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Original Article

Vitamins D Toxicity in Paediatric Age Group: A Retrospective Cross Sectional Study

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Abstract
Background: *Vitamin D is an essential element for body health with its supplements generally administered to prevent vitamin D deficiency. Since these supplements are available in domestic settings, vitamin D toxicity may happen in children.*
Methods: *All children younger than 12 years who presented to the pediatric emergency department of our Hospital with history of ingestion of more than 1500 IU/day of vitamin D supplements were enrolled. Patients' demographic data, on-presentation signs and symptoms, laboratory findings, treatments given, and outcome were evaluated.*
Result: *Fifteen patients presented during the study period. Their mean age was 46.53 ± 10.14 months and 12 (80%) were girls. All of them had unintentionally ingested vitamin D. Mean ingested dose was 406700.7 ± 227400.1 IU. In eight patients (53.3%), 25 hydroxy vitamin D level was more than 100 ng/mL. One patient experienced hypercalcemia while all of them were asymptomatic and discharged without complications. There was no significant difference between patients with and without high levels of 25 OH vitamin D regarding lab tests, toxicity course, and outcome.*
Conclusions: *It seems that acute vitamin D toxicity is a benign condition in our pediatric population which may be due to high prevalence of vitamin D deficiency in India.*
Keywords: *Vitamin D deficiency, Vitamin D toxicity, Paediatric age group.*

Background

Vitamin D is a fat-soluble pro-hormone primarily synthesized in skin by sun-light exposure[1, 2]. Dairy products, fish, and mushrooms may also contain small amounts of vitamin D[3,4]. This vitamin has a crucial role in the health of the musculoskeletal system. Furthermore, vitamin D has beneficial effects on cardiovascular, respiratory, and immune systems[4,5,6,7,8,9,10,11,12]. Due to issues including heavy clothing, air pollution, reduced exposure to direct sunlight, inadequate nutrition, and lack of access to vitamin D-rich food especially among children, vitamin D deficiency is a common health problem in our

country[13]. Thus, consumption of vitamin D containing supplements is encouraged in India during the recent years making them more available for unintentional poisonings in children although the frequency of poisoning with these supplements is still low compared to other poisonings in them[16,17,18,19,20]. Unintentional vitamin D poisoning has been associated with over fortification of milk, adulteration of table sugar, contamination of cooking oil and with use of an over-the-counter supplement by an adult(14,15,37,50). Vitamin D toxicity may also happen as a result of inappropriate dose administration by physicians or errors in manufacturing or unlicensed vitamin D preparations[21,22,23,24,25].

Daily recommended dose of vitamin D supplements is reported to be 400 IU in infants, 600 IU in people younger than 70 years of age, and 800 IU in people over 70[26,27,28,29]. Since studies in this regard are lacking in children, we aimed to assess all children with vitamin D toxicity referring to a tertiary referral center of toxicology during a year.

Methods

In a retrospective descriptive cross-sectional study performed between January 2018 and December 2018, all children younger than 12 years who presented to the pediatric emergency department with the history of vitamin D supplements ingestion of more than 1500 IU in a single occasion were enrolled in this study. Written informed consents were taken from the patients' parents before case enrolment. After taking history and physical examination, blood tests were performed 8 hours post admission.

All demographic data (age, sex, weight, amount of vitamin D ingested), vital signs(blood pressure, heart rate, dehydration signs), symptoms on presentation (nausea, vomiting, abdominal pain, loss of appetite, irritation, headache, constipation, polyuria, polydipsia, fever, and growth retardation), laboratory findings (25 OH vitamin D, serum calcium, phosphate, alkaline phosphatase, urea, creatinine, urine Ca/Cr), treatments given (close observation, hydration, steroid, bisphosphonate), and outcome (recovery, death) were recorded and analyzed.

Results

Fifteen patients presented during the study period. Their mean age was 46.53 ± 10.14 months (range; 24 to 60 months). Twelve patients (80%) were girls (male/female ratio was 1:4).Patients were referred 2.5 ± 1.6 h (range; 0.5 to 5 h) after the vitamin D supplement ingestion. Had all ingested vitamin D supplements unintentionally and accidentally (oral 50000-IU vitamin D pearls). Mean ingested dose was 8.13 ± 4.54 pearls (range; 3 to 18 pearls) or 406700.7 ± 227400.1 IU (range; 150000 to 900000 IU). One patient had serum calcium level of 12.5 mg/dL. She had ingested500000 IU vitamin D. After six hours of hydration, her serum calcium was normal.

Eight (53.3%) cases had 25 OH vitamin D levels more than 100 ng/mL. Mean serum 25-OH vitamin D was 111.3 ± 113.6 (range; 10 ng/mL to 500 ng/mL). There was no significant difference between variables in patient with and without high level of 25-OH vitamin D.

None of them had signs and symptoms of vitamin D intoxication; 46.7% were observed for eight hours and received activated charcoal. Additionally, 53.3% were hospitalized and treated by activated charcoal and fluid therapy. All cases were discharged without any complications. All patients were taking vitamin D regularly. We recommended them to discontinue consumption of vitamin D supplements, keep low-calcium and vitamin D diet, take more liquid for at least one month, and recheck 25-OH vitamin D levels.

Unfortunately, most of the patients did not refer for follow-up checkups.

Discussion

A definite amount of vitamin D ingestion to cause toxicity has not been elucidated. Although maximum tolerable ingested dose is various in different age groups, maximum tolerable and safe dose of vitamin D is 1000 IU/day in infants

younger than 6 months, 1500 IU/day in children older than 6 months, and 10000 IU/day in adults [27, 28, 30,31,32,33].

Vitamin D concentration is measured by 25-hydroxy vitamin D level because it has longer half-life compared to 1,25 OH vitamin D[27, 34]. Although there are different ranges of 25- OH vitamin D levels in several studies, the optimal level of 25-OH vitamin D is 30–100 ng/mL. Based on the normal range provided by the kit manufacturer, 25-OH vitamin D less than 10 ng/mL is deficient, while levels 11–30 ng/ml, 31–100, and over 100 ng/mL are insufficient, sufficient, and vitamin D toxicity, respectively[35]. The most important laboratory findings in vitamin D toxicity are high levels of 25-OH vitamin D and hypercalcemia[34].

Patients with vitamin D toxicity may be asymptomatic or have signs or symptoms including nausea, vomiting, dehydration, abdominal pain, loss of appetite, irritation, headache, constipation, polyuria, polydipsia, fever, and growth retardation. In fact, most of the patients' symptoms are compatible with high serum calcium level[32,36]. Differences between symptoms and laboratory parameters in patients may be related to gastrointestinal absorption, vitamin D binding protein, vitamin D receptor (VDR), vitamin D storage, and diet[21,32,36]. All of our patients were asymptomatic and it might be due to the maximum tolerable intake dose differences in various groups and high prevalence of vit D deficiency among Indian children[32]. Also further studies are needed to be performed in this regard.

Vitamin D deficiency is estimated to be approximately 35% in boys and 65% in girls in Indian pediatric population. Frequency of vitamin D insufficiency is reported to be 31%. It shows that vitamin D deficiency is a critical health problem among Indian children. Recently, the prevalence of vitamin D toxicity has increased because of more availability of its over-the-counter supplements[37,38].

All of our patients were between 24 and 60 months of age and had unintentionally ingested 60000 IU vitamin D capsules. In fact, Vitamin D in are form of small, soft gelatin capsules with 60000 IU of vitamin D3 in each capsule that may be attractive for children. Also, accidental poisoning in this age is more common. In the majority of studies, poisoning happens more frequently in boys, but in this study, poisoning was more common among girls[39,40]. This cannot be generalized to the whole population because our study is only a case series in one center during a year.

We observed all patients for eight hours in emergency room and received activated charcoal. Laboratory tests were checked six hours after vit D consumption. If they had hypercalcemia or 25-OH vit D more than 100 ng/ml, they were hospitalized and treated by activated charcoal and fluid therapy. Their serum calcium was rechecked after four hours of rehydration.

Some studies have demonstrated higher frequencies of symptoms and hypercalcemia in their patients compared to ours reporting hypervitaminosis D in adults and a few children, whereas in this study more than half of our cases (53.3%) had high levels of 25-OH vitamin D and just one had hypercalcemia without any symptoms who was hydrated. It may be due to high prevalence of vitamin D deficiency in Indian children. On the other hand, vitamin D has long half-life because of its lipid solubility which leads to tendency for prolonged hypercalcemia. The absence of symptoms in our patients may be due to early laboratory parameters assessment mandating re-checking of the lab tests in consecutive hours post admission[19, 41,42,43,44,45,46,47].

One patient with hypercalcemia had 25-OH vitamin D level of 10 ng/ml; this might be due to the prozone or hook effect which is a known drawback in vitamin D measurement by Enzyme-linked Immunosorbent Assay (ELISA) method leading to falsely low vit D levels[48,49].

We found only one study that had reported a patient with vitamin D intoxication in Indian children. Faraht reported a 50-day-old girl in

MGMMC & LSK Hosp, Kishanganj, Bihar with respiratory distress and hypotonia who had plasma creatinine of 1.4 mg/dL, BUN of 11 mg/dL, serum calcium level of 18.3 mg/dL, and 25-OH vitamin D of 75 ng/mL which were higher than normal range. It was due to the constant use of premature formula with high dose of vitamin D drop supplement (800 units /day)[50].

Conclusion

Although vitamin D toxicity is a rare poisoning among children, it is a critical condition due to serum calcium disturbances. It seems that acute vitamin D toxicity is a benign condition and has a good prognosis in Indian pediatric population may be due to high prevalence of vitamin D deficiency in Indian children. Due to insufficient and limited studies among children, we need more studies in this regard.

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