D) and Group 2 (allocated to intervention-received phototherapy and placebo). The total number of children included in the present study was 70, selected using purposive sampling technique.

Inclusion and Exclusion criteria: Full-term neonates (>37 weeks) admitted to SNCU with neonatal jaundice and total serum bilirubin levels ranging from 14-20 mg/dL were included in the study. Exclusion criteria comprised preterm neonates, conjugated hyperbilirubinaemia, sepsis, neonatal asphyxia, respiratory distress, major congenital anomalies, liver or kidney disease in the neonates or their mothers, bilirubin encephalopathy, hyperbilirubinaemia requiring exchange transfusion, and subjects residing more than 10 km from the hospital, those newborns who received vitamin D supplementation prior to admission, and newborns with haemolytic disorders.

Study Procedure

After inclusion, the study subjects were randomised into two groups using a simple randomisation method. The intervention group received vitamin D and phototherapy, while the comparative group received phototherapy and a placebo. Randomisation was performed by the principal investigator using computer-generated opaque sealed envelopes with random numbers. The intervention was administered using opaque vials of vitamin D and placebo prepared by a third person, with only the statistician aware of the coding [Table/Fig-1].



[Table/Fig-1]: Study flow chart.

Informed written consent was obtained from the parents of the neonates. Venous blood samples were collected from each neonate for bilirubin estimation using standard aseptic precautions. The bilirubin estimation was conducted in the Biochemistry Department of GR Medical College, Gwalior (MP) using a BA 400, fully automated Biosystem company machine based on the principle of photometry.

Phototherapy was administered using the Seefar Nice 4000 Spot Light-emitting Diode (LED) phototherapy machine, a microprocessor-controlled system with 24 Hi Bright Blue LED lamps and 3 white LED lamps. The irradiance level was maintained at 30 micro watt/cm^2/nm at a distance as close as possible. During the phototherapy process, there was no exposure of infrared rays and ultraviolet rays to the neonates. Infants under phototherapy lights were kept naked except for eye patches and genital covering, and they were turned every two hours. The infant's temperature was monitored at six-hour intervals.

Baseline parameters such as body weight, head circumference, and gestational age were recorded after enrollment. Newborns received phototherapy as per the standard unit protocol, along with vitamin D3 drops (400 IU) once daily orally in the intervention group, while the comparative group received phototherapy and a placebo. Treatment, investigations, and basic care were consistent across both groups. Newborns were evaluated with baseline serum bilirubin and compared for both groups at baseline, 48 hours, 96 hours, and 120 hours.

In both groups, phototherapy was discontinued once the serum bilirubin level declined to <14 mg. After discharge, vitamin D was continued for both groups as per the unit policy.

STATISTICAL ANALYSIS

Data were entered in Microsoft excel software and analysis were performed on SPSS 22.0 version. For comparison of two groups, independent t-test was applied. The p-value was calculated and statistical significance was set at 5% level.

RESULTS

The study included a total of 70 newborns, with 35 newborns in each group. The mean age in Group 1 was 3.89±1.41 days, while the mean age in Group 2 was 3.89±1.13 days (p=1.00), indicating that the mean age of newborns was matched in both groups. The mean birth weight in Group 1 was 2.62±0.39 kg, and in Group 2, it was 2.41±0.28 kg, with a statistically significant p-value (p<0.015). The mean gestational age in Group 1 was 38.11±1.28 weeks, and in Group 2, it was 37.63±0.84 weeks (p<0.06). The mean head circumference in Group 1 was 33.71±1.65 cm, and in Group 2, it was 32.93±1.47 cm, with a p-value of 0.04. The mean haemoglobin of Group 1 was 14.47±1.44 g/dL, and in Group 2, it was 15.05±1.54 g/dL, with a p-value of 0.11. The mean reticulocyte count of Group 1 was 4.86±0.8%, and in Group 2, it was 4.91±1.12%, with a p-value of 0.83 [Table/Fig-2].

Variables	Group 1 (mean±SD)	Group 2 (mean±SD)	p-value
Age (days)	3.89±1.41	3.89±1.13	1.00
Birth weight (kg)	2.62±0.39	2.41±0.28	0.015*
Gestational age (weeks)	38.11±1.28	37.63±0.84	0.06
Head circumference (cm)	33.71±1.65	32.93±1.47	0.04*
Haemoglobin (g/dL)	14.47±1.44	15.05±1.54	0.11
Reticulocyte count (%)	4.86±0.8	4.91±1.12	0.83

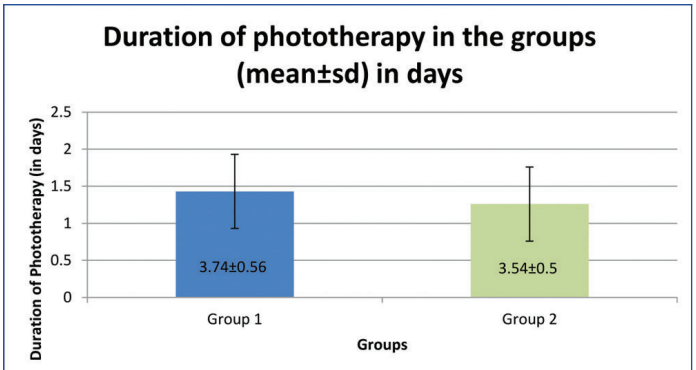
[Table/Fig-2]: Baseline characteristics of study subjects.
Independent t-test was applied; *p-value was significant at 5% level of significance

The mean total serum bilirubin at admission in Group 1 was 18.58±1.76 mg/dL, and in Group 2, it was 17.77±2.01 mg/dL, with a p-value of 0.077. At 48 hours, the mean total serum bilirubin in Group 1 was 15.11±1.99 mg/dL, and in Group 2, it was 14.69±1.53 mg/dL, with a p-value of 0.339. At 96 hours, the mean total serum bilirubin in Group 1 was 14.75±5.62 mg/dL, and in Group 2, it was 13.16±1.49 mg/dL, with a p-value of 0.223. At 120 hours, the mean total serum bilirubin in Group 1 was 8.90±4.66 mg/dL, and all Group 2 patients were discharged within three days [Table/Fig-3].

Total bilirubin (mg/dL)	Group 1 (mean±SD)	Group 2 (mean±SD)	t-value	p-value
At admission	18.58±1.76	17.77±2.01	1.739	0.077
At 48 hours	15.11±1.99	14.69±1.53	0.936	0.339
At 96 hours	14.75±5.62	13.16±1.49	1.199	0.237
At 120 hours	8.90±4.66	-	-	-

[Table/Fig-3]: Outcome: Mean serum bilirubin in both groups.
Independent t-test was applied; *p-value was significant at 5% level of significance

The mean duration of phototherapy in Group 1 was 3.74±0.56 days, and in Group 2, it was 3.54±0.50 days (p-value=0.122), which was not statistically significant [Table/Fig-4].



[Table/Fig-4]: Duration of phototherapy (in days) in both the groups.

DISCUSSION

Adding vitamin D to a pregnant women's diets is associated with a decrease in neonatal hyperbilirubinaemia [5,6]. Thus, the present study was framed to assess the additional role of vitamin D supplementation for the treatment of neonatal jaundice. The present study reported that there was no significant difference in Group 1 (phototherapy with adjuvant vitamin D) and Group 2 (phototherapy and placebo) in treatment of neonatal jaundice. Duration of phototherapy was found to be same in both the groups. Also, the baseline parameters of birth weight and head circumference showed significant difference; though these parameters may not overall affect the outcome.

Similar to current study results, the study conducted by Mehrpisheh S reported that the mean serum 25-hydroxyvitamin D levels were 10.76±8.6 ng/dL in the case group and 14.88±11.38 ng/dL in the control group. There were no significant differences between the two groups (p=0.11) [7]. Bhat JA et al., conducted a study on 100 newborns, who were divided into two groups (50 in each group) on the basis of their serum bilirubin level on the 5th day of life [8]. Newborns having serum bilirubin levels in the physiological range were included in the control group, and newborns having serum bilirubin levels out of the physiological range and who needed treatment were included in the case group. It was observed that the mean vitamin D level of newborn was in the normal range in controls but significantly decrease in cases and the difference were statistically significant.

Mutlu M et al., suggested that low level of serum vitamin D may be associated with hyperbilirubinaemia in full term neonates and noted a significant negative correlation between serum vitamin D and serum parathyroid hormone level among neonates [9]. Similarly another trial conducted by Abed NT et al., found that decreased levels of vitamin D significantly correlated with neonatal indirect hyperbilirubinaemia, therefore low vitamin D can be considered as risk factor for neonatal jaundice [10]. Another study done by Elfarangy MS et al., found that low serum levels of vitamins C, D and E were present in neonatal jaundice group indicating that neonatal jaundice is accompanied by decrease in the serum levels of these vitamins attracting the attention of researchers to study the effect of the vitamin supplementation as an adjuvant therapy in neonatal jaundice [3].

Huang J et al., also found that vitamin D levels were lower in neonates with hyperbilirubinaemia as compared to term neonates without hyperbilirubinaemia [5]. So this can possibly suggest that neonates with lower serum vitamin D levels are at higher risk of developing hyperbilirubinaemia. Interestingly, a trial by Shahriarpanah S et al., found that the mean serum vitamin D levels significantly increased after phototherapy [11]. They also found that serum calcium and magnesium significantly decrease after phototherapy, so the present study showed that phototherapy could decrease levels of calcium and magnesium and increase the level of vitamin D.

Another trial by Aletayeb SMH et al., compared serum vitamin D levels of healthy term jaundiced and non jaundiced newborns and their mothers. They showed significant differences in the serum vitamin D levels of term jaundiced newborns, despite a non significant difference in the vitamin D levels of their mothers. They found a negative correlation between vitamin D levels and serum Alkaline Phosphatase (ALP) and Parathyroid Hormone (PTH) [12]. Maternal vitamin D levels have also been found to be associated with neonatal jaundice.

In a previous study conducted by Jaiswal BP et al., it was found that the presence of maternal vitamin D deficiency could effectively predict the increased risk of neonatal jaundice [13]. Vitamin D deficiency is common in pregnant women, so vitamin D supplementation can be given for preventing maternal hypovitaminosis D and subsequent neonatal jaundice.

El Rifai NM et al., found that maternal vitamin D levels strongly correlate with neonatal levels [14]. They revealed that 68.9% of mothers and 92.4% of their neonates had vitamin D deficiency or insufficiency. They also revealed a strong correlation between neonatal vitamin D and calcium levels.

Rashwan NI et al., found that without vitamin D3 supplementation, neonates with low vitamin D and physiological jaundice who received phototherapy showed considerable improvement in vitamin D levels five days later [15]. They found significantly low vitamin D3 levels in full-term neonates with physiological hyperbilirubinaemia; however, whether this is an association or a pathogenic mechanism would require further investigation.

Zahrah MAAI et al., concluded that vitamin D and melatonin could be used as adjuvant treatment in neonatal jaundice in combination with phototherapy, with the superiority of vitamin D over melatonin [16]. In the present study, it was found that in Group 1, the mean duration of phototherapy was 3.74±0.56 days and in Group 2 was 3.54±0.50, although this difference was not statistically significant.

Similar to the study results, a prior study conducted by Mehrpisheh S et al., reported that the mean and standard deviation of serum 25-hydroxy vitamin D level were 10.76±8.6 ng/dL in the case group {term infant with Neonatal Indirect Hyperbilirubinemia (NIH)} and 14.88±11.38 ng/dL in the control group (non icteric term infant) [7]. Results suggested that there was a lack of relationship between vitamin D level and NIH.

In the study by Gilles DR et al., it was shown that there was no significant increase in plasma 25-hydroxy vitamin D3 after 48 hours of phototherapy. It was concluded that such treatment does not stimulate the biosynthesis of vitamin D [17].

It is known that vitamin D deficiency may increase the occurrence of neonatal jaundice. The present study's results showed that there is no significant role of vitamin D in neonatal jaundice in terms of the duration of phototherapy and the fall of serum bilirubin, thus accepting the null hypothesis.

Limitation(s)

The present study was conducted at a tertiary care centre and has limitations for generalisability. The mothers of the infants were not assessed for the vitamin D level, which may affect the outcome of the neonates. A multicentric study on a larger sample needs to be conducted in the future to confirm the present study findings.

CONCLUSION(S)

In the present study, vitamin D, along with phototherapy in the treatment of neonatal jaundice, did not have any role in the fall of serum bilirubin or the duration of phototherapy. However, previous studies show the association of vitamin D and neonatal jaundice, which may be due to region-specific, race, ethnicity related to vitamin D. Large multicentric trials are needed to confirm the role of vitamin D in the treatment of neonatal hyperbilirubinaemia along with phototherapy.

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