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Original Research Article

Effect of Phototherapy on Serum Vitamin D and Calcium Levels in Term Neonates with Hyperbilirubinemia: A Prospective Analytical Study from a Tertiary Care Hospital in Eastern India

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Abstract

Background: Neonatal hyperbilirubinaemia is one of the most frequent morbidities of the first week of life, occurring in approximately 60% of term and 80% of preterm infants. Phototherapy is the first-line treatment, but it is increasingly recognised to perturb mineral and vitamin D homeostasis. Hypocalcaemia and disturbances in 25-hydroxy-cholecalciferol [25(OH)D] levels are potentially preventable complications that remain under-investigated in the Indian subcontinent.

Objectives: To determine the effect of phototherapy on serum total calcium and 25-hydroxy-cholecalciferol concentrations in term neonates receiving phototherapy for unconjugated hyperbilirubinaemia at a tertiary care hospital, and to identify clinical correlates of post-phototherapy mineral changes.

Materials and Methods: This prospective analytical study was conducted in the Special Newborn Care Unit (SNCU), Department of Paediatrics, R. G. Kar Medical College and Hospital, Kolkata, over 18 months. A total of 150 term neonates weighing ≥2500 g and on exclusive breastfeeding who required phototherapy for unconjugated hyperbilirubinaemia were enrolled. Total serum bilirubin, total serum calcium and 25-hydroxy-cholecalciferol were measured before initiation of phototherapy and after 48 hours of continuous phototherapy. Hypocalcaemia was defined as total serum calcium <8 mg/dL and vitamin D deficiency as 25(OH)D <20 ng/dL. Data were analysed with SPSS v16.0 using paired t-test, Mann-Whitney U test, McNemar's test and Pearson correlation; p<0.05 was considered significant.

Results: The mean age of neonates was 4.17 ± 1.28 days; 60% were male; mean birth weight was 2.98 ± 0.27 kg; mean gestational age was 38.77 ± 0.76 weeks. Mean total serum bilirubin decreased significantly from 14.35 ± 2.04 mg/dL to 11.47 ± 1.74 mg/dL (mean change 2.88 ± 2.33 mg/dL; p=0.0001). Mean total serum calcium declined from 11.05 ± 1.62 mg/dL to 8.96 ± 1.05 mg/dL (mean change 2.09 ± 1.63 mg/dL; p=0.0001), and mean 25(OH)D fell from 36.64 ± 6.54 ng/dL to 14.06 ± 5.28 ng/dL (mean change 22.58 ± 6.02 ng/dL; p=0.0001). The incidence of hypocalcaemia rose from 0.7% to 8.7% (p=0.002) and that of vitamin D deficiency rose from 2.7% to 90.7% (p=0.0001). The mean fall in calcium was significantly greater in male neonates (2.35 ± 1.55 mg/dL) than in females (1.69 ± 1.68 mg/dL; p=0.01), and birth weight correlated positively with the magnitude of calcium decline (r=0.27, p=0.001).

Conclusion: Phototherapy administered for 48 hours to term neonates with unconjugated hyperbilirubinaemia produces a statistically significant fall in both serum calcium and 25-hydroxy-cholecalciferol concentrations and substantially increases the incidence of biochemical hypocalcaemia and vitamin D deficiency. Routine monitoring of serum calcium and vitamin D should be considered in neonates undergoing prolonged phototherapy, with prophylactic calcium and vitamin D supplementation in those receiving phototherapy beyond 48 hours.

Keywords: Phototherapy; Neonatal hyperbilirubinaemia; Hypocalcaemia; Vitamin D deficiency; 25-hydroxycholecalciferol; Term neonate.

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Introduction

Neonatal jaundice, the clinical manifestation of unconjugated hyperbilirubinaemia, is observed in approximately 60% of term and 80% of preterm infants during the first week of life, and around 5–10% of these neonates have bilirubin levels high enough to require active treatment [1,2]. Unconjugated bilirubin is lipophilic and can cross the immature neonatal blood-brain barrier;

sustained, elevated concentrations may produce acute bilirubin encephalopathy and the chronic neurologic sequelae collectively known as kernicterus [3]. The principal therapeutic goal in clinical practice is therefore to keep bilirubin below the threshold for neurotoxicity [4].

Phototherapy, introduced by Cremer in 1958 and now the cornerstone of treatment for neonatal indirect hyperbilirubinaemia, converts non-polar Z,Z-bilirubin in the skin into more water-soluble photoisomers (Z,E- and E,Z-bilirubin) and structural isomers (lumirubin) that are excreted in bile and urine without the need for hepatic conjugation [5,6]. Although the technique is simple, non-invasive and effective, it is not free of complications: rash, dehydration, hyperthermia, retinal injury, bronze-baby syndrome, transient lactose intolerance, DNA strand breaks and disturbances of mother–infant bonding have all been reported [7–10].

Among the less-recognised but clinically important effects of phototherapy is a fall in serum calcium concentration. The proposed mechanism involves transcranial illumination of the pineal gland, with consequent suppression of melatonin secretion; reduced melatonin removes its inhibitory action on cortisol, the rise in cortisol increases urinary calcium excretion and shifts calcium uptake into bone, and the resulting net loss from the extracellular compartment manifests as hypocalcaemia [11,12]. Hypocalcaemia is not benign — ionised calcium is essential for coagulation, neuromuscular excitability, membrane integrity and enzymatic function, and a deficit may present with jitteriness, apnoea, stridor, irritability or convulsions [13].

Vitamin D, a fat-soluble seco-steroid, is integral to calcium homeostasis. Endogenous synthesis begins in the skin when ultraviolet-B photons (280–315 nm) convert 7-dehydrocholesterol to pre-vitamin D3, which is subsequently isomerised to cholecalciferol and hydroxylated in the liver to its principal circulating form, 25-hydroxy-cholecalciferol [14]. Phototherapy lamps emit predominantly in the blue spectrum (peak ~460 nm) with a small UV-B contribution, raising the biological question of whether phototherapy might increase, decrease, or have no effect on circulating 25(OH)D levels in the neonate. Published data are sparse and contradictory: Gillies et al. and Shahriarpanah et al. reported a rise in 25(OH)D after phototherapy, whereas other workers have observed the opposite [15,16].

The Indian subcontinent has one of the highest reported prevalences of vitamin D deficiency in infants, mothers and neonates, and most newborns are therefore vitamin D-replete only to a modest degree before phototherapy is begun [17]. Quantifying how phototherapy alters this fragile mineral balance has direct implications for routine supplementation policy. The present study was designed to address this gap by measuring serum total calcium and 25-hydroxy-cholecalciferol before and 48 hours after phototherapy in a homogeneous cohort of term, exclusively breastfed neonates managed in a single tertiary care unit in Eastern India.

Materials and Methods

Study Design, Setting and Duration: A hospital-based prospective analytical study was conducted in the Special Newborn Care Unit (SNCU), Department of Paediatrics, R. G. Kar Medical College and Hospital, Kolkata, West Bengal, India, over a period of 18 months. The institution is a tertiary care teaching hospital affiliated to The West Bengal University of Health Sciences and receives referrals from across Kolkata and adjacent districts.

Study population and sample size: All term neonates (gestational age ≥37 completed weeks) admitted to the SNCU with unconjugated hyperbilirubinaemia of sufficient severity to require phototherapy according to the American Academy of Pediatrics guidelines were screened for eligibility. A total of 150 neonates fulfilling the eligibility criteria were enrolled by consecutive sampling.

Inclusion Criteria: Term neonates of either sex, birth weight ≥2500 g, on exclusive breastfeeding, with unconjugated hyperbilirubinaemia warranting phototherapy.

Exclusion Criteria: Neonates with ABO incompatibility, Rh incompatibility, glucose-6-phosphate dehydrogenase (G6PD) deficiency, suspected or confirmed sepsis, congenital hypothyroidism, conjugated/surgical jaundice, congenital anomalies, sick neonates receiving intravenous fluids or pharmacologic agents that could influence calcium or vitamin D metabolism, and neonates born to mothers with documented thyroid or parathyroid dysfunction were excluded.

Study Procedure: After detailed history-taking and clinical examination, a venous blood sample was drawn from each enrolled neonate before the initiation of phototherapy. Total serum bilirubin (direct and indirect fractions), total serum calcium and serum 25-hydroxy-cholecalciferol were estimated. Conventional double-surface phototherapy was administered using compact fluorescent lamps with peak emission at 460 nm, at a spectral irradiance of 30–40 μW/cm²/nm measured at the level of the infant. The neonates were nursed naked except for an opaque eye shield and a minimal diaper, fed on exclusive breastmilk on demand, and turned every 2–3 hours. A repeat venous sample was obtained after 48 hours of continuous phototherapy and processed in the same hospital biochemistry laboratory.

Laboratory methods and operational definitions: Total serum bilirubin was estimated by the diazo (Jendrassik-Grof) method, total serum calcium by the o-cresolphthalein-complexone method on an autoanalyser, and 25-hydroxy-cholecalciferol by chemiluminescent immunoassay. Hypocalcaemia was defined, for term neonates and preterm neonates weighing >1500 g, as a total serum calcium <8 mg/dL (2 mmol/L). Vitamin D status was categorised as sufficient (>20 ng/dL), insufficient (10–20 ng/dL) and deficient (<10 ng/dL); for the present analysis, vitamin D deficiency was defined as 25(OH)D <20 ng/dL.

Study Variables: The variables recorded for each neonate were: gestational age, sex, postnatal day of presentation with jaundice, birth weight, pre- and post-phototherapy total serum bilirubin, pre- and post-phototherapy total serum calcium, and pre- and post-phototherapy 25-hydroxy-cholecalciferol.

Statistical Analysis: Data were entered in Microsoft Excel and analysed with SPSS v16.0 (SPSS Inc., Chicago, IL, USA). Continuous variables are presented as mean ± standard deviation; categorical variables as frequencies and percentages. Pre- and post-phototherapy continuous variables were compared with the paired t-test. The Mann-Whitney U test was used to compare continuous variables between two strata; McNemar's test was used for paired dichotomous variables; Pearson's correlation coefficient was calculated to test linear association. A two-sided p-value <0.05 was considered statistically significant.

Ethical Considerations: The study protocol was approved by the Institutional Ethics Committee of R. G. Kar Medical College and Hospital. Written informed consent was obtained from the parents or legal guardians of each neonate before enrolment.

The investigations were performed using the hospital's own facilities at no additional cost to the participants; the principles of the Declaration of Helsinki and national ethical guidelines for biomedical research on human participants were observed throughout.

Results

Baseline demographic and clinical profile: A total of 150 term neonates fulfilling the inclusion criteria were enrolled during the study period. Their age at presentation ranged from 2 to 9 days, with a mean of 4.17 ± 1.28 days; about half of the cohort (49.3%) presented at 4–5 days of life, 34.0% at 2–3 days, and 16.7% beyond the fifth day (Table 1).

Table 1: Distribution of neonates according to age at presentation

Age (days)	Number (n=150)	Percentage (%)
2–3 days	51	34.0
4–5 days	74	49.3
>5 days	25	16.7
Mean ± SD (Range)	4.17 ± 1.28 (2–9)	—

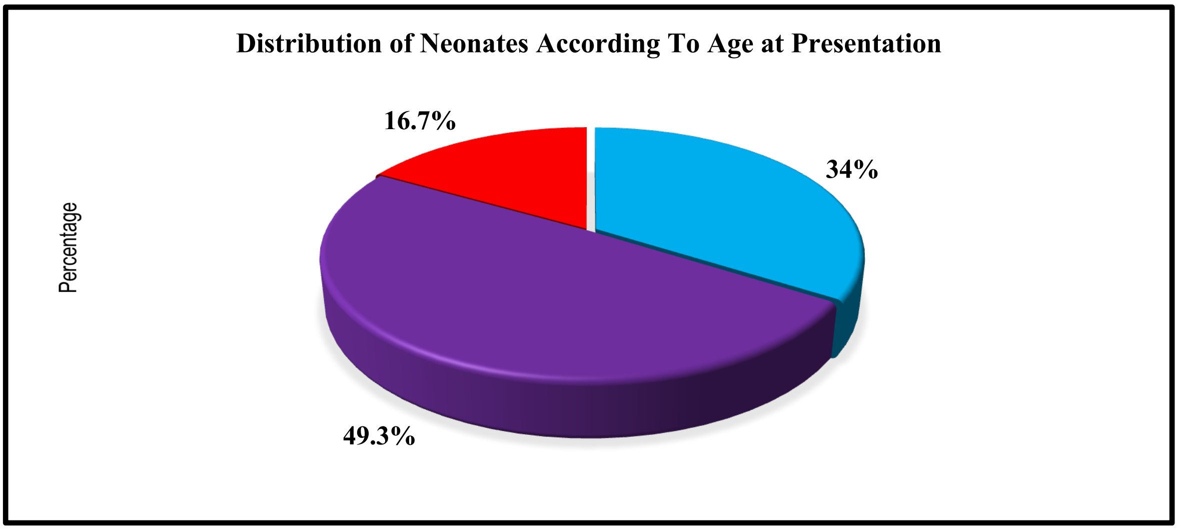

Figure 1: Distribution of neonates according to age at presentation

There was a male preponderance, with 90 (60.0%) of the 150 neonates being male and 60 (40.0%) female. The mean birth weight of the cohort was 2.98 ± 0.27 kg (median 2.90 kg). With respect to gestational age, 65 (43.3%) neonates had been born at 38 completed weeks, 55 (36.7%) at 39 weeks and 30 (20.0%) at 40 weeks, giving an overall mean gestational age of 38.77 ± 0.76 weeks (Table 2).

Table 2: Baseline demographic profile of the study cohort (n=150)

Variable	Value (n=150)
Sex – Male, n (%)	90 (60.0)
Sex – Female, n (%)	60 (40.0)
Birth weight (kg), mean ± SD	2.98 ± 0.27
Birth weight (kg), median	2.90
Gestational age 38 weeks, n (%)	65 (43.3)
Gestational age 39 weeks, n (%)	55 (36.7)
Gestational age 40 weeks, n (%)	30 (20.0)
Gestational age (weeks), mean ± SD	38.77 ± 0.76

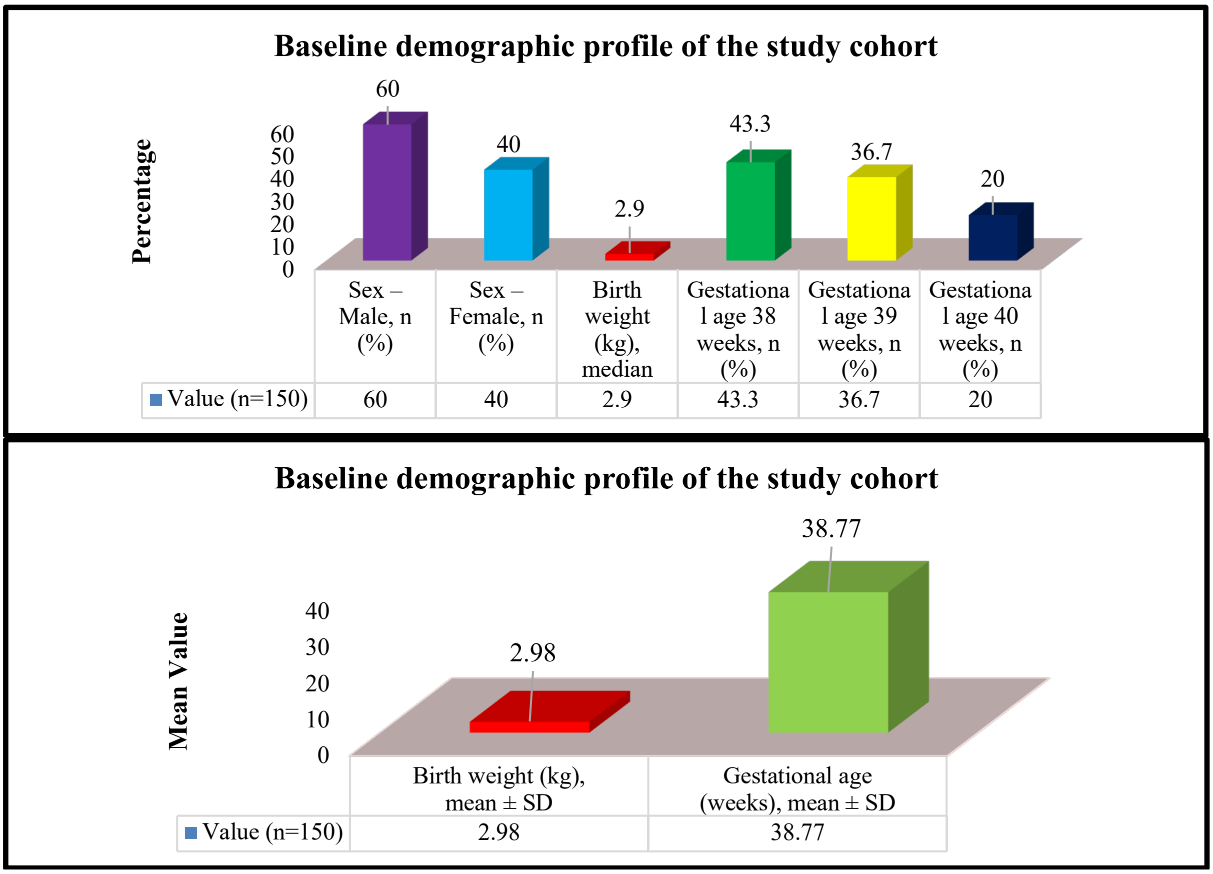

Figure 2: Baseline demographic profile of the study cohort (n=150)

Effect Of Phototherapy On Serum Bilirubin, Calcium And 25-Hydroxy-Cholecalciferol: Phototherapy Produced The Expected Reduction In Serum Bilirubin In Every Neonate. Mean Total Serum Bilirubin Fell From 14.35 ± 2.04 Mg/Dl Before Phototherapy To 11.47 ± 1.74 Mg/Dl After 48 Hours, An Absolute Mean Reduction Of 2.88 ± 2.33 Mg/Dl (Paired T-Test, P=0.0001). In Parallel, A Statistically Significant Fall Was Observed In Both Mineral Parameters. Mean Total Serum Calcium Dropped From 11.05 ± 1.62 Mg/Dl Pre-Phototherapy To 8.96 ± 1.05 Mg/Dl Post-Phototherapy, A Mean Change Of 2.09 ± 1.63 Mg/Dl (P=0.0001).

Mean 25-Hydroxy-Cholecalciferol Declined Even More Strikingly, From 36.64 ± 6.54 Ng/Dl To 14.06 ± 5.28 Ng/Dl — A Mean Change Of 22.58 ± 6.02 Ng/Dl (P=0.0001), Representing An Approximate 62% Relative Reduction (Table 3).

Table 3: Comparison of serum bilirubin, total serum calcium and 25-hydroxy-cholecalciferol before and after 48 hours of phototherapy

Parameter	Pre-phototherapy (Mean ± SD)	Post-phototherapy (Mean ± SD)	Mean change (p-value*)
Total serum bilirubin (mg/dL)	14.35 ± 2.04	11.47 ± 1.74	2.88 ± 2.33 (0.0001)
Total serum calcium (mg/dL)	11.05 ± 1.62	8.96 ± 1.05	2.09 ± 1.63 (0.0001)
25-hydroxy-vitamin D (ng/dL)	36.64 ± 6.54	14.06 ± 5.28	22.58 ± 6.02 (0.0001)

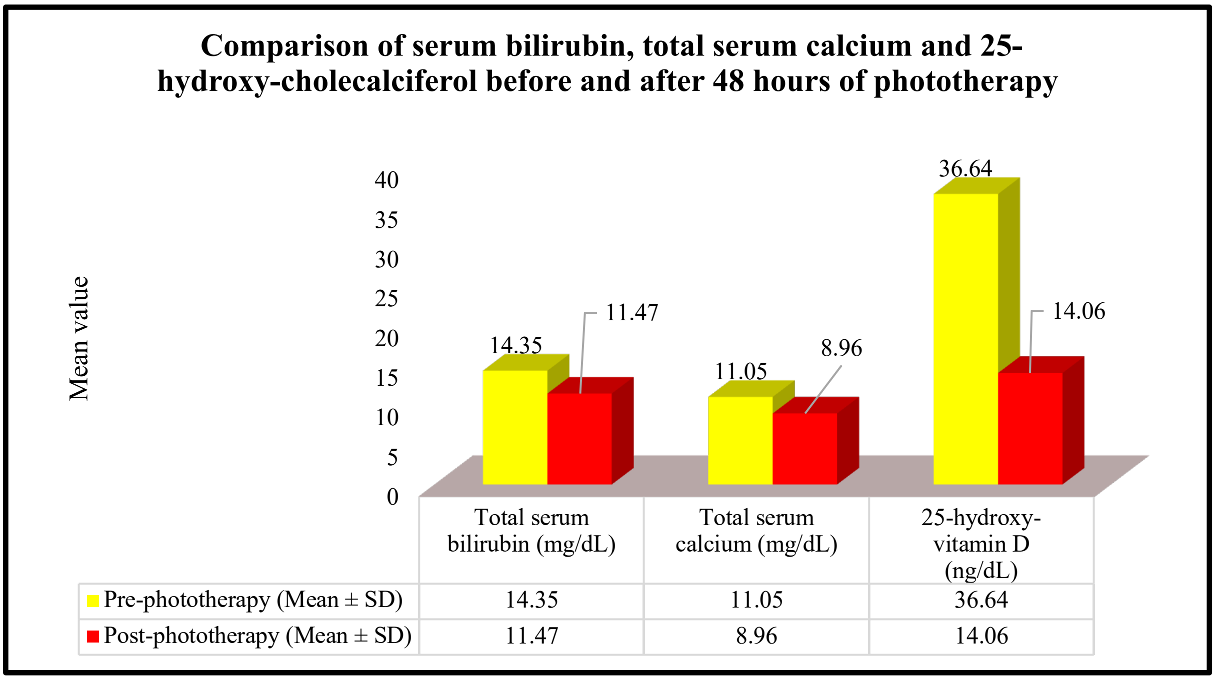

Figure 3. Comparison of serum bilirubin, total serum calcium and 25-hydroxy-cholecalciferol before and after 48 hours of phototherapy

Correlation with age and birth weight: Correlation analysis demonstrated that age at presentation had no significant linear relationship with the magnitude of change in any of the three biochemical parameters (Table 4). Birth weight likewise showed no significant correlation with the change in bilirubin (r=−0.14, p=0.07) or 25-hydroxy-cholecalciferol (r=+0.07, p=0.35). However, birth weight showed a weak but statistically significant positive correlation with the magnitude of fall in serum calcium (r=+0.27, p=0.001) — heavier term neonates experienced a slightly greater drop in calcium following phototherapy.

Table 4: Correlation of age and birth weight with the change in bilirubin, calcium and 25-hydroxy-cholecalciferol

Variable	**Pearson r — Δ Bilirubin**	**Pearson r — Δ Calcium**
Age (days)	−0.09 (p=0.25)	−0.02 (p=0.73)
Birth weight (kg)	−0.14 (p=0.07)	+0.27 (p=0.001)*
Variable		**Pearson r — Δ Vitamin D**
Age (days)		+0.08 (p=0.28)
Birth weight (kg)		+0.07 (p=0.35)

Effect of sex on biochemical changes: When the magnitude of change in each parameter was compared between male and female neonates, no significant difference emerged for bilirubin (p=0.53) or 25-hydroxy-cholecalciferol (p=0.16). The fall in serum calcium, however, was significantly larger in male neonates (2.35 ± 1.55 mg/dL) than in females (1.69 ± 1.68 mg/dL; Mann-Whitney U test, p=0.01), as summarised in Table 5.

Table 5: Comparison of change in bilirubin, calcium and 25-hydroxy-cholecalciferol with sex of neonate

Sex	**Δ Bilirubin (mg/dL)**	**Δ Calcium (mg/dL)**	**Δ Vitamin D (ng/dL)**
Male (n=90)	2.91 ± 2.19	2.35 ± 1.55	23.13 ± 5.68
Female (n=60)	2.83 ± 2.53	1.69 ± 1.68	21.75 ± 6.46
p-value (Mann-Whitney U)	0.53	0.01*	0.16

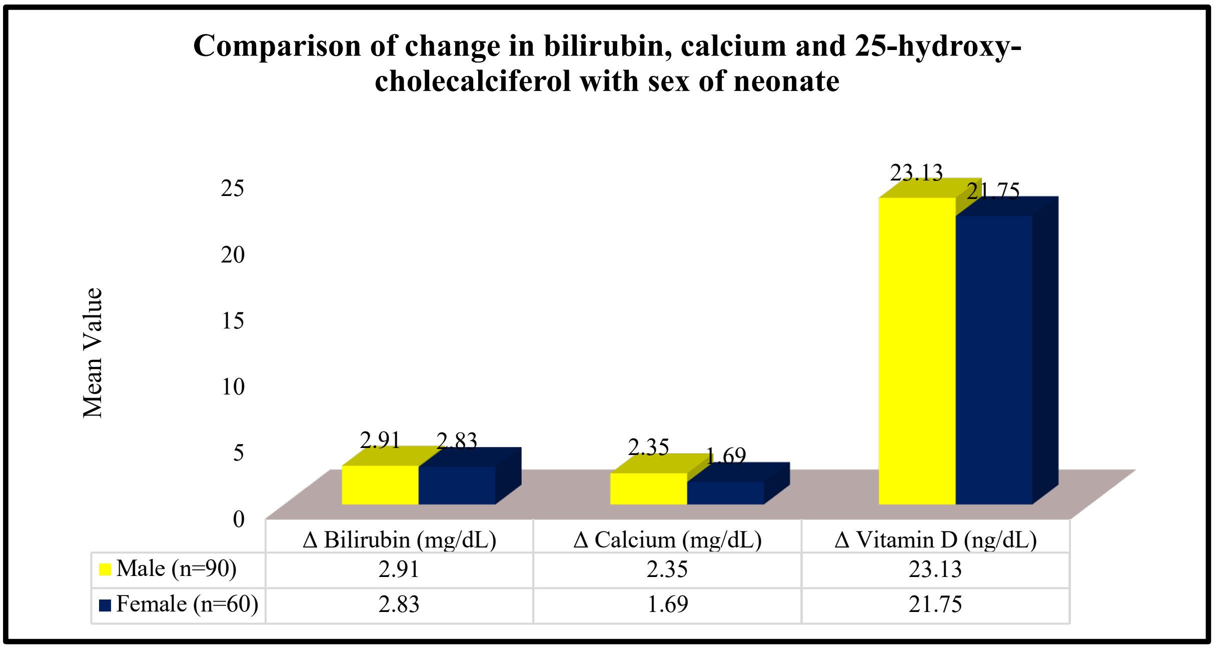

Figure 5. Comparison of change in bilirubin, calcium and 25-hydroxy-cholecalciferol with sex of neonate

Incidence of hypocalcaemia and vitamin D deficiency: Categorisation of neonates according to the operational definitions revealed striking shifts in the dichotomous outcomes. Hypocalcaemia (total serum calcium <8 mg/dL) was present in only 1 of 150 (0.7%) neonates at baseline, but in 13 (8.7%) after 48 hours of phototherapy; the change was statistically significant by McNemar's test (p=0.002). The effect on vitamin D status was far more dramatic. Vitamin D deficiency (25(OH)D <20 ng/dL) was present in only 4 (2.7%) neonates before phototherapy, but in 136 (90.7%) after phototherapy (p=0.0001).

The pre- and post-phototherapy prevalences of both outcomes are summarised in Table 6.

Table 6: Incidence of hypocalcaemia and vitamin D deficiency before and after 48 hours of phototherapy

Outcome	Pre-phototherapy n (%)	Post-phototherapy n (%)	p-value*
Hypocalcaemia (<8 mg/dL)	1 (0.7)	13 (8.7)	0.002
Vitamin D deficiency (<20 ng/dL)	4 (2.7)	136 (90.7)	0.0001

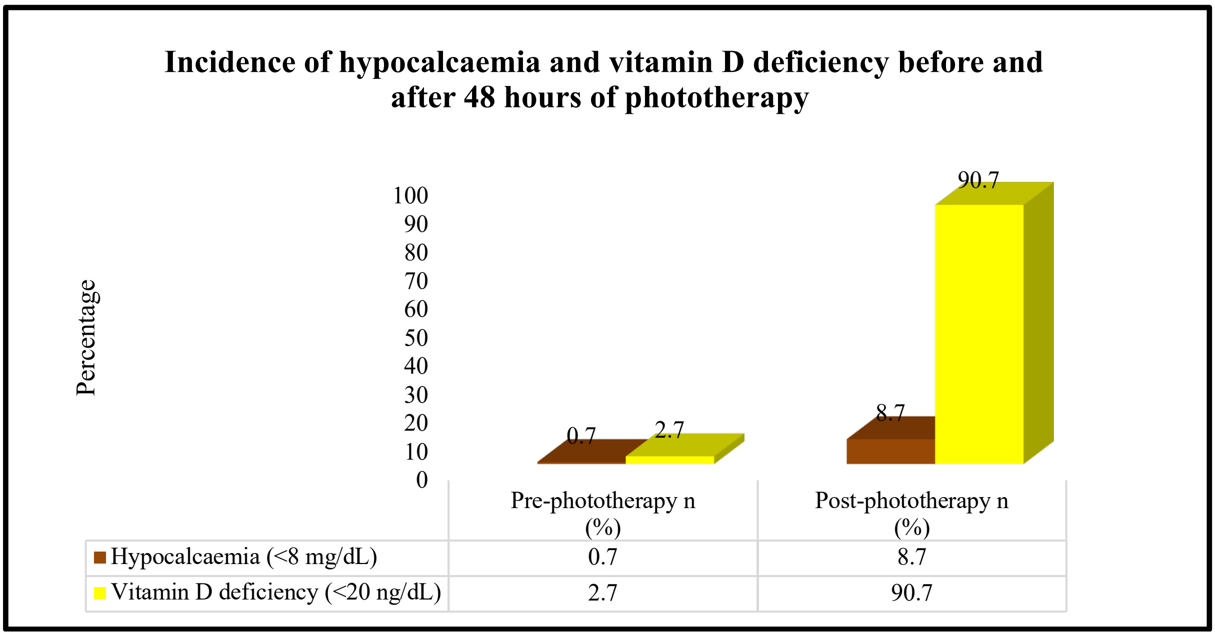

Figure 6. Incidence of hypocalcaemia and vitamin D deficiency before and after 48 hours of phototherapy

Discussion

Phototherapy remains the most widely used, safe and effective intervention for unconjugated hyperbilirubinaemia in the newborn. Nevertheless, the present prospective study of 150 term, exclusively breastfed neonates demonstrates that even a single 48-hour course of conventional double-surface phototherapy produces statistically significant reductions in both total serum calcium and 25-hydroxy-cholecalciferol, with a steep rise in the prevalence of biochemical hypocalcaemia and vitamin D deficiency. These findings are biologically plausible and consistent with the existing body of literature, but the magnitude of the fall in 25(OH)D observed in our cohort is among the most striking yet reported.

The demographic profile of our cohort — mean age 4.17 ± 1.28 days, mean birth weight 2.98 ± 0.27 kg, mean gestational age 38.77 ± 0.76 weeks — closely mirrors that of comparable Indian and South-Asian cohorts. Shrestha et al. reported a mean age of 4.12 ± 1.09 days and gestational age of 38.55 ± 2.34 weeks in their Nepalese series of 40 jaundiced neonates [18]. Lidia et al. observed a median birth weight of 2,900 g (range 2,600–3,950 g) and median gestational age of 38 weeks in their Indonesian cohort of 35 neonates [19]. The slight male preponderance (60%) we observed is also a recurrent finding in neonatal hyperbilirubinaemia series, although whether it reflects a true sex-based susceptibility or simply admission bias remains debated.

The mean fall in total serum bilirubin from 14.35 ± 2.04 mg/dL to 11.47 ± 1.74 mg/dL (p=0.0001) confirms that the phototherapy units in routine clinical use at our centre achieve a clinically meaningful response and is comparable to the pre- and post-phototherapy bilirubin levels of 14.53 ± 2.91 mg/dL and 10.29 ± 2.13 mg/dL reported by Shrestha et al. [18]. Rashwan et al. also documented a significant decline in total, direct and indirect bilirubin after 5 days of phototherapy in their Egyptian cohort [20], and Habibi et al. observed a comparable significant fall (p=0.0001) in their randomised comparison of phototherapy with and without oral calcium [21].

Our central observation — a fall in mean total serum calcium from 11.05 ± 1.62 mg/dL to 8.96 ± 1.05 mg/dL (p=0.0001) — reproduces, in directional and statistical terms, the consistent message of the international literature. Goyal et al. found a significant drop in serum calcium following phototherapy in 100 term Indian neonates [11]. Kale et al. reported a fall from 9.31 ± 0.69 mg/dL to 8.88 ± 0.73 mg/dL (p<0.0001) [4]. Elshenawi et al. documented a decline from 8.63 ± 1.54 mg/dL to 8.22 ± 1.64 mg/dL in 50 Egyptian neonates (p<0.001) [22]. Lidia et al. described a more modest mean decline of 0.24 mg/dL but with statistical significance (P=0.025) [19], and Shahriarpanah et al. similarly reported a significant fall from 9.85 to 9.51 mg/dL [16]. Notably, the pre-phototherapy mean calcium in our cohort (11.05 ± 1.62 mg/dL) is somewhat higher than in several published series; this is plausibly explained by the predominantly upper-normal calcium values in term Indian neonates on exclusive breastfeeding within the first week of life, and by methodological differences in calcium estimation across laboratories.

The mechanism by which phototherapy lowers serum calcium has been ascribed to the transcranial inhibition of the pineal gland: as light penetrates the thin neonatal cranium, melatonin secretion is suppressed; melatonin normally restrains cortisol, and the resulting unopposed cortisol drives calcium from the extracellular pool into bone and increases urinary calcium excretion [11,12,23]. Imani et al. demonstrated this directly by showing a significant rise in the urinary calcium-to-creatinine ratio after only 24 hours of phototherapy, with frank hypercalciuria appearing in 13% of their cohort [24]. The plausible mechanistic pathway therefore links pineal suppression → reduced melatonin → unopposed cortisol → hypocalcaemia and hypercalciuria.

The most novel and quantitatively striking finding of our study is the magnitude of fall in 25-hydroxy-cholecalciferol: from 36.64 ± 6.54 ng/dL to 14.06 ± 5.28 ng/dL (mean change 22.58 ± 6.02 ng/dL; p=0.0001), with a corresponding rise in the prevalence of biochemical vitamin D deficiency from 2.7% to 90.7%.

This contrasts with the report of Shahriarpanah et al., in which mean serum 25(OH)D actually increased after phototherapy (from 17.44 to 21.77 ng/dL, p<0.0001) [16], and with the small study of Gillies et al. (1984), in which plasma 25(OH)D rose non-significantly in 17 of 33 phototherapy-treated infants [25]. Rashwan et al. observed an improvement in vitamin D3 status after 5 days of phototherapy in Egyptian neonates with predominantly deficient baseline values [20]. The direction of change in our cohort is opposite to these earlier reports and warrants careful interpretation.

Several explanations may be advanced. First, the baseline 25(OH)D level in our cohort was high (36.64 ng/dL), and regression to a population mean rather than a true biological depletion may account for part of the observed change. Second, the assay platform used in our laboratory (chemiluminescent immunoassay) may behave differently from the assays used in earlier studies, with documented inter-method variability of up to 30% for 25(OH)D — a methodological caveat we acknowledge.

Third, although phototherapy lamps emit predominantly in the blue spectrum, contemporary devices have markedly reduced UV-B contamination compared with the units in use in the 1980s when Gillies et al. conducted their study; thus, modern phototherapy may provide little or no contribution to cutaneous vitamin D synthesis while still potentially accelerating its catabolism through accelerated bilirubin and 25(OH)D photo-isomerisation in the dermal capillary bed. Fourth, the increased urinary calcium excretion that follows phototherapy could indirectly accelerate the turnover of 25(OH)D through the action of fibroblast growth factor-23 and parathyroid hormone, although direct evidence for this pathway in neonates is lacking. Mehrpisheh et al. previously demonstrated a possible association between low serum vitamin D and neonatal indirect hyperbilirubinaemia (p=0.11) [26], hinting that pre-existing vitamin D status may itself be a determinant of jaundice severity — a relationship that deserves further mechanistic study.

The incidence of post-phototherapy hypocalcaemia in our cohort (8.7%) is markedly lower than that reported by several authors. Goyal et al. recorded hypocalcaemia in 35.0% of neonates after phototherapy [11]; Saeed et al. in 34.5% [27]; Javaid et al. in 41.58% [28]; Elshenawi et al. in 38.0% [22]; Shrestha et al. in 22.5% [18]; and Subhashini et al. in 26.0% [13]. Possible reasons for the lower rate observed here include the strict exclusion of preterm and growth-restricted neonates, the routine clinical practice of frequent breastfeeding in our unit (which provides a modest but continuous oral calcium intake), and the limitation of phototherapy duration to 48 hours in this analysis. The overall direction and statistical significance of the change, however, are entirely consistent with the published evidence base.

The observation that male neonates experienced a significantly greater fall in calcium (2.35 ± 1.55 mg/dL) than female neonates (1.69 ± 1.68 mg/dL; p=0.01) is intriguing and, to our knowledge, has been only inconsistently reported. Chandrashekar found no influence of sex on the incidence of post-phototherapy hypocalcaemia in his 200-neonate cohort [29].

Whether the present finding reflects a true biological sex difference — for example, in skin pigmentation, dermal thickness, calcium-regulating hormone milieu, or vitamin D-binding protein polymorphisms — or is a chance observation in a single-centre series, must remain open. The weak but significant positive correlation between birth weight and the magnitude of calcium fall (r=+0.27, p=0.001) likewise merits replication; one biologically reasonable explanation is that heavier term neonates have a larger surface area exposed to phototherapy lamps, with consequently greater photic stimulation of the pineal axis.

Taken together, our data reinforce the now well-established message that phototherapy, although indispensable, is not metabolically neutral. They add the further observation that 25-hydroxy-cholecalciferol may decline substantially during phototherapy in a population in which baseline vitamin D status is already at risk, and that this fall is independent of bilirubin reduction itself. From a clinical standpoint, our findings argue strongly for the routine measurement of serum calcium in neonates undergoing phototherapy beyond 48 hours, and for active consideration of supplementation strategies — particularly given the inexpensive nature of oral calcium and vitamin D preparations and the high prevalence of vitamin D insufficiency in Indian neonates.

Conclusion

In this prospective analytical study of 150 term, exclusively breastfed neonates managed at a tertiary care hospital in Eastern India, phototherapy administered for 48 hours for unconjugated hyperbilirubinaemia produced a statistically significant reduction in both total serum calcium (mean change 2.09 ± 1.63 mg/dL; p=0.0001) and 25-hydroxy-cholecalciferol (mean change 22.58 ± 6.02 ng/dL; p=0.0001). The incidence of biochemical hypocalcaemia rose from 0.7% to 8.7% (p=0.002), and the incidence of vitamin D deficiency rose from 2.7% to 90.7% (p=0.0001).

Male sex and higher birth weight were associated with a greater magnitude of post-phototherapy calcium decline.

Hypocalcaemia and vitamin D deficiency are therefore important, statistically robust and potentially preventable biochemical sequelae of phototherapy in term neonates. We recommend routine measurement of serum calcium, and where feasible 25-hydroxy-cholecalciferol, in neonates undergoing phototherapy — particularly when treatment is anticipated to exceed 48 hours — and we suggest that prophylactic oral calcium and vitamin D supplementation be actively considered in this group, pending the results of large randomised controlled trials.

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Authors' Contributions: DB conceived the study, enrolled and followed the patients, collected and curated the data, performed the statistical analysis and drafted the manuscript. AR conceptualised and supervised the study, contributed to the interpretation of the data, and critically reviewed and revised the manuscript for intellectual content. Both authors have read and approved the final version submitted for publication.

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