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Original Research Paper

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PHOTOTHERAPY INDUCED HYPOCALCEMIA: A STUDY FROM A TERTIARY CARE HOSPITAL OF EASTERN INDIA

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ABSTRACT Phototherapy is an extensively used intervention, thus its side effects need proper evaluation. Hypocalcaemia if proved to be more common post phototherapy, will be suspected, detected and treated more readily. In this perspective the present study aims to determine the risk of hypocalcaemia associated with phototherapy in all neonates and separately in term and preterm babies. The results can help in guiding the need for routine calcium supplementation in babies receiving phototherapy. **Materials And Methods:** The present study is a hospital based prospective, case control, observational study of 120 neonates (60 cases and 60 controls) Among the 60 babies in both the cases and control group, 30 (50%) were term and 30 (50%) were preterm . Blood samples collected pre and post phototherapy at 24hrs, 48hrs, 72hrs to determine total serum bilirubin (TSB) and ionized calcium (Ca2+) levels in both groups. **Results And Analysis:** The baseline serum Ca2+ level of the cases and controls were not significantly different ($p>0.05$). The mean Ca2+level in term babies at 48 hrs post phototherapy was 4.83 ±0.413 and in the control group it was 4.9 ±0.356. This difference was not statistically significant ($p>0.05$). However in preterm babies the cases had a mean Ca2+level of 4.02 ±0.657 versus 4.78±0.387 in controls. Statistical analysis showed highly significant difference ($p<0.001$) in the Ca2+ levels of the cases and controls in preterm. **Conclusion:** Phototherapy is associated with risk of hypocalcaemia in neonates when compared to controls, risk significantly greater in preterm.

KEYWORDS : neonatal jaundice, phototherapy, hypocalcaemia

INTRODUCTION:

Hyperbilirubinaemia is the single most common abnormal physical finding in the first week of life [1-3]. Phototherapy as an intervention has some side effects which include loose stools, hyperthermia, skin rash, hyperthermia and bronze baby syndrome [3-5]. Hypocalcaemia is one of the lesser known side effects of phototherapy.

Hypocalcaemia increases cellular permeability to sodium channel & increases cell membrane excitability [6-11].Clinical features are apnea, seizures, jitteriness, increased extensor tone, clonus, hyperreflexia & stridor. While early onset hypocalcaemia in preterm newborn is often asymptomatic, late onset hypocalcaemia is often associated with seizure [1-11].

Hakanson Do et al in their study in human infants and newborn rats have studied the effects of white light on the hypothalamo-pituitary-adrenal axis and calcium metabolism [12]. They have postulated phototherapy leads to inhibition of pineal gland via transcranial illumination, resulting in a decline in melatonin level [12, 13] due to an acute increase in corticosterone-mediated bone calcium uptake when circulating melatonin was decreased by reduction of the rate of melatonin synthesis [12-14].

There are a few studies in India and abroad showing the possible effects of phototherapy on serum ionised calcium levels in newborn human beings [15-18]. The results have been controversial and contradictory.

The main aim of the study was to find out the incidence of phototherapy induced hypocalcaemia in the neonates.

Objectives Of The Study Were:

To assess whether phototherapy is associated with the risk of hypocalcaemia compared to controls in all neonates and separately in term and preterm neonates

MATERIALS AND METHODS:

Study Area:

The study was carried out in the Baby Nursery of Department of Pediatrics, Burdwan Medical College & Hospital, Burdwan.

Study Design:

A hospital based, prospective, case control, observational study done among the neonates in the SNCU (Sick Newborn Care Unit) of Department of Paediatrics, of a tertiary care hospital.

Study Population:

Cases:

Sixty neonates consisting of thirty term and thirty preterm babies receiving phototherapy in the baby nursery during the data collection phase (twice a week over a period of one year) meeting the inclusion and exclusion criteria. Informed consent from the parents & Ethical Committee clearance was taken.

Controls:

Sixty neonates consisting of thirty term and thirty preterm babies fulfilling inclusion and exclusion criteria as for cases except that serum bilirubin levels lower than the cutoff for phototherapy. When the TSB reached the cutoff for phototherapy they were shifted to cases group.

Inclusion Criteria:

Term, or preterm neonates 0-7 days old with hyperbilirubinemia requiring phototherapy as per the American Academy of Paediatrics Guidelines, 2004 and NICE guidelines 2009 adapted in AIIMS protocol 2019(Fig no.1 & 2)[19-21].

Exclusion Criteria:

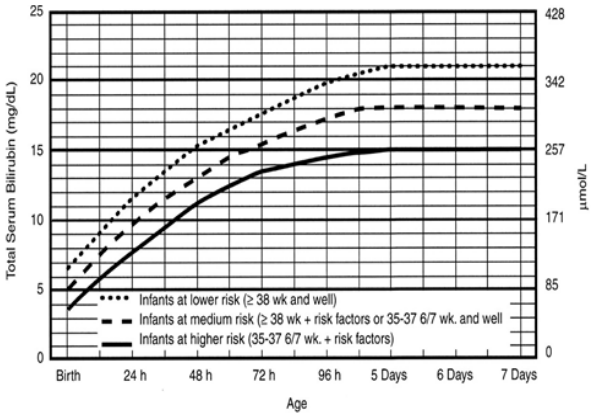
Neonate with Jaundice on day 1 of life, comorbidities like sepsis, acidosis, birth asphyxia, respiratory distress syndrome or congenital malformations, evidence of haemolysis like pallor, hepatosplenomegaly, positive family history;

Known cases hypo or hypercalcaemia or H/O maternal diabetes, hypo or hypercalcaemia, mother on anticonvulsant drugs, antithyroid drugs or any other medical condition complicating pregnancy;

Newborns requiring exchange transfusion and postnatal age > 7 days.

Management of hyperbilirubinaemia in low birth weight babies based on bilirubin levels (mg/dl) Phototherapy and exchange cut-offs of total serum bilirubin (mg/dL) for babies 34 weeks gestation or lower (Source: NICE guidelines 2009) adapted by AIIMS NICU protocols **[20, 21]**

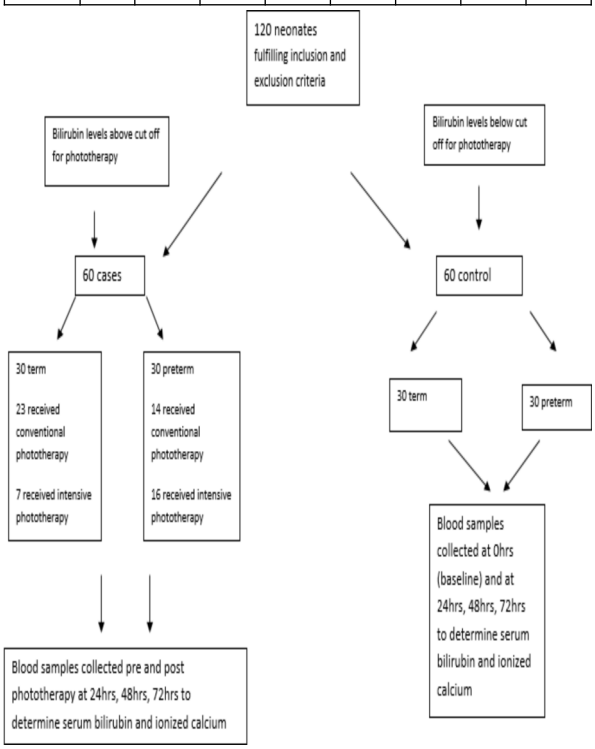
Fig no.1 AAP Nomogram For Phototherapy In Hospitalized Infants Of 35 Or More Weeks' Gestation.



- Use total bilirubin. Do not subtract direct reacting or conjugated bilirubin.
- Risk factors = isoimmune hemolytic disease, G6PD deficiency, asphyxia, significant lethargy, temperature instability, sepsis, acidosis, or albumin < 3.0g/dL (if measured)
- For well infants 35-37 6/7 wk can adjust TSB levels for intervention around the medium risk line. It is an option to intervene at lower TSB levels for infants closer to 35 wks and at higher TSB levels for those closer to 37 6/7 wk.
- It is an option to provide conventional phototherapy in hospital or at home at TSB levels 2-3 mg/dL (35-50mmol/L) below those shown but home phototherapy should not be used in any infant with risk factors.

Fig no.2

Gestational age(weeks)	Phototherapy (Bilirubin levels in mg/dl)				Exchange transfusion (Bilirubin levels in mg/dl)			
	12h	24h	48h	72h or more	12h	24h	48h	72h or more
23	3.2	4.0	5.9	7.6	6.1	7.6	10.5	13.5
24	3.2	4.4	6.4	8.2	6.1	7.9	11.1	14
25	3.5	4.7	6.7	8.8	6.4	8.2	11.4	14.6
26	3.5	4.7	7.0	9.4	6.4	8.2	11.7	15.2
27	3.6	5.0	7.3	10	6.5	8.5	12.0	15.8
28	3.8	5.0	7.6	10.5	6.7	8.5	12.3	16.4
29	3.8	5.3	8.2	11.1	6.7	8.8	12.9	17
30	4.0	5.3	8.5	11.7	6.9	8.8	13.2	17.6
31	4.1	5.6	9.0	12.3	7.0	9.1	13.7	18.1
32	4.1	5.9	9.4	12.9	7.0	9.4	14.0	18.7
33	4.2	6.1	9.9	13.5	7.1	9.7	14.6	19.3
34	4.2	6.1	10.2	14	7.1	9.7	14.9	19.9



Sample Design:

Study Tools:

- Information brochure and consent form
- Predesigned and pretested proforma
- Relevant medical records
- Standard phototherapy units[conventional phototherapy units (irradiance 4-6 microwatt/cm^{2}/nm), intensive phototherapy units (irradiance 30 microwatt/cm^{2}/nm), radiometers to measure irradiance]
- Laboratory equipments and chemical reagents
- Data analysis by student t test for paired data, odds ratio calculation using software programs SPSS and Prismpad

RESULT AND ANALYSIS:

Baseline/prephototherapy ionized calcium level was >4.5mg/dl in 80% of term cases (mean 4.94 ± 0.364 mg/dl) and 83.3% of the term controls. (Mean 4.47 ± 0.387 mg/dl). There was no significant difference between the initial calcium levels of cases and controls The initial total serum bilirubin(TSB) levels was in the range of 15-19.9 mg/dl in 90% of term neonates ;while 60% of preterm babies had TSB levels in the range of 10-14.9 mg/dl. Control group had TSB levels below the cut off for phototherapy.

Table no.1

Serum Ca2+ levels at 48 hrs	TERM NEONATES		PRETERM NEONATES	
	CASES	CONTROLS	CASES	CONTROLS
< 4 mg/dl	1	0	13	2
4-4.4 mg/dl	4	5	10	13
4.5 – 4.9mg/dl	9	10	3	10
5-5.4 mg/dl	15	10	4	5
>= 5.5 mg/dl	1	5	0	0
MEAN Ca2+ levels	4.83+/- 0.413	4.9 +/- 0.356	4.02+/- 0.657	4.78+/- 0.387

The mean calcium level at 48 hrs of phototherapy in term cases was 4.83 ± 0.413mg/dl while in the term controls was 4.9±0.356 mg/dl. The mean calcium level at 48 hrs of phototherapy in preterm cases was 4.02±0.657 mg/dl while in the preterm controls after 48 hrs without phototherapy was 4.78±0.387 mg/dl.

Statistical analysis of the post phototherapy serum ionised calcium levels of cases and controls in preterm babies by **student t test** for paired data gives a p value < 0.001which was highly significant. This was in sharp contrast to that found in term babies (p>0.5). Thus in preterm babies there is statistically significant change in serum ionised calcium levels post phototherapy when compared to age and sex matched controls with lower bilirubin levels who did not receive phototherapy. **Odds Ratio** for risk of serum Ca2+ dropping below 4mg/dl in cases when compared to controls is 8.8. Thus there is 8.8 times greater risk of hypocalcemia in neonates exposed to phototherapy compared to controls.

The incidence of hypocalcaemia in preterm babies in our study was only 16 % at 24 hrs, which increased to 43.33% at 48 hrs, and totaled at 56.67% at 72 hrs. In the control group there were only 2 cases of hypocalcaemia (6%). The commonest symptom was irritability, seen in 4 neonates. It was followed by apneic attacks in 2 neonates and a single case of seizure activity. The preterm babies became symptomatic at significantly lower Ca2+ levels (< 3.2 mg/dl). Only 1 of the term babies had hypocalcaemia.

DISCUSSION:

In the present study and that by Eghbalian et al serum Ca2+ levels have been taken into consideration. Serum Ca2+ values are roughly half of total calcium levels and are a better indicator of hypocalcaemia as they are not altered by changing serum albumin levels. However in studies by Sethi et al and Jain et al serum total calcium levels have been

compared [15-18]. The control group included babies with physiological jaundice. Whenever their TSB levels reached the phototherapy levels they were shifted to cases group or excluded from the study. In our study **the baseline** serum Ca2+ **levels in the cases and controls were not significantly different** (p>0.05). They also corroborated with previous studies. Studies by Sethi et al and Jain et al 48 hrs post phototherapy was set as the point for comparing the serum Ca2+ levels .In the study by Eghbalian et al 72hrs was the average duration of phototherapy [15-18].

Our study is different from the previous studies in two important aspects. First is that we have measured the serum Ca2+levels. Second is that post phototherapy Ca2+ levels have been measured over three days and not at a single point of time. **Thus the changing trends of serum bilirubin levels as well as serum calcium level were determined.**

However the values at 48 hrs were used for comparison and correlation because of three important reasons. First significant decrease in ionised calcium was noted at 48 hrs with incidence of hypocalcaemia. Secondly there was attrition of the study group at 72 hrs. Thirdly preterm babies had already developed hypocalcaemia by 48 hrs and were under treatment. Eghbalian et al in their study showed a mean serum total calcium level of 9.09±0.93 mg/dl at the completion of phototherapy. There was a statistically significant decrease (p<0.05) from the pre phototherapy calcium levels of 9.85±1.23 mg/dl in their study. In the study by Jain et al Mean (± SD) serum total calcium levels after 48 hrs of phototherapy in term babies was 7.9 (± 1.41) and in preterm babies was 6.32 (±1.32); while in the control group it was 9.19 (± 0.78) in term babies and 9.44(±0.91) in preterm babies. There was a statistically significant (p < 0.05) difference in the serum total calcium levels at 48 hours between the study group and controls.

In our study the mean serum Ca2+levels in term babies at 48 hrs was 4.83 ±0.413. In the control group it was 4.9 ±0.356. There were no statistically significant difference calcium levels between cases and controls, in term babies. **This was against the findings in the previous studies by Sethi et al and Jain et al [16, 17].**

However in preterm babies the cases had a mean serum Ca2+ level of 4.02 ±0.657 versus 4.78±0.387 in controls. **Statistical analysis showed highly significant difference (p<0.001) in the** serum Ca2+ **levels of the cases and controls in preterm. This was in sync with previous studies done by Sethi et al and Jain et al.**

In our study there was only a single case of symptomatic hypocalcaemia in the term babies (3%) in the cases group. The incidence of hypocalcaemia in preterm babies in our study was only 16 % at 24 hrs, which increased to 43.33% at 48 hrs, and totaled at 56.67% at 72 hrs. In the control group there were only 2 cases of hypocalcaemia (6%). The result of our study was in consonance with earlier studies by Romangoli et al (52.3%) and by Jain et al (55.0%). In our study one of the term babies had hypocalcaemia and was symptomatic with irritability and jitteriness. Among the 17 preterm babies with hypocalcaemia 7 (54%) were symptomatic. The commonest symptom was irritability followed by apneic attacks and seizure activity. While the term babies became symptomatic at Ca2+ levels below 4mg/dl, the preterm babies became symptomatic at significantly lower Ca2+ levels (< 3.2 mg/dl).

Previous studies had shown a significant change in total calcium levels after phototherapy in both term and preterm babies [15-17]. In our study we got a significant change only in preterm babies. The reason for this difference is not clear. One of the causes may be the already low baseline calcium levels in preterm babies. Secondly the serum calcium levels reach a physiological nadir at 48hrs post natal age. Also we have measured the serum Ca2+ **levels and not the total calcium.**

CONCLUSION:

Phototherapy is associated with the risk of decrease in serum Ca2+ levels to the extent of hypocalcaemia. Risk is insignificant in term neonates but significant in preterm (OR =10). Further studies with larger sample size are required to consider routine oral calcium prophylaxis.

Limitations Of The Study

1. Small study population
2. Intrauterine growth restricted (IUGR) babies included in study
3. All cases and controls could not be followed up for 72 hrs as planned
4. Study needed to show effects of calcium supplementation

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