International Journal of Science and Research (IJSR)
ISSN (Online): 2319-7064
Index Copernicus Value (2013): 6.14 | Impact Factor (2015): 6.391

Comparative Study of Incidence of Phototherapy Induced Hypocalcemia in Preterm V/S Term Neonates

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Abstract: ***Objective: comparative study of incidence of phototherapy induced hypocalcaemia in preterm vs term neonates. Design: A prospective study. Setting: A tertiary care center of north east India. Participants: 100 full term and 100 preterm neonates with gestational age between 34 to 42 weeks were included in study. Main outcome measures: Blood was drawn from these neonates to measure serum bilirubin and serum calcium at the time of initiation of phototherapy (0 hours) and at 48 hours of phototherapy or at the end of phototherapy in case duration of phototherapy is less than 48 hours. Result: Total incidence of phototherapy induced hypocalcaemia in neonates getting phototherapy is 43 % (86 out of 200). Out of which incidence was more in preterm than in term neonates, more in SGA neonates then AGA. Incidence is not affected by sex of newborn and mode of delivery and parity of mother. Conclusion: These values show that incidence of hypocalcaemia is a significant side effect of phototherapy and more being in preterm and SGA neonates. So while starting phototherapy for neonatal jaundice, one need to be cautious about serum calcium status.***

Keywords: hypocalcaemia, neonates, phototherapy, SGA- small for gestational age, AGA- appropriate for gestational age TSB= total serum bilirubin PT=phototherapy

1. Introduction

Jaundice is an important problem in the first week of life. It is a cause of concern for the physician and a source of anxiety for the parents. About 60% of term and 80% of preterm infants develop jaundice in the first week of life (1). Hyper bilirubinemia leading to encephalopathy is a devastating brain injury, which can cause permanent neurodevelopmental handicap (2).

Neonatal jaundice is benign and no intervention is required in most of the cases. Approximately 5-10% of them have clinically significant hyperbilirubinemia in whom the use of phototherapy becomes mandatory. Basic pathophysiology of jaundice is same in term and preterm neonates, but premature babies are at a higher risk of developing hyperbilirubinemia.

It is commonly managed by phototherapy with its inherent complications. It is very fortunate that a non-invasive and easily available, phototherapy, is effective in degrading unconjugated bilirubin (3). Phototherapy with blue light is widely used in the clinical practice (7). The commonly known side effects of phototherapy are loose stools, hyperthermia, dehydration fluid loss, skin burn, photoretinitis, low platelet count, increased red cell osmotic fragility, bronze baby syndrome, riboflavin deficiency and DNA damage.

A lesser known side effect, but potential complication of phototherapy is hypocalcemia(9). Most of the preterm and some of term neonates develop hypocalcaemia after being subjected to phototherapy(3,4). This effect is because of decrease secretion of melatonin from pineal gland, which is needed to inhibit hypocalcaemia action of serum cortisol.

Serum calcium is crucial for many biochemical processes, including blood coagulation, neuromuscular excitability, cell membrane integrity and function, and cellular enzymatic and secretary activity (5, 6). Hypocalcaemia can cause serious complications like convulsions, apnoea, irritability, jitteriness (8).

Most of the reports with regards to incidence of hypocalcaemia in phototherapy are from studies conducted on either term or preterm separately. Only few studies done comparison and there are very less studies conducted in India.

2. Materials and Method

This study conducted in NICU, Silchar Medical College, Silchar. Stable 100 term neonates (37 weeks to 42 weeks) and 100 preterm neonates (34 weeks to <37 weeks) were included in study. Neonates with jaundice in first 24 hours of life, born to a diabetic mother, hypothyroid mother, hyperparathyroidism mother, whose mother had history of taking anti-convulsants, fed with cow's milk, who had exchange transfusion, with jaundice lasting more than 14 days of life, with sepsis, hypocalcaemia before starting of phototherapy, Preterm<34 weeks were excluded from the study. Study done over a period of one year. Clearance of ethical committee taken.

The blood samples were analyzed at SMCH clinical laboratory for Serum TSB and serum calcium at the time of admission and at 48hours of phototherapy or by the end of phototherapy if duration of phototherapy is less than 48hours. Pretest and post-test counseling was given to parents. After written consent from the parents, those neonates fulfilling the above mentioned criteria were subjected to blood test like serum calcium and serum TSB

levels, at initiation and after 48 hours of phototherapy or at the end of phototherapy in case duration of phototherapy is less than 48 hours. And "hypocalcaemia defined as <8mg/dl in term and <7mg/dl in preterm neonates as defined in AIIMS NICU protocol of 2010"[10]

Data analysis was performed using statistical package of social science (SPSS) version 16.0 for windows. Proportions will be compared using chi-square test and student t test. Mean between the groups will be compared using T-test or ANNOVA.

3. Results

The study consisted of total 200 neonates (100 full term and 100 preterm). Out of 200 neonates 36(18%) were small for gestational age (SGA) and 164(82%) were appropriate for gestational age (AGA).

Study consisted of 122(61%) male and 78(39%) female neonates. 123(61.5%) neonates were born by normal veginal delivery and 77(38.5%) were LSCS. 133(66.5%) neonates were born to primipara and 67(33.5%) neonates were born to multipara.

These babies were put on phototherapy (PT) and blood was drawn from these neonates for serum bilirubin and serum calcium at the time of starting of phototherapy and at 48hours of phototherapy or at the end of phototherapy if duration is less than 48 hours. Out of 200 neonates 104 (52%) needed 48hours (54 preterm and 50 term) of PT, 96 neonates needed <48hrs of PT (46 preterm and 50 term).

Table 1: Averages of birth weight, gestation, duration of PT and gender distribution in term, preterm and total study population

Parameter	*Pre term*	*Term*	*Total study population*
Weight(kg)	2.0034±0.25	2.988±0.4	2.59±0.33
Gestational age(weeks)	35.19±0.79	39.15±0.8	37.17±0.8
Duration of PT(hours)	41.96±6.88	40.97±7.45	41.46±14.33
Male : female ratio	1.32:1	1.86:1	1.56:1

PT=phototherapy

From table it's seen that preterm needed prolonged phototherapy compared to term neonates.

Table 2: Conclusive comparative evaluation of study variables pre and post PT in neonates.

	Pre PT TSB mg/dl	*Post PT TSB mg/dl*	*difference*	*Pre PT Ca mg/dl*	*Post PT Ca mg/dl*	*difference*	*P value*
Term	18.49±1.7	13.13±1.2	5.4	9.42±0.8	8.18±0.9	1.24	<0.05
Pre term	17.99±1.6	10.76±1.9	7.23	9.27±1.0	7.60±1.1	1.67	
SGA	18.9±2.09	11.61±1.9	7.3	9.5±1.11	8.2±1.14	1.3	
AGA	18.44±2.5	13.2±1.28	5.24	9.41±0.8	8.18±0.9	1.23	

PT: phototherapy Ca: calcium TSB: total serum bilirubin

From table its seen that range of decline in post PT serum calcium, is more in preterm compared to term and more in SGA neonates then in AGA neonates. Indicating that preterm neonates and SGA neonates are more at a risk of developing phototherapy induced hypocalcaemia. And p value is significant as shown in table 2.

Table 3: Relation between range of decline in serum TSB to decline in serum calcium according to gestational age (GA) and birth weight

	GA (mg/dl)	*BW (mg/dl)*	*Average*
Serum TSB	6.32	6.27	6.3
Serum Ca2+	1.46	1.15	1.3

GA - gestational age BW - birth weight TSB: total serum bilirubin

From above table it's seen that for every 6.3mg/dl decline in serum TSB there is ≈1.3mg/dl decline in serum calcium with confounding factors being gestational age and birth weight.

Table 4: Incidence of phototherapy induced hypocalcaemia.

Parameter	*Total no. of neonates*	*No. of neonates who developed hypocalcaemia*	*Incidence of hypocalcaemia*	*P value*
Total study population	200	86	43%	<0.05
Pre term	100	48	48%	<0.05
Term	100	38	38%	
SGA	36	20	55.5%	<0.05
AGA	164	66	40%	

From table it seen that incidence of hypocalcaemia is more in preterm neonates and SGA neonates as compared to term and AGA neonates respectively. And incidence of hypocalcaemia is significant (p value <0.05) and difference of incidence of hypocalcaemia between TERM vs PRETERM and SGA vs AGA is also significant as p value is <0.05.

4. Discussion

Jaundice is a well-known clinical entity in Indian medicine. And about jaundice in neonates, 1st mentioned in a book published in 15th century (11). Neonatal jaundice is one of the leading causes of NICU admission. And phototherapy is one of the best and safe method as a treatment option in neonatal jaundice as described by Cremer et al in 1953,alternative being exchange transfusion which is risky and has many complications and one more treatment option being pharmacotherapy which is until now, not so effective, still being under study. Every safe method has its own side effects and even the phototherapy. One of the known side effects of phototherapy is hypocalcaemia.

We conducted a prospective study to confirm that phototherapy in jaundiced neonates causes hypocalcaemia and comparison of incidence of hypocalcaemia in preterm and term neonates. The study group includes 200 neonates admitted in NICU for neonatal jaundice considering inclusion and exclusion criteria.

We took a cut value of serum calcium of <7mg/dl for preterm and <8mg/dl for term to define hypocalcaemia from AIIMS NICU protocol 2010. Which is comparable to Arora et al (Preterm <7mg/dl, Term <8mg/dl), Karamifar et al (<7mg/dl preterm, <7.5mg/dl term), Taheri et al <8mg/dl)

Our study population contains large population and equal distribution of term and preterm neonates as compared to karamifer el al who total 153 neonates out of which 62 were preterm and 91 are term, Taheri et al took total 147 term neonates, Kumar et al took 100 neonates out of which 45 preterm and 55 term and Arora et al took 100 neonates out of which 46 preterm and 54 term.

After subjecting 200 neonates with jaundice for phototherapy pre and post phototherapy serum TSB and serum calcium were measured and difference were taken as shown in table 2. The difference was more in term and SGA neonates compared to preterm and AGA neonates. Similar results were seen in Karamifar et al, Kumar et al, Eghbalian et al and Arora et al.

Total incidence of hypocalcaemia was 43%, in preterm incidence was 48% and in term incidence was 38%. Incidence of hypocalcaemia in SGA neonates was 55.5 % than compared to AGA neonates with 40% incidence as shown in table 4. Which is comparable to study conducted by Kumar et al (46% total, in term 66.6% and in preterm 80%) with incidence being almost equal in total population but high in term and preterm may be because of small population distribution. And in other studies like Karamifar et al (22% incidence), Taheri et al (10% incidence in term), Eghbalian et al and Arora et al incidence of hypocalcaemia was significant.

No study mentions the relation between decline in serum calcium and serum TSB which is mentioned in our study as shown in table 3. And there need to be more studies to confirm this finding.

What we already know?

- Hypocalcaemia is a known side of phototherapy in neonates with jaundice.

What's new in this study?

- Incidence of hypocalcaemia more pronounced in preterm neonates, and SGA neonates compared to term and AGA neonates respectively. And for every 6.3mg/dl decline in serum TSB there is ≈1.3mg/dl decline is serum calcium with confounding factors being gestational age, birth weight and duration of phototherapy.

5. Conclusion

In conclusion we need to be careful about calcium status while starting phototherapy for neonatal jaundice. More specifically in preterm, SGA and when duration is >48hours. And it's better to supplement calcium in both these scenarios.

Based on our study and experience we recommend few points to prevent phototherapy induced hypocalcaemia:

- Regular monitoring of serum calcium should be done periodically in all newborn getting phototherapy for neonatal jaundice. Pre phototherapy and during phototherapy every 12 hourly along with serum TSB.
- Preterm are more at a risk of developing hypocalcaemia than term and chance of developing hypocalcaemia is more if duration of phototherapy is ≥48hours so in these 2 scenarios it's advisable to monitor serum calcium very frequently may be every 6 hourly and better to give prophylactic calcium supplementation (oral or I V).

As we see for every 6.3mg/dl decrease in TSB there is decrease of approximately ≈1.3mg/dl in serum calcium it is advisable that if there is need to decrease serum TSB to >6mg/dl and if pre phototherapy serum calcium is at cut of level i.e. in preterm around 7mg/dl and in term around 8mg/dl then to avoid hypocalcaemia and its symptoms it's better to give prophylactic calcium supplementation (oral or I V).

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