Title: Vitamin D levels of the term Small for date newborns at birth and at 3 month of age after vitamin D supplementation with 2 different doses 400IU v/s 800IU - A Randomized control trial

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Abstract

Introduction: Daily supplementation of vitamin D seems to be the most appropriate way to prevent its deficiency and its manifestations. Many studies have suggested Vitamin D Deficiency in New born, but we do not have any standard guidelines for Vitamin D supplementation in these patients. The objective was to study the effect of vitamin D supplementation in a dose of 400IU v/s 800IU on vitamin D status of healthy small for date term newborn babies who are exclusively breast fed for 3 months.

Methods: In this randomized trial healthy term small for date babies (n=44 in both groups) who are exclusively breast fed till 3 months were given oral vitamin 400 IU in Group A and 800 IU in Group B. Serum Vitamin D was estimated at birth and at 3 months of age. Vitamin D deficiency was defined as <20ng/ml, Insufficiency as 20-30ng/ml and >30ng as Normal value.

Results: Of the total of 50 babies enrolled in both groups 6 babies were excluded due to non compliance and dropouts. The Vitamin D levels were comparable at birth 17.82±6.5ng/ml in group A and 17.54±7.4ng/ml in Group B. At 3 months the Vitamin D level increased to 31.43±6.6ng/ml and 34.06±8.2ng/ml in Group A and Group B respectively. There was no significant difference between the 2 groups (p value 0.101).

Conclusion: Daily Vitamin D supplementation of 400IU seems to be sufficient for small for gestation (SGA) babies who are exclusively breast fed.

Key words: Small for Gestation, Vitamin D deficiency, Supplementation.

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INTRODUCTION

Vitamin D is the essential precursor of 1, 25-hydroxyvitamin D, the steroid hormone required for calcium absorption, bone development and growth in children. During the first 6-8 wk of life, the vitamin D status of infants is determined by the vitamin D levels at birth. Breast milk concentration of vitamin D is low (<20 IU/l) and is inadequate for the needs of the growing infant. Vitamin D in breast milk relates to moother's vitamin D intake, skin pigmentation and sunlight exposure.

Vitamin D deficiency with a resurgence of rickets is increasingly being reported in infants and toddlers from various parts of the world, especially from temperate regions and among African American babies. Rickets and hypocalcemic seizures due to vitamin D deficiency in exclusively breastfed young infants have been recently reported from southern India. There are a few reports of vitamin D deficiency among pregnant women and cord blood of their small for date babies and breastfed young infants from India.

Daily vitamin D supplementation is considered to be the most appropriate way to prevent vitamin D deficiency and its clinical manifestations such as rickets, growth failure, lethargy, or irritability. Guidelines for vitamin D supplementation in the first year of life differ from country to country and have been modified several times during the past decade. The American Academy of Pediatrics recommends a daily intake of 400 IU vitamin D for all infants, children, and adults. On the other hand, the European Society of Pediatric Gastroenterology, Hepatology and Nutrition recommend daily supplementation of 800 to 1000 IU/day for preterm infants in the first months of life. The World Health Organization recommends 400 IU to 1000 IU/day of vitamin D supplementation in low birth weight infants.

Even though many studies in India suggest deficiency of Vitamin D in Newborns, we do not have any standard guidelines for Vitamin D supplementation in these patients. Many studies suggest daily oral supplementation of 400 IU for term babies and 800 IU for pre term babies. The recommended dose of Vitamin D of 400 IU seems to be inadequate to normalize the serum Vitamin D level. The effective dose of Vitamin D to prevent its deficiency is yet to be defined for Indian population. We did a randomized trial comparing two different regimes of oral Vitamin D supplementation (i.e. 400 IU vs. 800IU) on serum vitamin D levels in exclusively breast fed term Smal for date infants at 3 months. To the best of our knowledge no similar study has been done in this part of the country. The main objective of the study is to evaluate the level of Vitamin D in small for date newborns and compare the effect of 800 IU & 400 IU of Vitamin D supplementation on Vitamin d levels.

Material & Methods

SUBJECTS AND SETTING:

We conducted this prospective randomized trial at neonatology unit, department of paediatrics in collaboration with department of endocrinology JNMC, AMU, Aligarh, over a period of two years (September 2015 to September 2017). The subjects included were new born babies who had all the following features like healthy term small for date babies born of normal delivery (gestation period between 37-41 weeks or 259-293 days),
birth weight <2500 grams, who are exclusively breast feed for 3 months and babies who were given daily supplementation of oral vitamin D.

Preterm babies with birth weight <\=2500 grams, liver renal intestinal problems, on medications like Anticonvulsants Glucocorticoids, mothers having any systemic diseases, malignancy were excluded. Gestational age was calculated by using either first day of last menstrual period or modified New Ballard score. Informed written consent was obtained from the parents or legal guardians before enrolment. The study was approved by the Institutes Ethics Committee (JNMC, AMU, Aligarh). The trial has also been registered at Clinical Trial Registry of India (CTRI).

RANDOMIZATION:

Babies in both the groups were randomly assigned to receive two oral doses of Vitamin D at a dose of 400 IU or 800 IU/day. We used computer generated random numbers to allocate infants to one of the study groups with a fixed block size of 4, which was maintained by a colleague not directly involved in this trial. Allocated interventions were kept in a sealed opaque envelope which was opened at the time of randomization. Subjects were allocated to either of the two interventions in order of their enrollment for study.

STATISTICAL ANALYSIS:

The continuous variables were expressed as mean, standard deviation and confidence intervals (95% CI) frequency and range. Independent sample T test was used to compare means of variables of 2 groups of cases. Paired sample T test was used to compare means of 2 variables for a single group (at birth and at 3 months). P value <0.05 was taken as significant. Analysis was performed by intention to treat.

SAMPLE SIZE:

In an earlier study by Natarajan et al, 2014 The prevalence of vitamin D deficiency in 800 IU was significantly lower than the 400 IU group at 40 wks GA (38.1% v/s 66.7%); relative risk of 0.57% , At 3 months (12.5% v/s 35% relative risk :0.36). Assuming an estimate of prevalence of deficiency of 75% in 400 IU group we needed to enroll 35 babies per group to detect a decrease in prevalence of vitamin D deficiency after supplementation with 800 IU /day with a power of 90% and an alpha error of 0.05%. We planned to enroll 50 babies per group to account for loss to follow up.

BRIEF PROCEDURE:

This was a prospective randomized study done over a period of two years (from Sep 2015 to Sep 2017) at Neonatology unit, Dept of Pediatrics in collaboration with Dept of Endocrinology JNMC, AMU, Aligarh. 130 New born SGA Babies after delivery were evaluated for the study of which 100 babies were recruited as per inclusion and exclusion criteria. These 100 Eligible SGA babies were randomly divided into two groups.

Group 1: Babies who received single oral Vitamin D dose 400 IU/day for 3mths
**Group 2:** Babies who received single oral Vitamin D dose 800 IU/day for 3mths

A written and informed consent was taken from Parents/ legal Guardians Detail Antenatal History, Postnatal history and Examination findings were recorded. The birth weight, Length, Head circumference and Chest Circumference was documented at birth. About 3 ml of cord blood sample from the neonates within 48 hours of Delivery and refrigerated at about -20°C in the department after labeling.

The mothers of both the groups are advised to exclusively breast feed the child and inform any deviation from it. They were advised to give daily oral supplementation of 400 IU or 800IU of Vitamin D suspension in the bottle as per the allotment. The drug was Oral Vitamin D suspension (D pura SANOFI India Limited 1ml=800IU). About 0.5ml was administered for the group 1 and 1ml was administered for the group 2. It was administered once daily to infant either directly or mixed with expressed breast milk. Mothers were counseled for exclusive breastfeeding at discharge .Compliance of the Vitamin D intake was checked with return of empty bottles at follow up and telephonically during intervention periods. These infants are followed up upto 3 months when they visit for routine Immunization. Detailed history about any illness and breast feeding were recorded. Repeat examination was done at the follow up and Anthropometric measurements were recorded as done at enrolment. Another 3 ml of venous blood sample was be collected from Infants and refrigerated after labeling till analysis was done.

The laboratory technician conducting the test was unaware of the treatment allocation group and whether the levels were assessed pre- or post-supplementation with vitamin D. All These blood Samples will be subjected for estimation of serum vitamin D level. Total circulating 25(OH)-D were assayed on Access 2 immunoassay system (Beckman Coulter) using chemiluminescence in the laboratory of Rajiv Gandhi Centre for endocrinology, AMU. The assay measures total 25(OH) vitamin D with equimolar measurement of 25(OH) vitamin D2 and 25(OH) vitamin D3

The values of the serum Vitamin D levels was classified as follows:

- **Deficiency:** <20ng/ml
- **Insufficiency:** 20-30ng/ml
- **Sufficiency:** >30ng/ml
- **Toxicity:** >150ng/ml

**RESULTS**

Of the 130 small for Gestation new born babies considered during the study period. After excluding 30 patients on the basis of prespecified criteria, we enrolled 100 SGA babies in the study (Fig 1). Study intervention was initiated in 100 infants after randomization. Of these 6 patients were excluded from the study due to poor compliance, not exclusively breast feed and loss of Follow up. So at the final follow up there were 44 patients in both groups for final analysis.
Clinical Parameters

The ratio of male and females in both the groups is almost equal (Fig 2). The mean age of the mother at delivery in both the groups are comparable and not significant (Fig 3). The mean age of mothers was 24.9±2.9 years in group 1 and 25.7±3.9 years in Group 2.
There was more number of caeseration sections than normal deliveries in Group 1 (23:21) when compared to Group 2 (11:33). This seems to be an incidental finding may need more evaluation (Fig 4).
The clinical parameters at birth and at 3 months are comparable except the Weight and Length which shows statistically significant improvement in group 2 (Table 1 and Table 2).

<table>
<thead>
<tr>
<th></th>
<th>Group 1 (n=44)</th>
<th>Group 2 (n=44)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Weight (in Kgs)</td>
<td>2.14 ± 0.28</td>
<td>2.12 ± 0.29</td>
<td>0.742</td>
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<tr>
<td>Length (in Cms)</td>
<td>46.2 ± 2.9</td>
<td>45.6 ± 3.1</td>
<td>0.351</td>
</tr>
<tr>
<td>Head Circumference (in Cms)</td>
<td>31.4 ± 2.0</td>
<td>31.4 ± 2.4</td>
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</tr>
<tr>
<td>Chest Circumference (in Cms)</td>
<td>29.6 ± 2.2</td>
<td>29.7 ± 2.3</td>
<td>0.835</td>
</tr>
</tbody>
</table>

Table 1. Showing Clinical parameters at Birth
Table 2. Showing Clinical parameters at 3 months

Lab Parameters
On comparison of Vitamin D levels between the groups, the mean Vitamin D level at birth was was 17.81 ± 6.51 and 17.54 ± 7.46 ng/ml in Group 1 and Group 2 respectively. After supplementation of Vitamin D for 3 months The mean Vitamin D level was 31.43 ± 6.60 in Group 1 and 34.06 ± 8.21 in Group 2. On comparing between groups there was some increase in value of Vitamin D but it was not statistically significant (Table 3).

<table>
<thead>
<tr>
<th></th>
<th>Group 1 (n=44)</th>
<th>Group 2 (n=44)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>At Birth</td>
<td>17.81 ± 6.51</td>
<td>17.54 ± 7.46</td>
<td>0.856</td>
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<tr>
<td>At 3 Months</td>
<td>31.43 ± 6.60</td>
<td>34.06 ± 8.21</td>
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</tbody>
</table>

Table 3. Comparing Vitamin D levels in both groups

The status of Vitamin D at birth showed that in Group 1 all patients (n=44) were Deficient or insufficient. Where as in group 2 42 patients were Deficient or insufficient and 2 patients were normal. At 3 months more than 60% of patients had normal Vitamin D level and about 33% had insufficient levels of Vitamin D in both groups. Two patients in both groups were deficient at 3 months.
**DISCUSSION**

This RCT was planned to determine the dose of Vitamin D required in SGA babies. The Vitamin D level was below baseline in both the groups at birth (except 3 babies had normal levels in Group 2). This is comparable to other studies and similar to Pre term babies with Low Vit D levels at birth. This may due to high prevalence of Vitamin D deficiency in the Mothers as suggested in many other studies.

Vitamin D level was significantly improved in at 3 months when compared to at birth in both the groups (Only 2 patients were deficient in both groups at 3 months). This improvement at 3 months could be attributed solely to daily supplementation of vitamin D. All our patients are exclusively breast fed, Breast milk probably is a poor source of vitamin due to the high prevalence of VDD in lactating mothers in India.

Denovo synthesis from sun exposure is not a reliable source of vitamin D in infants. More than one-third of infants in the both groups were still had vitamin D insufficiency at 3 months. This may confer that either 400 or 800 IU of vitamin D daily may be inadequate in achieving sufficient vitamin D levels by 3 months. This finding was probably due to the duration of vitamin D supplementation being not long enough.

**To the best of our knowledge no similar study has been done, As it was done on SGA babies.** Most of the studies are done on Pre term babies. Nataraj et al studied on preterm babies showed decreased prevalence of Vitamin D with 800IU compared to 400IU. They had reported a small risk of Vitamin D toxicity with 800IU. But in our study we did not had any case of Vitamin D toxicity levels. Also we had comparable improvement in Vitamin D levels in both the groups

As with any study we also had few limitations in Our study like Short duration (only 3 months), Limited number of patients, Sun Exposure not accounted and Dietary intake of Breast feeding mother not taken

**CONCLUSION**

In Small for Gestation babies with significant deficiency, daily oral supplementation of 400 IU of Vitamin D seems adequate when compared to 800 IU upto 3 months. However long term study with larger sample may demonstrate the sufficient dose or duration of Vitamin D requirement

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**Contributions:** Conceptualized the study SMA, Finalized the methodology SMA&UF, Collected the data and drafted JN, Planned and conducted statistical analysis. JN, Critically reviewed the article for intellectual content JA. All authors approved the final paper. SMA shall stand as the guarantor for this paper.

<table>
<thead>
<tr>
<th>Sufficiency</th>
<th>28 (63.6%)</th>
<th>3 (6.8%)</th>
<th>27 (61.4%)</th>
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**Table 4.** Showing status of Vitamin D levels in both groups
REFERENCES:


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