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A Prospective Study of Vitamin D Levels in Term Neonates with Jaundice Requiring Phototherapy

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ABSTRACT
Physiological jaundice is frequently encountered in the newborn period. Almost all newborn infants have a serum or plasma total bilirubin (TB) level >1 mg dL^{-1} in contrast to normal adults in whom the normal TB level is <1 mg dL^{-1}. In our study newborns requiring phototherapy and newborns not requiring phototherapy were taken into study. A total of 150 babies were considered in the study, of which 68 babies were excluded from the study. Eighty two babies were included in the study. The babies were divided into study group (N = 41) and Controls (N = 41). Socio-economic and demographic data were collected for all babies. Mean serum total bilirubin levels in study group-14.3 mg dL^{-1}, Control group- 13.2 mg dL^{-1}. Mean serum Vitamin D levels in study group-15.48 mg dL^{-1}, Control group-19.92 mg dL^{-1}. Risk factors for Neonatal Hyperbilirubinemia like prematurity, Rh incompatibility, ABO incompatibility, dehydration were excluded. There is significant difference between the two groups in terms of Vitamin D levels ($p = 0.02$). In our study, we found that total bilirubin levels has weak negative correlation with serum Vitamin D levels which is not statistically significant. ($p = 0.3$,$r = 0.1$). However it was found that serum direct bilirubin has a significant relation with serum Vitamin D. There is no significant association between indirect hyperbilirubinaemia and serum vitamin D levels in new borns with jaundice at a level necessitating phototherapy. We conclude that our study needs to be verified by future research.

INTRODUCTION

Approximately 85% of all term newborns and most preterm infants develop clinical jaundice. Also, 6.1% of well term newborns have a peak TB level >12.9 mg dL^{-1}. A TB level >15 mg dL^{-1} is found in 3% of normal term infants[1]. Research in recent years identified vitamin D receptors in cells derived from different tissues such as liver, pancreas, brain and prostate. They are also found on surface of immune cells including lymphocytes and macrophages. The potential extra-osseous effects have also been reported. On the other hand, vitamin D synthesis begins with the effect of solar rays on skin tissue and active vitamin D synthesis takes place with 25-hydroxylation in the liver first and finally 1-hydroxylation in the kidney. In addition, while liver tissue is involved in vitamin D synthesis, it also plays an important role in the conversion of indirect bilirubin into direct bilirubin[2].

The 25-hydroxylation stage, one of the important phases of vitamin D synthesis, takes place in the liver, as does bilirubin conjugation. Bilirubin is the final product of heme catabolism. The enzymes hemeoxygenase and biliverdin reductase play a role in the conversion of heme into bilirubin. The bilirubin that forms is made soluble in water by being conjugated with the catalyser effect of the enzyme uridine di-phosphoglucuronosiltransferase present in the endoplasmic reticulum of the hepatocytes. The conjugated bilirubin is released into the bile canaliculi with active transport[3]. At the same time, the bilirubin has an antioxidant property[4]. Vitamin D and bilirubin have two distinct routes of metabolism yet part of their syntheses is common in the liver and thus they may influence each other's synthesis[5].

MATERIALS AND METHODS

A total of 150 babies were considered in the study, of which 68 babies were excluded from the study. Eighty two babies were included in the study. The babies were divided into study group (N = 41) and Controls (N = 41). Socio-economic and demographic data were collected for all babies. Maternal history, past medical History including Thyroid status, GDM, PIH, APH, was collected. Maternal blood investigations like CBC, Blood group were done. Neonatal Blood investigations like Hb, Hematocrit, WBC, Blood group, CRP were done. The babies of day 4 age were taken into study. Serum total Bilirubin and Serum Vitamin D was analysed on Day 4 of life. Vitamin D levels were analysed by Chemilumiescent immune Assay.

- Subjects with serum Vitamin D3 levels

greater than 20ng dL^{-1} are regarded as normal
15-20ng dL^{-1} are regarded as insufficiency
<15ng dL^{-1} as Deficiency
<5ng dL^{-1} as Severe Deficiency

- Serum total Bilirubin was assessed by Van Den Bergh Test using Diazo dye
- Healthy Term neonates with jaundice requiring phototherapy (12-15mg dL^{-1})
- Control group- Healthy Term Neonates with jaundice (bilirubin <12mg dL^{-1})
- All the data were entered in Excel sheet. Both the groups were compared to identify any significant differences
- It was identified that no significant differences were found between the basic backgrounds of each groups
- Statistical Analysis was done which is presented as below

Sample size: Based on the previous study Mutlu *et al*. According to previous study in comparing the association between Vitamin D and Hyperbilirubinemia where vitamin D in cases = 10.7+/-4.9 and in controls =15.7+/-4.9. The sample size calculation is $n=2(Z_a+Z_{1-b})^2(s^2)$ d

Where Z_a = Standard table value for 95% CI
= 1.96
Z1-b= Standard table values for 80% of CI
= 0.84
s= Standard deviation
= s1-s2/2
= 4.9+4.9/2
= 4.9
d= effect size
Assuming 3% of absolute precision value
$n = 2(1.9+0.84)^2(4.9)^2/3^2$
= 41.3
n = 41

Statistical analysis: The Statistical software SPSS 22.0 was used for the analysis of the data and Microsoft word and Excel have been used to generate graphs, tables etc. Descriptive and Inferential statistical analysis has been carried out in the present study. Results on categorical measurements are presented in Number and Percentage. Results on continuous measurements are presented as Mean and SD Significance is assessed at 5% level of significance. The unpaired t test was used to compare mean Bilirubin and Vitamin D across the groups. Pearson correlation was used to assess correlation between Total Bilirubin, Direct Bilirubin and Vitamin D. Chi-square test was performed to check for association between categorical variables.

RESULTS

There is no significant differences in terms of basic demographic details. All the newborns were considered into study on Day 4 of postanatal life. Hence in both groups age is not significant to compare. There is no significant differences in-terms of gestational age and maternal age between the two

Table 1: Distribution Based on Maternal Anaemia

	Study Group		Control Group	
Maternal Anemia	No.	Percentage	No.	Percentage
Absent	14	34.1	10	24.4
Present	27	65.9	31	75.6
TOTAL	41	100	41	100

Chi-Square-0.5;p=0.4

Table 2: maternal blood group distribution

	Study Group		Control Group	
Blood Distribution	No.	Percentage	No.	Percentage
A Negative	1	2.4	10	24.4
A Positive	10	24.4	2	4.8
AB Positive	3	7.3	2	4.9
AB Negative	0	0	1	2.4
B Positive	10	24.4	14	34.1
O Positive	17	41.5	12	29.3
Total	41	100.0	41	100

Table 3: Distribution of newborn blood groups

	Study Group		Control Group	
Blood group	No.	Percentage	No.	Percentage
A Positive	7	17.1	9	22.0
AB Positive	2	4.9	5	12.2
B Negative	1	2.4	1	2.4
B Positive	7	17.1	12	29.3
O Positive	24	58.5	12	29.3
O Negative	0	0	1	2.4
AB Negative	0	0	1	2.4
Grand Total	41	100.0	41	100.0

Table 4: comparison of clinical parameters across the groups

	study group	control group		
	mean	SD	mean	SD
Gestational Age	38.7	1.2	38.6	1.2
Mother's Age	24.5	3.2	24.4	4.0
Maternal Hb	10.5	0.7	10.3	0.9
Birth wt	2.8	0.2	2.9	0.4
Admission wt	2.7	0.2	2.8	0.4
Neonatal Hb	17.6	2.5	17.9	2.8
Hematocrit	45.6	5.8	47.5	5.0
WBC	12162.2	9507.7	10782.9	3895.5
Platelet Count	268707.3	78448.8	266975.6	76668.6

Table 5: Correlation between total bilirubin, direct bilirubin and vitamin d among study group

		Vitamin D	DB
TB	Pearson Correlation	-.158	.339
	Sig. (2-tailed)	.323	.030
	N	41	41
DB	Pearson Correlation	.339	
	Sig. (2-tailed)	.030	
	N	41	

Correlation is significant at the 0.05 level (2-tailed).

Table 6: Comparison of mean tb, db and vitamin d between study and control group

	GRP	Mean	Std. Deviation	T	P
Tb	study	14.3	.71	0.3	0.6
	control	13.2	16.96		
Db	study	.82	.45	2.8	0.005
	control	.57	.33		
Vitamind	study	15.48	7.45	-2.2	0.02
	control	19.92	9.89		

groups. There was no significant association between the order of pregnancy and hyperbilirubinemia in newborns. (p = 0.06). Maternal history with risk factors for Neonatal Hyperbilirubinemia including PIH, GDM, APH, Thyroid disorders, Oligohydrmnios, Fever, PROM were not significant. Neonatal risk factors like Isoimmunisation, Sepsis, breast feeding were not significant. Many other parameters like age, birth weight, admission weight, neonatal hemoglobin, Total leukocyte count, platelets have statistically comparable mean values. There is no significant difference between two groups in terms of order of pregnanacy (p = 0.6). Significant association found between Mode of delivery and study groups.

Many other parameters like vitals, age, gestational age, birth weight, admission weight, neonatal hemoglobin, BIND and Sepsis have statistically comparable mean values.

- Neonatal risk factors like Isoimmunisation, Sepsis were not significantly between the groups
- Neonatal hemoglobin, Total leukocyte count, platelets have statistically comparable mean values

All the mean values of renal parameters of either groups are in normal range. There is no significant difference between the two groups.

- There is a weak negative correlation between TB and Vitamin D (r=-0.15, p=0.3)
- There is a positive correlation between TB and DB and the correlation is found to be statistically significant (r =0.33, p=0.03)
- There is a positive correlation between DB and Vitamin D and the correlation is found to be statistically significant (r = 0.33, p=0.03)

DISCUSSIONS

In addition to vitamin D effect on bone metabolism, it has also been shown to have anti-proliferative, prodifferentiative and immunomodulatory effects[6]. Vitamin D has also been reported to have antioxidant properties. Vitamin D3 (cholecalciferol) and its active metabolite 1,25 dihydro xycholecalciferol, as well as vitamin D2 (ergocalciferol) and 7-dehydrocholesterol (pro-vitamin D3) all inhibit iron-dependent liposomal lipid peroxidation[7]. Jaundice is less seen in infants that have exposure to sunlight[8]. This supports that there may be a relationship between vitamin D and jaundice. In Vitamin D deficiency, Serum Calcium may be low or normal, Phosphate levels low or normal, ALP normal or high. In a study done in Poland from 1981-2011 to analyse the correlation between calcaemia and vitamin D status revealed that in more than 80% of patients with 25(OH)D <10 ng mL^{-1} (severe vitamin D deficiency) Ca levels were within reference range (2.25-2.65 mmol L^{-1}). On the other hand, in subgroup with hypocalcaemia (Ca <2.25 mmol L^{-1}) severe vitamin D deficiency was not a serious problem. Only 11% of hypocalcaemic patients revealed 25(OH)D concentration values lower than 20 ng mL^{-1}, whereas 39% of these patients demonstrated 25(OH)D below 30 ng mL^{-1}[9].

In another study done in Australia in 2020 revealed that Vitamin D deficiency is prevalent in

neonates of high-risk mothers but the risk of hypocalcaemia due to vitamin D deficiency at birth is low[10]. In our study there was no difference between study group and control group in terms of type of feeding and religion. Mothers and babies did not receive regular Vitamin D supplement and neonatal exposure to sunlight.

In our study we included all term babies in both groups (mean gestational age = 38.4 weeks) and similar birth weight (2.8kg) and admission weight (2.7kg). In our study, it was observed that all the basic sociodemographic details like age, religion and geographical distribution of mothers were not significantly different.All the laboratorical values of newborn are comparable between the groups.

In our study we also found that mean Vitamin D levels of newborns of both study group and control group were in deficiency range, however their difference between the two was statistically significant. Similar results were found in J.A. Bhat et al, but the Vitamin D levels were in normal range in control group. In our study it was suggested that there is weakly negative correlation between the Vitamin D and neonatal Hyperbilirunemia. There is insufficient evidence to conclude that there is a significant linear relationship between. However According to Mutlu et al, there is an association between indirect hyper bilirubinaemia and serum vitamin D levels in new borns with jaundice at a level necessitating phototherapy. Another study done Iran, S.M.H. Aletayeb *et al*, Newborn vitamin D levels were significantly lower in jaundiced cases compared with those in the non-jaundiced healthy groups.

According to Bhat *et al*. term healthy newborn having hyperbilirubinemia, with serum bilirubin levels out of the physiological range, have significantly low vitamin D levels and show a statistically negatively correlation with neonatal hyperbilirubinemiawhich was statistically insignificant. However, Mehrpisheh et al. BMC Pediatrics (2018) 18:178 states that the results suggest the lack of a relationship between vitamin D levels and NIH. Fatemeh Haji Ebrahim Tehrani et al, a study done at Shahed University, Tehran, Iran, shows that the mean of serum Vitamin D significantly increased after phototherapy (before 17.44 mg/dL and after 21.77 mg dL^{-1}) (P <0.0001). Weinert *et al*., a study in Brazil shows that there is no clinical significance of jaundice in relation to Vitamin D deficiency.

CONCLUSION

Vitamin D deficiency is a prevalent condition in the india scenario. In our study we observed the inceidence of Vitamin D deficiency as 59% in control group and 76% in study group. Mean values were observed as 19.92 ng dL^{-1} and 15.48 ng dL^{-1} in control and study group respectively. In our study we considered to study the relationship of serum Vitamin D with serum Total bilirubin. As stated earlier some studies postulate a positive correlation between the two. In our study it was suggested that there is weakly negative correlation between the Vitamin D and neonatal Hyperbilirunemia. There is insufficient evidence to conclude that there is a significant linear relationship between.

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