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FREQUENCY OF HYPOCALCAEMIA AFTER 48 HOURS OF PHOTOTHERAPY IN FULL TERM INFANTS WITH NEONATAL JAUNDICE

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Abstract:

Introduction: *Neonatal jaundice is a common clinical problem observed during the first week of life affecting approximately 60% of term and 80% of preterm infants. While majority of these infants recover, in a proportion of infants, jaundice may become severe, progressing to acute bilirubin encephalopathy (ABE) or kernicterus with a substantial risk of neonatal mortality. Phototherapy for neonatal jaundice is a common treatment in neonatal medicine and is used to prevent the neurotoxic effects of bilirubin. There is evidence that its use is associated with hypocalcaemia which is a serious concern. However, the frequency of hypocalcemia varies greatly between the studies ranging from as low as 6% to as high as 80%. The type of fluorescent tube, serum vitamin D, bilirubin levels and also the patient's skin colour might be responsible for this variation in the existing literature. Owing to the observed variation among various populations and lack of local such local published material, need for the present study was felt.*

Objective: *The objective of this study was to determine the frequency of hypocalcaemia after 48 hours of phototherapy in full term infants presenting with neonatal jaundice at a teaching hospital in Punjab.*

Material and Methods: *It was a descriptive case series. This study was conducted at Department of Pediatric Medicine Unit-I, Lahore General Hospital, Lahore. And the duration of this study was 6 months after the approval of synopsis from 27 January 2016 to 26 July 2016. This study involved 246 full term neonates of both genders presenting with neonatal jaundice with serum calcium level >8 mg/dl before the start of phototherapy. These patients were followed for the development of hypocalcemia (serum calcium ≤8 mg/dl). A written informed consent was taken from parents of each patient.*

Results: *The mean age of the patients was 6.04±3.50 days. There were 149 (60.6%) male and 97 (39.4%) female patients with a male to female ratio of 1.5:1. The weight of the neonates ranged from 2 kg to 3 kg with a mean of 2.64±0.23 kg. 162 (65.9%) neonates have weight more than 2.5 Kg. Serum calcium level upon admission ranged from 8.1 mg/dl to 12.0 mg/dl with a mean of 9.04±0.93 mg/dl. Majority (69.1%) of the neonates had serum calcium at admission between 8.1-9 mg/dl followed by 76 (30.9%) neonates whose serum calcium at admission was ≥9 mg/dl. Mean serum calcium level after 48 hours of phototherapy was 7.69±0.54 mg/dl with a mean decrease of 1.35±0.90 mg/dl. This difference was statistically significant (p=0.000). 167 (67.9%) neonates had hypocalcemia. There was no significant difference in the frequency of hypocalcemia across age (p=0.964), gender (p=0.812), weight (p=0.994) and serum calcium level at admission (p=0.904).*

Conclusion: *The frequency of hypocalcemia was found to be 67.9% in full term infants with neonatal jaundice undergoing phototherapy. There was no significant difference in the frequency of hypocalcemia across age (p=0.964), gender (p=0.812), weight (p=0.994) and serum calcium level at admission (p=0.904).*

KEYWORDS: *Neonatal Jaundice, Phototherapy, Hypocalcemia*

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INTRODUCTION:

Neonatal jaundice is a common clinical problem observed during the first week of life affecting approximately 60% of term and 80% of preterm infants [1]. In a recent local study (Karachi, Pakistan), the incidence of neonatal jaundice was recorded as 39.7/1000 live births [2]. While majority of these infants recover, in a proportion of infants, jaundice may become severe, progressing to acute bilirubin encephalopathy (ABE) or kernicterus with a substantial risk of neonatal mortality [3]. Phototherapy for neonatal jaundice is a common treatment in neonatal medicine and is used to prevent the neurotoxic effects of bilirubin. It is a cost-effective and non-invasive treatment opted as a first line in most of the infants with neonatal jaundice. Exchange transfusion is another option with its own merits and demerits [4]. Due to its non-invasive nature; phototherapy was believed to be a safer option as compared to exchange transfusion. But now there is evidence that its use is associated with hypocalcaemia which is a serious concern [5-13]. The possible explanation of this hypocalcemia is by inhibition of pineal gland via transcranial illumination, causing decline of melatonin secretion which otherwise blocks the effect of cortisol on bone calcium. Cortisol increases bone uptake of calcium and induces hypocalcaemia [6].

Srinivasa et al. in 2015 (India) reported the frequency of hypocalcaemia to be 80% after 48 hours of phototherapy in full term icteric neonates [6]. Arora et al. in 2014 (6%) [7], Yadav et al. in 2012 (66%) [8] and Jain et al. in 1998 (30%) [9] made similar observation in Indian population.

Tehrani et al. in 2014 reported the frequency of hypocalcaemia after 48 hours of phototherapy to be 7.5% in Irani population [10]. Similar observation was made previously by Alizadeh-Taheri et al. in 2013 (7%) [11], Ehsanipoor et al. in 2008 (15%) [12], Karamifar in 2002 (8.7%) [13] in the same population. Medhat in 2006 reported this frequency to be 75% in Egypt [14]. Thus hypocalcaemia after photo therapy is a frequent complication. However, its frequency varies greatly between the studies ranging from as low as 6% [7] to as high as 80% [6] in Indian population and from 7% [11] to 15% [12] in Irani population. The exact reason for this conflict is not known in the existing literature. However, the type of fluorescent tube, serum vitamin D, bilirubin levels and also the patient's skin color might play a role [6]. Owing to the observed variation among various populations [6-14], various subsets of a single population (India [6-9], Iran [10-13]) and lack of local research, the purpose of the current study is to determine the frequency of hypocalcaemia after 48 hours of phototherapy in full terms infants with neonatal jaundice in local population. 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.

MATERIALS AND METHODS:

It's a descriptive case series. This study was conducted at Department of Pediatric Medicine Unit-I, Lahore General Hospital, Lahore and the duration of this study was 6 months after the approval of synopsis from 27 January 2016 to 26 July 2016. Sample size of 246 cases was calculated with 95% confidence level and 5% margin of error while taking expected frequency of hypocalcaemia to be 80% in full term infants after 48 hours of phototherapy in Indian population (2015). Patients were selected by Non-Probability, Consecutive Sampling.

Inclusion Criteria

1. Full term infants (as per operational definition) of both genders who presented with neonatal jaundice (as per operational definition) for ≤24 hours' duration subjected to phototherapy (consultant pediatrician decision).
2. Total serum calcium level at admission >8mg/dL
3. Patients where written informed consent was given by the parents or legal guardians of the infant to participate in the study.

Exclusion Criteria

1. The newborns with jaundice in the first 24 hours of life (history), infants of diabetic mothers (history and clinical record of the mother, Fasting Blood Sugar≥110mg/dl), and those with an Apgar score <7 at birth (delivery notes).
2. History of use of anti-convulsants (phenobarbital) by the mother in ante-natal period.
3. Cow milk fed new-born (history from mother)
4. Infants who had received exchange transfusion previously (as per history and clinical record)

DATA COLLECTION PROCEDURE

246 infants presenting in the emergency of Department of Pediatric Medicine, Unit-I, Lahore General Hospital Lahore meeting the inclusion criteria, were enrolled into this study. Detailed history and written informed consent was obtained from the patients or attendants. All the infants were given phototherapy (as per operational definition) and other treatment like IV fluids and antibiotics (as per department protocol). Serum calcium levels were acquired at admission and after 48 hours of phototherapy. Hypocalcaemia was labeled as per operational definition. Patient's demographic

details, total serum calcium level at admission, at 48 hours and occurrence of hypocalcaemia were recorded into the attached proforma. All the sampling was performed by a single resident and all serum calcium level estimations were acquired from a single (Hospital) lab to eliminate bias. Confounding variables were controlled by exclusion.

DATA ANALYSIS PROCEDURE

All the collected data was entered and analyzed through SPSS version 18.

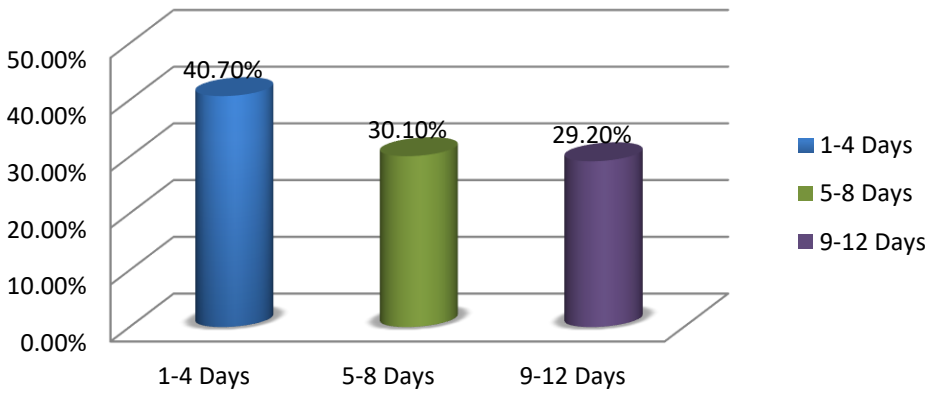
1. Numerical variables; age, weight, serum calcium level at admission and 48 hours have been presented by mean ±SD.
2. Categorical variables i-e gender and hypocalcaemia have been presented as frequency and percentage.
3. Data has been stratified for age, gender, weight and serum calcium level upon admission to address effect modifiers. Post-stratification chi-square test has been applied taking p value ≤ 0.05 as significant.

RESULTS:

The age of the patients ranged from 1 day to 12 days with a mean of 6.04±3.50 days. Majority of the patients were aged between 1-4 days (n=100, 40.7%). There were 149 (60.6%) male and 97 (39.4%) female patients with a male to female ratio of 1.5:1. The weight of the neonates ranged from 2 kg to 3 kg with a mean of 2.64±0.23 kg. 162 (65.9%) neonates have weight more than 2.5 Kg. Serum calcium level upon admission ranged from 8.1 mg/dl to 12.0 mg/dl with a mean of 9.04±0.93 mg/dl. Majority (69.1%) neonates had serum calcium at admission between 8.1-9 mg/dl followed by 76 (30.9%) neonates whose serum calcium at admission was ≥9 mg/dl as shown in charts 8.1 – 8.4.

Mean serum calcium level after 48 hours of phototherapy was 7.69±0.54 mg/dl with a mean decrease of 1.35±0.90 mg/dl. This difference was statistically significant (p=0.000). 167 (67.9%) neonates had hypocalcemia. There was no significant difference in the frequency of hypocalcemia across age (p=0.964), gender (p=0.812), weight (p=0.994) and serum calcium at admission (p=0.904) as shown in Table 8.5.

Bar-Chart 0.1 Age Group Distribution



Pie-Chart 0.2 Gender Distribution

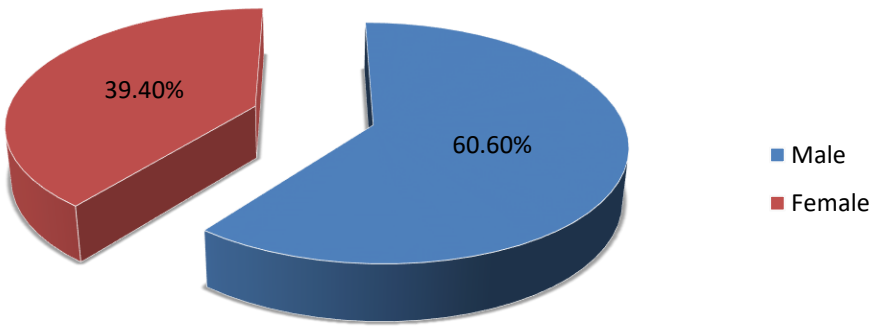


Figure 0.3 Various Presenting Symptoms of Newborns

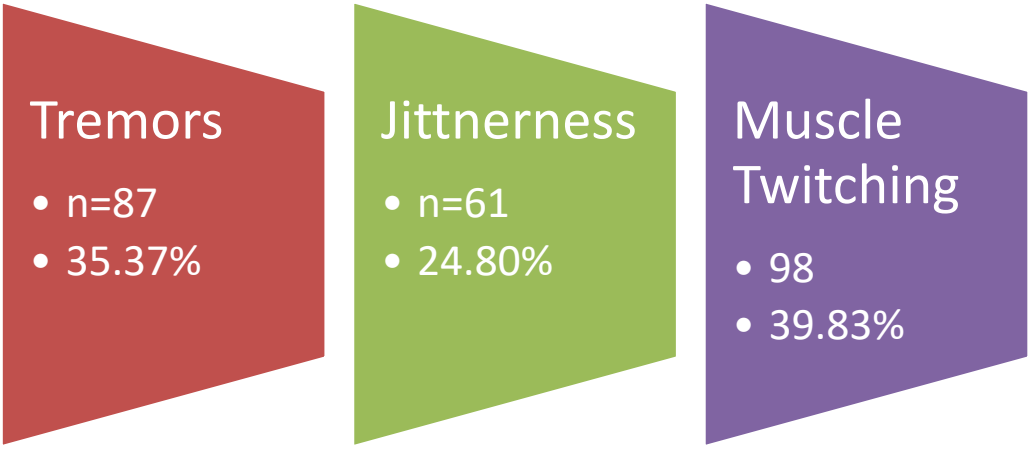


Chart 0.4 Feeding patterns of neonates

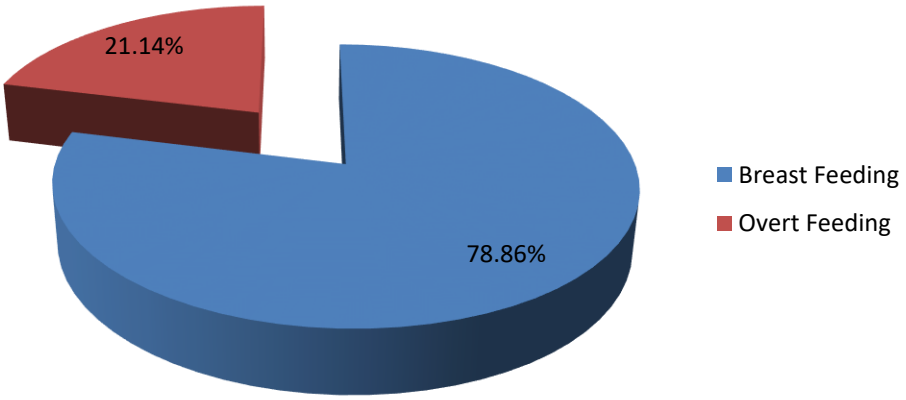


Chart 0.5 Groups according to Weight of the Newborns

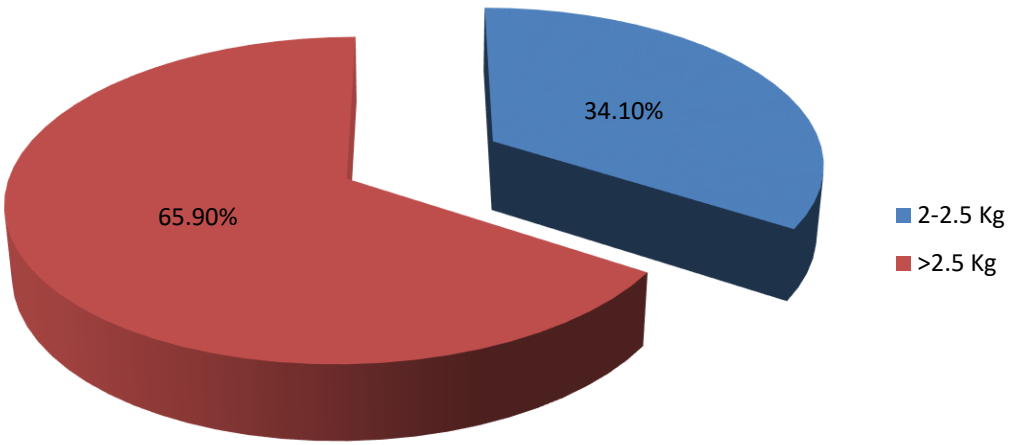


Chart 0.6 Level of Serum Calcium at the start of study

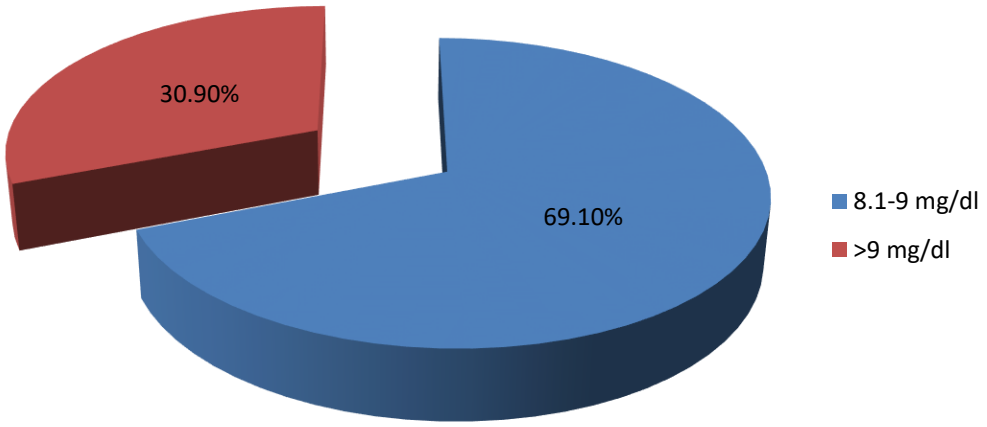


Table 0.3 Frequency of Hypocalcemia

Characteristics	Hypocalcemia n (%)	P value
Overall	**167/246 (67.9%)**	-
Age Groups		
• 1-4 days	67/100 (67.0%)	
• 5-8 days	51/74 (68.9%)	0.964
• 9-12 days	49/72 (68.1%)	
Gender		
• Male	102/149 (68.5%)	
• Female	65/97 (67.0%)	0.812
Weight Groups		
• 2-2.5 Kg	57/84 (67.9%)	0.994
• >2.5 Kg	110/162 (67.9%)	
Serum calcium at admission Groups		
• 8.1-9 mg/dl	115/170 (67.6%)	0.904
• ≥9 mg/dl	52/76 (68.4%)	

Chi-square test, observed difference was statistically insignificant

DISCUSSION:

Neonatal jaundice is a common clinical problem observed during the first week of life affecting approximately 60% of term and 80% of preterm infants [14]. While majority of these infants recover, in a proportion of infants, jaundice may become severe, progressing to acute bilirubin encephalopathy (ABE) or kernicterus with a substantial risk of neonatal mortality [15]. Phototherapy for neonatal jaundice is a common treatment in neonatal medicine and is used to prevent the neurotoxic effects of bilirubin. It is a cost-effective and non-invasive treatment opted as a first line in most of the infants with neonatal jaundice. However, there is evidence that its use is associated with hypocalcaemia which is a serious concern [15-16]. The reported frequency of phototherapy induced hypocalcemia varies greatly between the studies ranging from as low as 6% [17] to as high as 80% in Indian population and from 7% to 15% in Irani population. The exact reason for this conflict is not known in the existing

literature. However, the type of fluorescent tube, serum vitamin D, bilirubin levels and also the patient's skin colour might play a role [18]. Owing to the observed variation among various populations and lack of local such local published material, need for the present study was felt. The objective of this study was to determine the frequency of hypocalcaemia after 48 hours of phototherapy in full term infants presenting with neonatal jaundice at a teaching hospital in Punjab [19,20]. It was a descriptive case series conducted at Department of Pediatric Medicine Unit-I, Lahore General Hospital, Lahore over 6 months after the approval of synopsis from 27 January 2016 to 26 July 2016 [21].

This study involved 246 full term neonates of both genders presenting with neonatal jaundice with serum calcium level >8 mg/dl before the start of phototherapy. These patients were followed for the development of hypocalcemia (serum calcium ≤8 mg/dl) [22]. A written informed consent was taken from parents of each patient. In the present study, the age of the patients ranged from 1 day to 12 days with a mean of 6.04±3.50 days [23,24]. A similar mean age of 6.24±2.91 days has been reported previously by Tehrani et al. among Irani neonates receiving phototherapy for neonatal jaundice [25]. Alizadeh-Taheri et al. (6±3 days) [26] and Karamifar et al. (6.7±3.7 days) [27] also reported similar mean age in Irani population. While relatively lower mean age of 4.0±1.38 days has been reported by Tandon et al. in Indian such neonates [28]. There were 149 (60.6%) male and 97 (39.4%) female patients with a male to female ratio of 1.5:1. A similar male predominance was observed previously by Karamifar et al. [13] and Tehrani et al. [29] who reported it to be 1.7:1 and 1.3:1 respectively. However, Srinivasa et al. observed a female predominance instead with a male to female ratio of 1:1.1 [6]. The weight of the neonates ranged from 2 kg to 3 kg with a mean of 2.64±0.23 kg. Our observation is in line with that of Tandon et al. (2.15±0.15 Kg) [30,31] and Karamifar et al. (2.08±0.3 Kg) [13]. Alizadeh-Taheri et al. (3.18±0.43Kg) and Tehrani et al. (3.23±3.7 Kg) reported relatively higher mean weight at admission among such neonates in Iran [7,11].

Serum calcium level upon admission ranged from 8.1 mg/dl to 12.0 mg/dl with a mean of 9.04±0.93 mg/dl. A similar mean serum calcium level at admission has been reported previously by Alizadeh-Taheri et al. (9.8±0.8 mg/dl) [11], Tehrani et al. (9.46±0.8 mg/dl) [10] and Karamifar et al. (9.53±0.92 mg/dl) [13] in Irani patients of neonatal jaundice. Majority (69.1%) neonates had serum calcium at admission between 8.1-9 mg/dl followed by 76 (30.9%) neonates whose serum calcium at admission was ≥9 mg/dl. A similar higher frequency of 8.1-9 mg/dl serum calcium group has been reported previously by Arora et al. (72.0%) in Indian such neonates [7]. Mean serum calcium level after 48 hours of phototherapy was 7.69±0.54 mg/dl with a mean decrease of 1.35±0.90 mg/dl. This difference was statistically significant (p=0.000). Our observation equals with that of Tandon et al. who observed mean serum calcium level to be 7.9±1.41 mg/dl after 48 hours of phototherapy [32].

In the present study, 167 (67.9%) neonates developed hypocalcemia. There was no significant difference in the frequency of hypocalcemia across age (p=0.964), gender (p=0.812), weight (p=0.994) and serum calcium at admission (p=0.904). A similar frequency of phototherapy induced hypocalcemia has been reported previously by Yadav et al. in 2012 (66%) in Indian [8] and Medhat in 2006 (75%) in Egyptian [14] neonates with neonatal jaundice. The present study is first of its kind in local population and has found that phototherapy induced hypocalcemia is a frequent complication in neonates with neonatal jaundice which can further complicate the course of disease [33]. Routine screening of serum calcium at admission and during the course of phototherapy is therefore advisable to timely identify and later supplement serum calcium to avoid hypocalcemia with its associated morbidity [34]. The strengths of the present study were its large sample size of 246 cases, strict exclusion criteria and stratification of results for effect modifiers which make the results of the present study more reliable. A very strong limitation to the present study was that we didn't consider the effect of phototherapy induced hypocalcemia on neonatal outcome which needs to be discussed in future studies.

CONCLUSION:

The frequency of hypocalcemia was found to be 67.9% in full term infants with neonatal jaundice undergoing phototherapy. There was no significant difference in the frequency of hypocalcemia across age (p=0.964), gender (p=0.812), weight (p=0.994) and serum calcium level at admission (p=0.904).

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