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STUDY OF VITAMIN D DEFICIENCY IN INFANTS IN PEDIATRIC ICU

Paediatrics

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ABSTRACT

Background Due to the limited data available in the pediatric population and lack of interventional studies to show that administration of vitamin D indeed improves clinical outcomes, opinion is still divided as to whether it is just an innocent bystander or a marker of severe disease. **Objectives of the study** To study the prevalence of vitamin D deficiency in infants admitted in Pediatric ICU 2) To study the risk factors associated with vitamin D deficiency and correlation with primary illness with which the child is admitted in PICU. 3) To study association with duration of ICU stay and vitamin D deficiency. **Design and setting** An Observational study conducted from February 2015 to June 2016 in PICU, Jaipur Golden Hospital, Rohini, New Delhi. A total of 222 infants, 161 males and 61 female infants admitted in PICU during study period were recruited in the study as per inclusion and exclusion criteria.**Measurement** Serum 25-(OH) vitamin D levels **Results** Prevalence of vitamin D deficiency in our study was 61.7% (137/222). Even though maximum number of vitamin D deficient infants include <6 months infants (83/137), males (104/137) and Term infants (99/137), no statistically significant correlation was found between vitamin D deficiency and Age, Gender, Gestation at birth respectively. A statistically significant correlation was found between **Hypovitaminosis D** and **feeding pattern** of the child with P value of **0.003.** A statistically significant correlation was found when EBF infants were compared to mixed feeding and top feeding infants with p values of **0.001** and **0.008** respectively**.** Out of 222 infants, 86 infants had 1-5 days of ICU stay, out of which 38 (44.2%) are vitamin D deficient and 98 infants had a stay of 6-10 days out of which 72 (73.5%) are vitamin D deficient and 38 infants had 11-16 days stay in PICU out of which 27 (71.1%) are vitamin D deficient. A statistically significant correlation was found between **length of stay** in vitamin D deficient infants compared to vitamin D sufficient infants with a p value of **0.001.** Mean difference in length of stay is **1.71 ± 0.457 days.** No significant correlation was found between primary illness and vitamin D deficiency. **Conclusion** High prevalence of vitamin D deficiency was observed in our study population. Exclusive breast feeding was identified as significant risk factor for Vitamin D deficiency and prior supplementation was found to be beneficial.

KEYWORDS

Vitamin D deficiency, Infants, Prevalence, Duration of PICU stay.

INTRODUCTION

Vitamin-D, popularly known as the Sunshine Vitamin, is the only nutrient that could be gained by the body without intake of any nutrition. Till a few decades ago, it was related only to bone health and calcium homeostasis. Now it is better known as a Hormonal vitamin rather than a simple component of our daily bread. Medical and nonmedical fraternities across the world have started to realize its potential role in health & disease.(1-4)

Hypovitaminosis D is a risk factor for many diseases right from conception throughout lifespan. In fact, more and more scientific evidence linking vitamin D to various chronic diseases in children and adults is emerging.

Vitamin D deficiency is considered to be the most common nutritional deficiency (5) Recent data indicates that vitamin D deficiency is pandemic, even the healthy and the young are not spared (1) High prevalence rates are reported in otherwise healthy infants, children and adolescents and also from diverse countries around the world including India (6).

Vitamin D deficiency in India is common due to several reasons:

1. Changing food fads and food habits contribute to low dietary calcium and vitamin D intake (6).
2. High fibre diet & exclusive vegetarian diet contain phosphates and phytates which can deplete vitamin D stores and increase calcium requirement (6).
3. Genetic factors like having increased 25, 24- hydroxylase which degrades 25(OH)D to inactive metabolites (7).
4. With modernization, the number of hours spent outdoor have decreased thereby preventing adequate sun exposure. This is particularly true in the urban Indians.(8)
5. Increased air pollution can hamper the ultra violet rays to adequately synthesize vitamin D in the skin (9).
6. Repeated and unplanned, unspaced pregnancies in dietary deficient patients can aggravate vitamin D deficiency in the mother and the fetus (7).
7. Harsh weather conditions do not permit people to have adequate sunlight exposure (6).

Vitamin D deficiency can be easily diagnosed in the presence of clinical features of rickets. But clinical rickets is a late feature and it represents only the tip of the iceberg. Clinical features other than those related to bone malformation appear at an early stage of the deficiency. Improved understanding of these detrimental effects of insufficient vitamin D, which appear well before rickets, led to a growing interest in the insufficiency. So diagnosing this pre rachitic, subclinical vitamin D deficiency is important for non skeletal health benefits as well as to prevent the morbid bone deformities (10).

Among the population, newborns have less vitamin D stores and are dependent on breast milk, sunlight or supplements as sources of vitamin D in the first few months of life. Vitamin D deficiency is common in infancy due to several factors such as decreased dietary intake, decreased cutaneous synthesis (because of cultural and religious practices, seasonal variation, less exposure to sunlight, increase in pigmentation) , increasing rate of exclusive breast feeding by the mothers being themselves deficient in vitamin D (11,12)

Observational studies suggest that correction of vitamin D deficiency lowers the risk of infections and cardiovascular diseases (13); improves bone health, muscle function and exercise performance; improves fetal health; and have a positive effect on long latency diseases like autoimmune diseases and cancers (14-17). But larger studies are needed before any recommendation for its use can be made.

Though the evidence, about the non-skeletal effects of Vitamin D and the pre-rachitic detrimental features of its deficiency, is growing day by day still there is need for more studies before the routine supplementation could be strongly recommended. So, we have taken up this cross-sectional study to measure the prevalence of vitamin D deficiency and its association with the primary illness in critically ill infants admitted in our PICU.

MATERIALS AND METHODS

Study Design

This is a Prospective Observational study conducted in the Pediatric Intensive Care Unit at Jaipur Golden Hospital. Infants are recruited in the study according to the Inclusion and Exclusion criteria as mentioned below.

Place Of Study

This study was conducted in PICU of JAIPUR GOLDEN HOSPITAL, Rohini, New Delhi. The hospital is a 270-bedded Tertiary Care Referral Centre. The Department of Pediatrics and Neonatology runs three well equipped ICUs (2NICUs and 1 PICU).

The Department is well-versed with round the clock Laboratory services, Blood bank, Radiology, Pediatric Surgery and Pediatric sub-speciality Departments.

Duration Of Study
The study was conducted from February 2015 to June 2016.

Sample Size
Previously researches have performed studies on prevalence of vitamin D deficiency in infants admitted in Paediatric ICU. The prevalence found in articles ranges 50% to 95%. Therefore, assuming (p)=60% as the prevalence of vitamin D deficiency in infants and 7% margin of error, the minimum required sample size at 5% level of significance is 200 patients.

Formula used was

$$n = \frac{Z^2_{\alpha} pq}{d^2}$$

where *p* is the observed prevalence of vitamin D deficiency
$q = 1 - p$
d is the margin of error

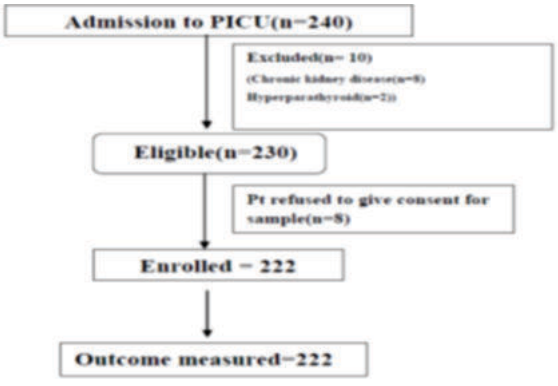
Statistical methods used
Descriptive statistics was analyzed with SPSS version 17.0 software. Continuous variables are presented as mean ± SD. Categorical variables are expressed as frequencies and percentages. The Pearson's chi-square test or the chi-square test of association was used to determine if there is a relationship between Vitamin D and various parameters. P<0.05 was considered statistically significant.

Inclusion Criteria
All infants admitted in PICU of JGH during the study period.

Exclusion Criteria
- Chronic Renal Failure Cases
- Known cases of parathyroid disorders

RESULTS AND DISCUSSION :
A total of the two hundred and twenty two infants were recruited in the study as per inclusion & exclusion criteria during the study period. Serum 25-OH Vitamin D levels of all infants admitted in PICU was measured at the time of admission.

Followings results were obtained.



Comparison of demographic and clinical variables between vitamin D deficient and 'not deficient' groups

Variable	n(study population)	n=137(Vit D deficient)	n=85(Normal vit D levels)	P value
Age				
1- 6 months	133	83	50	0.795
7-12 months	89	54	35	
Gender				
Males	161	104	57	0.151
Females	61	33	28	
Gestational age				
Term	168	99	69	0.132
Preterm	54	38	16	
Mode of delivery				
LSCS	131	78	53	0.425
NVD	91	59	32	
Feeding history				
EBM	77	59	18	0.008
Top feed	78	44	34	
Mix feed	67	34	33	
Prior supplementation				
Yes	112	59	53	0.014
No	110	78	32	
Primary illness				
CNS	26	19	7	0.205
CVS	16	8	8	0.317
GIT	61	35	26	0.413
RS	56	35	21	0.888
RESP/GIT	2	2	0	0.525
CVS/RS	4	4	0	0.301
OTHERS	57	34	23	0.710
Length of stay				<0.001
1-5 days	86	38	48	
6-10 days	98	72	26	
11-15 days	38	27	11	
Mean SD		7.68±3.31 days	5.97±3.29 days	<0.001

A. Prevalence Of Vitamin D Deficeincy :
Out of the total 222 infants included in the study, 137 were found to have Vitamin D deficiency at the time of admission. Prevalence in our study is 61.7%.

Mean average value of vitamin D in the study population is 19.65 ng/mL with a SD of 16.66 & median value is 8.1 ng/mL.

Range of vitamin D levels observed in our study is 8.1-86.2 ng/ml.

vit D level	Frequency	%
Deficient (<20ng/mL)	137	61.7%
Sufficient (>20nh/mL)	85	38.3%
Total Subjects	222	100%
Mean ± SD	19.65 ± 16.66	
Median	8.1 ng/mL	
Range of vit D levels	8.1 - 86.2 ng/mL	

Prevalence of vitamin D deficiency in our PICU infants was found to be 61.7% (137/222), consistent with other studies .

In a case control study conducted by **Kiran B. Hebbar** (2014), it was found that 60% of the cases were vitamin D insufficient against less than 1/3 of the controls who were found to have Vitamin D insufficiency. (P value< 0.0001)(23). **Lodha R (**2014**)** reported prevalence of 71.43% in critically ill children with 95% CI: 64.2, 78.6%)(24).

Ponnarmeni S (2013) reported high prevalence among critically ill children with sepsis compared to healthy controls (50.8% v/s 40.2%, P Value 0.04) (25)

McNallyet al in 2012 reported prevalence of 69% in critically ill children & he mentioned that lower levels were associated with hypocalcemia, catecholamine utilization, and significant fluid bolus administration (21).

Higher percentage of prevalence than that of our study was reported by Sankar et al, Satish kumar shah et al and Prasad S et al. and others. **Sankar et al** in 2016 reported prevalence of Vitamin D deficient children as 74 % in PICU admitted children (26).

Satish Kumar Shah et al in 2016 concluded that Vitamin D deficiency and hypocalcemia were observed in 125 (83.1%) at admission(27).

Prasad S et al in 2015 reported prevalence of Vitamin D deficiency in 2months to 12 year old children as 83.8% (28).

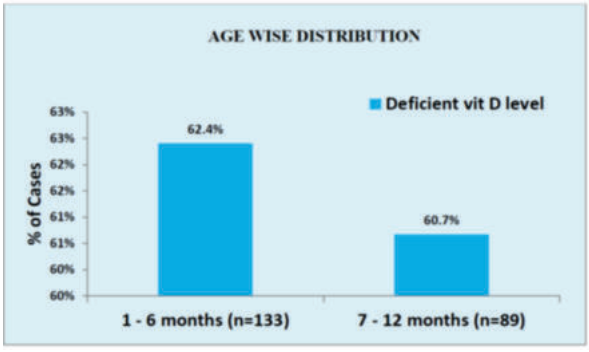
Azim et al, **(2013)** reported prevalence of 80.4% in critically ill children as a consequence of vitamin D deficiency among 158 critically ill ICU patients.(20). The high prevalence reported in these studies might be because they included pediatric population from 0.5-12 yrs where as our study included only infants who are routinely supplemented with vitamin D.

A lower prevalence than that of our study was reported by **Ebenezer K, C Rey, Rippel C** as 40.3%, 29.5%, 34.5% respectively**. Ebenezer K et al** in 2016 reported that Vitamin D deficiency was seen in 40.3 % of the critically ill children (19). **C Rey et al 2014** has reported a high incidence of vitamin D in critically ill children(29). **Rippel C et al** in 2012 reported prevalence of hypovitaminosis D as 34.5 %(18).

S no	Year of study	Authors	Prevalence
1	2016	Present study	61.7%
2	2016	Shankar	74%
3	2016	Satish kumar shah	83%
4	2016	Ebnezer K	40.3%
5	2015	Prasad S	83.3%
6	2014	Kiran B Hebbar	60%
7	2014	C Rey	29.5%
8	2014	Ayuloet al	28%
9	2013	Azim et al	80.4%
10	2013	Poonarmeni S	50.8%
11	2012	Mc nally	69%
12	2012	Rippel C	34.5%

B. Distribution According To Age:
Out of the 222 infants included in the study, infants of the age group 1-6 months formed the major chunk of 133(59.9%) followed by 7-12 months group with 89 (40.1%). Out Of them vitamin D deficiency infants account to be 83(62.4%), 54(60.7%) respectively.

There is no statistically significant correlation between Age distribution and hypovitaminosis D (P value 0.795).



Study conducted by **C Rey** (2014) et al could not found significant relation between age group distribution and vitamin D deficiency(29).

However, **Manal kassab RN et al** (2016) reported significant higher prevalence in infants less than 6 months old compared with older infants (7–12 months of age)(30). This could be due to selection of infants as they included only breast fed babies where as we included top fed and mix fed infants along with exclusively breast fed infants.

C. Distribution According To Gender:
Out of the 222 infants enrolled in the study 61 (27.5%) were females and 161 (72.5%) were males. Out of the 137 vitamin D deficient infants, 33 (24.1%) were females and 104 (75.9%) were males.

The higher percentage of vitamin D deficiency in males might be due to higher percentage of 26admission of males in our PICU during the study period. There is no statistically significant correlation between gender and vitamin D deficiency.

Sankar et al (2016)(26) & **Korchia G et al** (2013)(31) also reported no such correlation.

Contrary to this, **Jaishree vasudevan et al** (2014) also reported that female children to be 1.9 times more at risk of having vitamin D deficiency when compared to males (95% CI 1.3 to 4.0)(32). **Abdul-Razzak et al**, (2011) found more prevalence in female infants compared to male infants {odds ratio of 2.78 (CI = 1.09–7.14)} (33). The higher prevalence of Vitamin D deficiency in males in our study can be attributed to higher number of male admissions as compared to the females.

D. Distribution According To Gestational Age
Out of the 222 infants in the study, 168 (75.7%) were Term and the remaining 54 (24.3%) were Preterm. Out of 137 vitamin D deficient infants, 99 (72.3%) were term and 38 (27.7%) were Preterm.

There was no statistical significant correlation between Hypovitaminosis D and gestation at birth found in our study (P value 0.132).

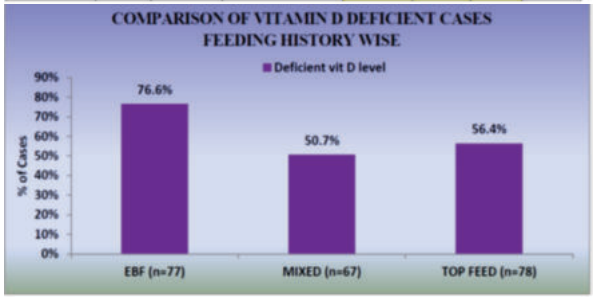
Study done by **Minoo Fallahi et al** (2016) also did not find statistical significance between gestational age at birth and risk of hypovitaminosis D(34).

E. Feeding Pattern
Out of 222 infants in our study , 77 (34.7%) were breast fed, 78 (35.1%) were top fed, 67 (30.2%) were mix fed. Out of them 59 (76.6%), 44 (56.4%) and 34 (50.7%) were vitamin D deficient respectively.

A statistically significant correlation was found between hypovitaminosis D and feeding pattern of the child with **p value of 0.003.**

A statistical`ly significant correlation was found when EBF infants were compared to mixed fed and top fed infants with p values of **0.001 and 0.008** respectively.

Feeding history	Total cases	No.of vit D deficient cases		P Value	EBF vs Mixed	EBF vs Top Feed	Mixed vs Top Feed
		n	%				
EBF	77	59	76.6%	0.003	0.001	0.008	0.495
MIXED	67	34	50.7%				
TOP FEED	78	44	56.4%				
Total	222	137	61.7%				



Manal kassab RN et al (2016) reported more prevalence of vitamin D deficiency among 1-6 month infants who were predominantly breast fed(30). Similarly, **Abdul-Razzak et al**. in 2011 also reported exclusive breast feeding as an independent risk factor for vitamin D deficiency in their study(33).

Seth A et al (2009) found high prevalence of vitamin D deficiency in lactating mothers and their exclusively breast fed infants and concluded that infants born to mothers with Hypovitaminosis D had 3.8 times higher risk of developing Hypovitaminosis D as compared to those born to mothers with normal vitamin D levels.(36)

Kreiter SR (2000), **Daaboul J** (1997) reported increased risk of vitamin D deficiency in exclusively breastfed but who do not receive supplemental vitamin D.(37)(38)
V Jain(2011) and colleagues from New Delhi have reported their significant observations on the prevalence of vitamin D deficiency and insufficiency [serum 25 hydroxy vitamin D (25OHD) < 15 ng/ml and 15-20 ng/ml, respectively] among healthy term breastfed 3 month-old infants and their mothers.(35)

All these studies indicate a significant association between infant feeding practices and vitamin D status was found as a contributing factor of vitamin D deficiency, as infants who were exclusively breastfed had higher risk for vitamin D deficiency than those who were bottle fed.

S No	Year of study	Study	High prevalence
1	2016	Our study	EBF
2	2016	Manalkassab RN et al	EBF
3	2011	Abdul-Razzak et al.	EBF
4	2011	V Jain	EBF
5	2009	Seth A et al	EBF
6	2000	Kreiter SR	EBF
7	1997	Daaboul J	EBF

F. Assosiation With Primary Illness:
Out of 222 infants in our study 26 (11.7%) had CNS dysfunction, 56 (25.2%) had Respiratory illness, 16 (7.2%) had CVS dysfunction, 61 (27.4%) had GI illness, 6 (2.7%) infants presented with mixed etiology and 57 (25.6%) had other features as primary illness.

Out of 137 Vitamin D deficient infants 19 (13.8%) had CNS dysfunction, 35 (25.5%) had Respiratory illness, 8 (5.8%) had CVS dysfunction, 35 (25.5%) had GI illness, 6 (4.3%) infants presented with mixed etiology and 34 (24.8%) had other features as primary illness.

Similarly**, Sankar et al** (2016)(26) did not find any correlation of vitamin D deficiency and presentation of primary illness however, **Rey C et al** (2014) found significant correlation with respiratory (P value-0.042) and metabolic diseases (P value-0.004) in vitamin D deficient cases.(29)

Clinical features	Total cases	No. of vit D deficient cases		P Value
		n	%	
CNS	26	19	73.1%	0.205
CVS	16	8	50.0%	0.317
RS	56	35	62.5%	0.888
GIT	61	35	57.4%	0.413
CVS/RS	4	4	100.0%	0.301
RESP/GIT	2	2	100.0%	0.525
OTHERS	57	34	59.6%	0.710

G. Length Of Stay

Out of 222 infants in our study 86 infants (38.7%) had 1-5 days, 98 infants (44.1%) had 6-10 days and 38 infants (32.4%) had 11-16 days stay in PICU.

Out of 137 infants in our study 38 infants (44.2%) had 1-5 days, 72 infants (73.5%) had 6-10 days and 27 infants (71.1%) had 11-16 days stay in PICU. A statistically significant correlation was found between length of stay in vitamin D deficient infants compared to optimal level of vitamin D infants with a p value of **0.001.**

Mean difference in length of stay is **1.71 ± 0.45 days**

Length of stay	Total cases	No.of vit D deficient cases		P Value
		n	%	
1 - 5 days	86	38	44.2%	<0.001
6 - 10 days	98	72	73.5%	
11 - 16 days	38	27	71.1%	
Total	222	137	61.7%	

	Deficient vit D level (n=137)	No Deficient vit D level (n=85)	Mean Difference ± SD	P Value
	Mean ± SD	Mean ± SD		
Length of stay (days)	7.68 ± 3.31	5.97 ± 3.29	1.71 ± 0.457	<0.001

Sankar et al (2016) (26)study found significant association between length of ICU stay and vitamin D deficiency with a adjusted mean difference **3.5 days (95% CI=0.50–6.53;*p* = 0.024)**.

McNally JD et al (2012) found an association of vitamin D deficiency with longer length of stay and concluded Vitamin D deficiency as independent risk factor associated with a longer PICU length of stay **(+1.92 days, P=0.03). (21)**

H. Effectiveness Of Supplementation:

Out of 222 infants in the study 110 infants took prior vitamin D therapy and 112 infants did not took prior vitamin D supplements.

A statistically significant correlation was found in between patients who took prior therapy and vitamin D levels at the time of admission with a **P value of 0.014**.

Infants with prior supplementation of vitamin D has less vitamin D deficiency in our study.

Prior supplementation	Total cases	No.of vit D deficient cases		P Value
		n	%	
No	112	78	69.6%	0.014
Yes	110	59	53.6%	
Total	222	137	61.7%	

In the Clinical report published by **Wagner CL** (2010), oral vitamin D3 supplementation as an oil emulsion has been shown to be associated with significant and sustained increases in 25 (OH) D from baseline in fully breastfeeding infants through 7 months(22) . **Korchia G** (2013) recommended routine supplementation of vitamin D in more than 1 year age group also(31).

CONCLUSIONS

- Out of 222 infants under the study 137 (61.7%) infants were diagnosed to have Vitamin D deficiency.
- Exclusive breast feeding was found to be an independent risk factor for vitamin D deficiency from our study ***(P value-0.003).***
- A statistically significant difference was found in vitamin D levels in infants with and without prior supplementation ***(P value-0.014).***
- Prior routine supplementation with vitamin D was found to be beneficial.
- A statistically significant increase in length of hospital stay (1.71±0.45 days) was observed in vitamin D deficient infants ***(P Value of <0.001)***
- No statistically significant correlation was found between Hypovitaminosis D in infants and age, gender and gestation of birth.

Recommendations :

1. To check vitamin D levels for every patient admitted in PICU with any medical illness as Hypovitaminosis D is common especially in critically ill children.
2. Vitamin D deficiency to be treated accordingly at the earliest.
3. To initiate vitamin D supplementation at the time of discharge of newborn.

Vitamin D deficiency in infants can be prevented by the following measures:

a. Supplementing vitamin D to all pregnant and lactating mothers.
b. Supplementing vitamin D to all infants.
c. Exposing pregnant and lactating women and their infants to sufficient amount of sunlight

Limitations Of Our Study

1. Study could be done with large sample size and population could be recruited from different centers so as to add more evidence to the subject of discussion.
2. The strength of association between low levels of serum alkaline phosphatase and vitamin D was not checked in our study due to cost constrains.
3. Association of mortality with vitamin D could not be analyzed from our study because of lesser sample size.

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