jcrpe-2018-0131.R4

Original Article

Comparison of Treatment Regimens for the Management of Severe Hypercalcemia due to Vitamin D Intoxication in Children

Short Title: Treatment Options for Vitamin D Intoxication

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Conflict of interest: None declared

Received: 18-May-2018

Accepted: 23-Oct-2018

What is already known on this topic?

There are various treatment options for hypercalcemia. Pamidronate treatment efficiently lowers serum calcium levels in children with hypercalcemia due to vitamin D intoxication.

What this study adds?

This study is the first to compare first-line treatment options for hypercalcemia due to vitamin D intoxication. Children receiving prednisolone for severe hypercalcemia often requires another type of drug treatment. Pamidronate treatment prevents recurrence of hypercalcemia.

ABSTRACT

Background/Aims: No large study has been conducted so far to compare the efficiencies of prednisolone, alendronate, and pamidronate as first-line treatment in children with hypercalcemia due to vitamin D intoxication. We aimed to perform a multicenter, retrospective study assessing clinical characteristics and treatment results.

Methods: A standard questionnaire was uploaded to an online national database system to collect data of children with hypercalcemia (serum calcium level >10.5 mg/dL) due to vitamin D intoxication (serum 25-hydroxyvitamin D level >150 ng/mL) who were treated in pediatric endocrinology clinics.

Results: Seventy-four children [median age 1.06 (0.65-1.60) years, 45 males (61%) from 11 centers] were included. High-dose vitamin D intake was obvious in 77% of the cases. At diagnosis, serum calcium, phosphorus, ALP, 25-hydroxyvitamin D, and PTH levels were 15±3.2 mg/dl, 5.2±1.2 mg/dL, 268±132 IU/L, 322 (236-454) ng/mL, and 5.5 (3-10.5) pg/mL, respectively. Calcium levels showed only weak correlation with 25-hydroxyvitamin D levels (r_s=0.402, $p<0.001$). Patients were designated into five groups according to the initial specific treatment regimens (hydration-only, prednisolone, alendronate, pamidronate, and combination). Need for another type of specific drug treatment was higher in children who initially received prednisolone ($p<0.001$). Recurrence rate of hypercalcemia was significantly lower in children who were treated with pamidronate ($p=0.02$).

Conclusion: In mild cases, prednisolone or bisphosphonate treatments are not needed. Prednisolone is less effective in the treatment of children with severe hypercalcaemia secondary to vitamin D intoxication and timely implementation of other treatment regimens would be considered.

Key Words: Nutrition, rickets, stoss therapy, steroid, over-the-counter drugs

INTRODUCTION

Vitamin D exerts significant effects on intestinal absorption of calcium and phosphorus, renal reabsorption of calcium, and mineralization of bone. The primary source of vitamin D in humans is its synthesis in skin, which requires adequate sunlight exposure, since vitamin D content of foods are low. Clinical problems associated with vitamin D metabolism mostly include its deficiency and, accordingly, several guidelines exist for its evaluation and management (1-3).

On the other hand, pediatricians are encountering children with mild-to-severe consequences associated with hypercalcemia due to vitamin D intoxication, which is generally defined when serum levels of 25-hydroxyvitamin D are above 100-150 ng/mL (250-375 nmol/L) (1, 3-5). Possible causes include treatment of vitamin D-deficient rickets with single large (6) or pharmacologic daily doses of vitamin D (7), manufacturing errors of over-the-counter drugs (8, 9), parental dosing error (10), overfortification of milk from a home-delivery dairy (11), and prescription of vitamin D without prior measurement of its serum level or definite diagnosis of rickets (12-15). Treatment options for vitamin D intoxication in children currently include discontinuation of vitamin D intake, intravenous hydration with normal saline, furosemide, glucocorticoids, calcitonin, alendronate, pamidronate, and hemodialysis, mainly based on case reports and small studies (4, 5, 7-10, 12, 13, 15-21). We aimed to perform a multicenter, retrospective study to assess clinical characteristics and to compare the results of first-line treatments in the largest number of children reported so far.

METHODS

A standard questionnaire was established in an online national database system (formerly www.favorsci.org, currently http://cedd.saglik-network.org/) to collect clinical and laboratory data of children with hypercalcemia (serum calcium level >10.5 mg/dL) due to vitamin D intoxication [serum 25-hydroxyvitamin D (25(OH)D) level >150 ng/mL] who were treated in pediatric endocrinology clinics. Data were collected by a nominated pediatric endocrinologist per center, who was responsible in registering patients onto the online database. The study protocol was approved by the institutional ethical review board (Dr. Behçet Uz Children's Hospital, 2014-01). Informed consent was not taken from the parents of the patients given the retrospective design of the study, for which the data were extracted from patient files.

Seventy-four patients from 11 tertiary referral centers were enrolled. Participating centers are located in five of the seven geographical regions of Turkey. Forty of the cases were previously reported elsewhere (8, 12, 14, 19, 20). All of the biochemical evaluations were performed in a regular laboratory setting. Hypercalcemia was classified according to following serum calcium levels: mild, 10.5-11.9 mg/dL, moderate 12-14 mg/dL, and severe >14 mg/dL (22). Hypercalciuria was defined when spot urine calcium/creatinine ratio exceeded upper limits of normal calcium excretion for different age groups: ≤6 months of age, >0.8; 7-12 months of age, >0.6; 1-3 years of age, >0.53; 3-5 years of age, > 0,39; 5-7 years of age, >0.28; > 7 years of age, >0.21 (23).

At first, patients were assessed regarding clinical characteristics of vitamin D intoxication. Secondly, patients were designated into groups according to the specific treatment type given in the first 48 hours:

Group 1 (n=25): Oral hydration (OH) or intravenous hydration (IH) ± Furosemide (F)

Group 2 (n=9): IH ± F + Prednisolone

Group 3 (n=11): IH + F + Alendronate

Group 4 (n=21): IH + F + Pamidronate

Group 5 (n=8): IH + F + Prednisolone + Pamidronate ± Alendronate

Primary outcome measures related to treatment efficacy include a) requirement of another specific drug treatment, b) the time to achieve normocalcemia (8.5-10.5 mg/dL), and c) recurrence of hypercalcemia (elevation of calcium levels above >10.5 mg/dL after achievement of normocalcemia). Secondary outcome measures were clinical features of and factors associated with hypercalcemia in children with vitamin D intoxication.

Statistical Analysis

The data were statistically analyzed using computer software SPSS 15.0 (Chicago, Illinois, USA). At first, descriptive analyses were made. Depending on the distribution type of the variables, Pearson or Spearman correlation analysis was performed to detect the factors associated with serum calcium levels at the time of admission. Subsequently, variables associated with serum calcium levels at the time of admission were entered into a multiple linear regression analysis. The least explanatory covariates were consecutively removed from the model in a backward stepwise elimination method. Two separate Kruskal–Wallis tests were performed for comparison of nonparametric numerical data between Groups 1-5 and 2-4. Chi-square or Fisher's exact test (if expected count was below 5 in any of the cells) was used to compare

categorical variables. All data were presented as n (%), mean ± standard deviation or median (25^{th} – 75^{th} percentile), where appropriate. Figures were prepared using GraphPad Prism version 6.01 for Windows, GraphPad Software, La Jolla, California, USA, www.graphpad.com.

RESULTS

The study group included 74 children who were treated for vitamin D intoxication between 2002 and 2014 [median age 1.06 (0.65-1.60) years; range, 0.04-7.38), 45 males (60.8%)] (Table 1). The median number of patients enrolled per center was 4 (2-7) (range, 1-27). Nearly half of patients were younger than 1 year of age (n=33, 44.6%). Twenty-one cases were between 1-2 years of age (39.2%) and 12 (16.2%) subjects were older than 2 years of age. Only seven (9.5%) of the cases had chronic illnesses (hypotonic infant, n=2; developmental dysplasia of the hip, n=2, meningomyelocele, n=1; wheezy infant, n=1; cerebral palsy and epilepsy, n=1). The most common presenting symptoms were vomiting (n=47, 63.5%), loss of appetite (n=35, 47.3%), and constipation (n=27, 36.5%). Five of the patients were asymptomatic and were incidentally found to have mild-to-moderate hypercalcemia (serum calcium levels, 10.8-13 mg/dL).

Approximately three-quarters of the patients (n=57, 77%) had a clear history of high-dose vitamin D intake [median dose, 600,000 (600,000-900,000) units (range, 300,000-5,400,000); median dose per kilogram of body weight, 77,900 (63,800-126,700) units (range, 1,900 - 842,000)]. Majority of the patients (n=40, 70.2%) had received multiple doses of vitamin D on separate days due to accidental overdose by parents or overdose secondary to wrong dose. The median time from first dose of vitamin D to admission was 6.2 (3.6-9.4) weeks (range, 1.5-67.1) (Table 1). Most common reason for vitamin D use was presumptive diagnosis of vitamin D deficiency for nonspecific complaints including delay in walking or eruption of tooth without proper evaluation (n=41, 71.9%). Active rickets was the cause of vitamin D treatment in only three cases (5.3%, serum calcium levels, 10.8, 10.8, and 15 mg/dL, the latter was due to parental dosing error).

Serum calcium, phosphorus, ALP, 25(OH)D, and PTH levels of the study group were as follows: 15±3.2 mg/dL (range, 10.8-23.5), 5.2±1.2 mg/dL (range, 2.48-7.7), 268±132 IU/L (range, 89-652), 322 (236-454) ng/mL (range, 150-1978), 5.5 (3-10.5) pg/mL (range, 0.5-38), respectively (Table 1). Majority of the patients had severe hypercalcemia (>14 mg/dL) (n=43, 58.1%), normal phosphate values [55 out of 69 cases (79.7%) with available data], and suppressed PTH levels [51 out of 65 cases (78.4%) with available data]. At the time of admission, hypercalciuria and nephrocalcinosis and/or nephrolithiasis were found in 46 (81% of 57 cases with available data) and 33 patients (48.5% of 68 cases with available data), respectively.

Serum calcium levels at onset showed moderate correlation with serum parathormone levels (n=65, r_s=-0.588, p<0.001) and weak correlation with serum levels of 25(OH)D (n=74, r_s=0.402, p<0.001), phosphorus (n=69, r=-0.379, p=0.001), ALP (n=66, r=-0.416, p=0.001), vitamin D dose (n=57, r_s=0.383, p=0.004), and vitamin D dose per kilogram of body weight (n=57, r_s=0.483, p<0.001) (Figure 1). On the other hand, spot urine calcium/creatinine ratio (n=57, r=-0.095, p=0.484) and time to admission from first dose of vitamin D (n=57, r=-0.169, p=0.235) showed no correlation with serum calcium levels. In the multiple linear regression analysis including age, vitamin D dose, vitamin D dose per kilogram of body weight, time to admission from first dose of vitamin D, and serum levels of 25(OH)D, the final model contained two baseline variables which were independently associated with serum calcium levels: serum levels of 25(OH)D (B = 0.005 (95%CI 0.02, 0.008), p = 0.001) and vitamin D dose (per 100,000 IU) (B = 0.089 (95%CI 0.023, 0.155), p = 0.009). These two variables together explained 22.6% of the variance of serum calcium levels [R2 = 0.226, F(4) = 9.327, p <0.001].

Patients were designated into five groups according to their specific treatment regimens in the first 48 hours (Table 2). None of the patients had renal failure or required hemodialysis. Vitamin D intake and serum levels of calcium, phosphorus, ALP, 25(OH)D, and parathormone were significantly different among Groups 1-5 (Table 2). We considered that calcium and 25(OH)D levels at the time of admission should be similar among groups to be included in comparison regarding treatment efficiency. Figure 2 shows that only Groups 2, 3, and 4 met this criterion.

The data regarding treatments and outcomes are shown in Table 3. Type and volume of hydration fluid, dose and duration of furosemide treatment were similar among Groups 2, 3, and 4. Six subjects (66.7%) in Group 2 required another specific drug treatment after first 48 hours of admission (one patient, pamidronate and calcitonin on the 10^{th} day; two patients, pamidronate on 3^{rd} and 4^{th} days; three patients, calcitonin) while this was the case for one patient (4.8%) in Group 4 (prednisolone, starting from 6^{th} day of treatment) and none in Group 3 ($p<0.001$). The time to achieve normocalcemia was comparable ($p=0.099$) among Groups 2, 3, and 4. However, recurrence rate of hypercalcemia was significantly lower in Group 4 compared to Groups 2 and 3 [0 (0%), 2 (25%), and 3 (30%), respectively, $p=0.02$]. Sixty-four of 68 subjects with initial renal sonogram were reassessed during follow-up and the ratio of nephrocalcinosis and/or nephrolithiasis was found to be decreased to 28.1% (n=18) after follow-up duration of 1±0.9 years. The distribution was not significantly different among Groups 2, 3, and 4 ($p=0.268$).

DISCUSSION

In our study group, majority of the children were younger than 2 years of age and did not have a preexisting chronic health condition. Their pretreatment serum 25(OH)D levels were unknown. Upper limit of daily dietary intake of vitamin D for healthy children aged <1 and 1-3 years are reported to be 1000-1500 IU and 2000-2500 IU, respectively (1). In the present study, minimum and mean doses of vitamin D intake that resulted with hypercalcemia were 300,000 IU and 1,020,000 IU, respectively. Treatment with 300,000 IU of vitamin D among 3- to 36-month-old subjects with nutritional vitamin D deficiency rickets (n=20) was reported to cause hypercalcemia in two patients (10%) (24). On the other hand, calcium levels did not exceed the upper limit after treatment with the same vitamin D dose in 32 children aged between 3-17 years with vitamin D deficiency/insufficiency (25). In addition, vitamin D dose (both total and per kg of body weight) and serum 25(OH)D levels in our study were only weakly correlated with the degree of hypercalcemia. Dietary calcium intake and existence of conditions leading to vitamin D hypersensitivity might contribute to development and severity of hypercalcemia associated with vitamin D intoxication (1, 3, 26).

Treatment is warranted in vitamin D intoxication, as resulting hypercalcemia is associated with mild-to-severe gastrointestinal, renal, central nervous system, cardiovascular, musculoskeletal, ophthalmological, and skin complications (4). The most common symptoms in our series were related with gastrointestinal system [vomiting (63.5%), loss of appetite (47.3%), and constipation (36.5%)] and the most common finding was nephrocalcinosis and/or nephrolithiasis (48.5%). Various studies demonstrated that majority of vitamin D-induced nephrocalcinosis persist over the years (27, 28). In the present study, nephrocalcinosis and/or nephrolithiasis disappeared in nearly half of the affected cases.

Currently, there are various treatment regimens for vitamin D intoxication. A report including 11 adults from 1948 indicates that the only available methods at that time were elimination of vitamin D, low calcium diet, and oral hydration. The shortest time to achieve normocalcemia was 3-12 weeks in four subjects (36.3%, calcium levels 12.4-14.9 mg/dL) while it took over a year in three cases (27.2%, calcium levels 13.7-14.9 mg/dL) (29). In the present study, similar treatment was applied in Group 1 [median calcium level 11.6 mg/dL (11.1-12.4)]. In addition, intravenous fluids and furosemide were also used. Both additional therapies as well as milder degree of hypercalcemia at presentation resulted in a much shorter duration to reach normocalcemia.

Other treatment regimens for vitamin D intoxication include calcitonin, prednisolone, alendronate, pamidronate, and hemodialysis (3, 4). Glucocorticoids decrease both renal reabsorption and intestinal absorption of calcium. However, their onset of action may take up to 3 days (3). Hatun et al. noted that normocalcemia could not be achieved and bisphosphonates were needed after over one month of glucocorticoid treatment in the two infants with vitamin D intoxication (calcium levels at the time of admission, 14.9 and 18 mg/dL) (16). Sezer et al. reported that four infants with vitamin D intoxication were given prednisolone (2 mg/kg/d) initially and two of them (calcium levels at the time of admission 16.5 and 19.1 mg/dL) required further alendronate treatment due to persistence of hypercalcemia after 15 and 23 days (13). Kara et al. reported that three children who were given prednisolone (1 mg/kg/d) for vitamin D intoxication (calcium levels at the time

of admission: 16.0, 16.7, and, 19.7 mg/dL) reached normocalcemia after 12-26 days but hypercalcemia recurred in all of them after discontinuation of treatment (15). In the present study, nine patients with median calcium and 25(OH)D levels of 17.1 mg/dL and 361 ng/mL, respectively, were started prednisolone [Group 2, 1 (1-2) mg/kg/day, 5 (3-10) days] as first-line treatment. However, two-thirds of these patients required another specific drug treatment due to persistence of hypercalcemia and recurrence rate in this group was 25%. These data, along with the abovementioned reports, indicate that prednisolone treatment has low efficiency in "severe" hypercalcemia.

Bisphosphonates can lower calcium levels in subjects with vitamin D intoxication via their antiresorptive effect on bones (3). Alendronate as a first-choice treatment for vitamin D intoxication was first reported by Bereket and Erdogan in 2003 in a 3-month-old infant with a serum calcium level of 18.5 mg/dL. A total of 30 mg of alendronate was given between 2nd and 6th days of treatment resulting in normocalcemia (17). Orbak et al. reported a 7-year-old male child who was given 4,500,000 units of vitamin D for suspected vitamin D deficiency. Alendronate treatment was started when serum calcium level was 14.8 mg/dL and normocalcemia was achieved by the 15th day after a cumulative dose of 45 mg that was given in five doses 2-7 days apart (21). Sezer et al. described two subjects (serum calcium levels at the time of admission, 15.2 and 17 mg/dL) who were given alendronate 10 mg for once. Calcium levels returned to normal after 5 days and did not increase afterwards (13). Kara et al. reported two cases (serum calcium levels at the time of admission, 13.7 and 16.9 mg/dL) for whom alendronate (10 mg/d for 7 consecutive days) was used directly. Normocalcemia was achieved after 3 and 4 days and no recurrence was reported (15). Eleven patients (Group 3, median calcium level, 14.5 mg/dL) in the present study received alendronate at a median dose of 6.7 mg [median number of administration, 3 (1-10)]. None of the cases required another specific drug treatment; however, hypercalcemia recurred in three patients.

First experience with pamidronate, an intravenously given bisphosphonate, for vitamin D intoxication in children was reported by Ezgu et al. in 2004. The patient was a 3-month-old infant and was first treated with prednisolone. Four doses of pamidronate (0.2 mg/dose) was needed to achieve normocalcemia (18). Kara et al. reported pamidronate use as the first-line treatment in 13 children with vitamin D intoxication (median calcium level at the time of admission 16.5 (range, 13.6-18.8). The first dose of pamidronate was 1 mg/kg when serum calcium levels were between 12-15 mg/dL and 2 mg/kg for levels above 15 mg/dL. Two cases required second pamidronate dose. None of them required prednisolone or alendronate and no recurrence was noted (15). In the present study, 21 children (median calcium level 16.1 mg/dL) received pamidronate (median dose 1 mg/kg) as first-choice treatment. Similarly, none of the subjects required an alternative drug treatment or experienced recurrent hypercalcemia.

There exist two studies comparing the consequences of different treatments. Sezer et al. noted the superiority of alendronate (n=4) compared to prednisolone (n=4) and Kara et al. reported superiority of pamidronate (n=18) to prednisolone (n=6) and alendronate (n=3) (11, 15). However, in both studies, some of the children compared had received the other treatment regimen previously. In the present study including a larger group of children, we were able to group the subjects according to the first-line treatments only. In mild hypercalcemia (Group 1), oral or intravenous hydration and furosemide were sufficient to achieve normocalcemia. For very severe hypercalcemia, physicians tended to use combination therapies as

first-line treatment (Group 5). Groups 2, 3, and 4 had similar patient characteristics and serum calcium and 25(OH)D levels enabling us to compare the consequences of prednisolone (Group 2), alendronate (Group 3), and pamidronate (Group 4) treatments. Pamidronate as a first-line treatment resulted in shorter duration of intravenous hydration and no recurrence of hypercalcemia. Prednisolone treatment was not as effective as other regimens to lower serum calcium levels and children who were given prednisolone subsequently required another specific drug treatment in order to achieve normocalcemia.

There were some limitations associated with the study. The centers have contributed to the study with dissimilar number of patients. Overrepresentation of one center in a particular treatment group might have influenced other unmeasured factors including variability in laboratory measurements that could affect outcomes. In addition, lower number of cases in Group 2 (n=9) compared to Group 4 (n=21) might rise questions regarding our judgements regarding the efficiency of prednisolone. However, as discussed above, there are many case reports in the medical literature supporting our relevant findings.

In conclusion, evaluation of this largest cohort of pediatric vitamin D intoxication resulting in hypercalcemia suggests that cases with serum calcium levels below 12 mg/dL can be treated without prednisolone and bisphosphonates. Prednisolone treatment is less effective in the treatment of children with “severe” hypercalcemia (serum calcium levels above 14 mg/dL) and timely implementation of pamidronate would be considered.

Acknowledgement

This work was supported by a grant from the Turkish Pediatric Endocrinology and Diabetes Society (2014-000522).

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Table 1. Characteristics of whole study group at the time of admission.

	Children with vitamin D intoxication (n=74)
Age (years)	1.06 (0.65-1.60)
Male gender (%)	45 (60.8%)
Vitamin D intake (units)[a]	600,000 (600,000-900,000)
Vitamin D intake (units/kg) [a]	77,900 (63,800-126,700)
Time to admission (weeks) [a]	6.2 (3.6-9.4)
Calcium (mg/dL)	15±3.2
Phosphorus (mg/dL)[b]	5.2±1.2
ALP (IU/L) [c]	268±132
25-hydroxyvitamin D (ng/mL)	322 (236-454)
Parathormone (pg/mL)[d]	5.5 (3-10.5)

Data were presented as median (25th – 75th percentile), mean ± standard deviation, and n (%). [a]n=57 (77%), [b]n=69 (93.2%), [c]n=66 (89.2%), [d]n=65 (87.8%). Normal ranges: calcium (mg/dL), 8.5-10.5; phosphorus (mg/dL), 4.3-8.7 (newborns), 3.8-6.5 (1-3 years), and 3.7-5.6 (4-11 years); ALP (U/L), 48-406 (newborns), 82-383 (1 month-2 years), 69-325 (2-8 years); 25(OH)D (ng/mL), 20-100; parathormone (pg/mL), 15-88.

Table 2. Characteristics of the patients among the groups at the time of admission.

	Group 1 (n=25)	Group 2 (n=9)	Group 3 (n=11)	Group 4 (n=21)	Group 5 (n=8)	*p* (Groups 1-5)	*p* (Groups 2-4)
Age	1.06 (0.72-1.39)	0.96 (0.25-2.10)	0.85 (0.54-1.80)	1.2 (0.9-1.8)	0.9 (0.5-1.9)	0.285	0.272
Male gender	15 (60%)	5 (55.6%)	8 (72.7%)	14 (66.7%)	3 (37.5%)	0.576	0.662
Vitamin D intake (units)	600,000 (525,000-600,000)	600,000 (300,000-4,275,000)	600,000 (525,000-975,000)	900,000 (600,000-1,200,000)	1,950,000 (750,000-4,125,000)	0.005	0.693
Vitamin D intake (units/kg)	65,200 (49,400-76,000)	71,700 (64,700-622,500)	115,800 (19,000-140,000)	98,100 (73,900-129,400)	329,700 (109,100-441,200)	0.002	0.497
Time to admission (weeks)	8.3 (3.9-17.2)	8.5 (2.9-19.4)	6.5 (2.1-8.3)	5.7 (3.6-8.7)	4.2 (2.1-9.4)	0.992	0.977
Calcium (mg/dL)	11.6 (11.1-12.4)	17.1 (14.2-18.8)	14.5 (14.2-16.8)	16.1 (14.8-17.6)	19.5 (17.1-22)	<0.001	0.248
Phosphorus (mg/dL)	6.1 (5.8-6.3)	4.5 (3.3-5.1)	4.6 (4.1-5.0)	5.1 (4.2-6.3)	3.8 (3.1-4.5)	<0.001	0.103
ALP (IU/L)	345 (290-390)	192 (112-307)	195 (139-243)	186 (134-343)	174 (116-219)	<0.001	0.909
25-hydroxyvitamin D (ng/mL)	245 (186-300)	361 (193-760)	348 (240-422)	450 (327-714)	312 (198-418)	<0.001	0.893
Parathormone (pg/mL)	11 (7.1-19)	3 (1.9-6.7)	3 (2.5-3.1)	6 (3-9)	1.7 (0.5-3)	<0.001	0.005
Nephrocalcinosis and/or nephrolithiasis[a]	3 (12.5%)	6 (66.7%)	8 (80%)	12 (66.7%)	4 (57.1%)	<0.001	0.733

Group 1: Oral hydration (OH) or intravenous hydration (IH) ± Furosemide (F); Group 2: IH ± F + Prednisolone, Group 3: IH + F + Alendronate, Group 4: IH + F + Pamidronate, Group 5: IH + F + Prednisolone + Pamidronate ± Alendronate; [a]Data are lacking for 1 case in each of Groups 1, 3, and 5 and for 3 cases in Group 4. Data were presented as median (25th – 75th percentile) and n (%).

Table 3. Treatment characteristics of the patients among the groups.

	Group 1 (n=25)	Group 2 (n=9)	Group 3 (n=11)	Group 4 (n=21)	Group 5 (n=8)	*p* (Groups 1-5)	*p* (Groups 2-4)
Intravenous hydration with isotonic[a]	20 (80%)*	4 (44.4%)	5 (45.5%)	13 (61.9%)	3 (37.5%)	0.089	0.544
Volume of hydration fluid (lt/m^2/day)	2.5 (2-2.5)*	3 (2.3-3)	2.5 (2-3)	2.5 (2-3)	2.8 (2.1-3)	0.238	0.400
Duration of hydration fluid (days)	4 (3-5)	6 (3-10)	6 (3-9)	4 (3-4.8)	10 (4.5-15.5)	0.005	0.047
Furosemide dose (mg/kg/day)	2 (2-2)**	2 (2-2)***	2 (2-2)	3 (2-4)	4 (3.4-4)	<0.001	0.221
Duration of furosemide (days)	4 (3-5)	6 (5-7)	5 (4-9)	7 (3-9)	4.5 (2.8-9.3)	0.118	0.916
Specific drug treatment in the first 48 hours	N/A	Pr, 1 (1-2) mg/kg/day, 5 (3-10) days	A, 6.7 (5-10) mg/dose, 3 (1-10) times	P, 1 (0.8-1) mg/kg/dose, 2 (1-3) times	Pr, n=8, 1 (1-2) mg/kg/day, 4 (2-14) days P, n=7, 1 (1-1) mg/kg/dose, 2 (2-3) times A, n=2, 5 (5-5) mg/dose, 13 (9-13) times	N/A	N/A
Need for another type of specific drug treatment after 48 hours of therapy	0 (0%)	6 (66.7%)	0 (0%)	1 (4.8%)	0 (0%)	<0.001	<0.001
Days to normocalcemia	3 (2-4.5)	6 (3.5-11.5)	5 (4-12)	4 (3-6)	6.3 (4.3-11)	0.001	0.099
Duration of follow-up (years)	1 (0.6-1.4)	1.2 (0.2-2.4)	0.15 (0.1-0.2)	1 (0.4-2.2)	0.4 (0.1-0.8)	0.010	0.006
Recurrence rate[b]	0 (0%)	2 (25%)	3 (30%)	0 (0%)	1 (12.5%)	0.012	0.02
Nephrocalcinosis and/or nephrolithiasis[c]	1 (4.2%)	2 (33.3%)	5 (50%)	5 (27.8%)	5 (83.3%)	0.018	0.268

Group 1: Oral hydration (OH) or intravenous hydration (IH) ± Furosemide (F); Group 2: IH ± F + Prednisolone, Group 3: IH + F + Alendronate, Group 4: IH + F + Pamidronate, Group 5: IH + F + Prednisolone + Pamidronate ± Alendronate**:** Pr, prednisolone; A, alendronate; P, pamidronate; C, calcitonin; N/A, not applicable; [a]All of the patients except 5 cases in Group 1 received

intravenous hydration with various fluid types, [b]Data are lacking for 1 case in each of groups 1-4.*5 cases (20%) received oral hydration; **Seventeen cases (68%) received furosemide, none of them were treated with oral hydration; ***Eight cases (88.9%) received furosemide; [c]Data are lacking for 1 case in each of Groups 1, 3, for 3 cases in each of Groups 2 and 4, and for 2 cases in Group 5. Data were presented as median (25th – 75th percentile) and n (%).

Figure 1. Correlation analyses of various variables with calcium and 25(OH)D levels at the time of admission.

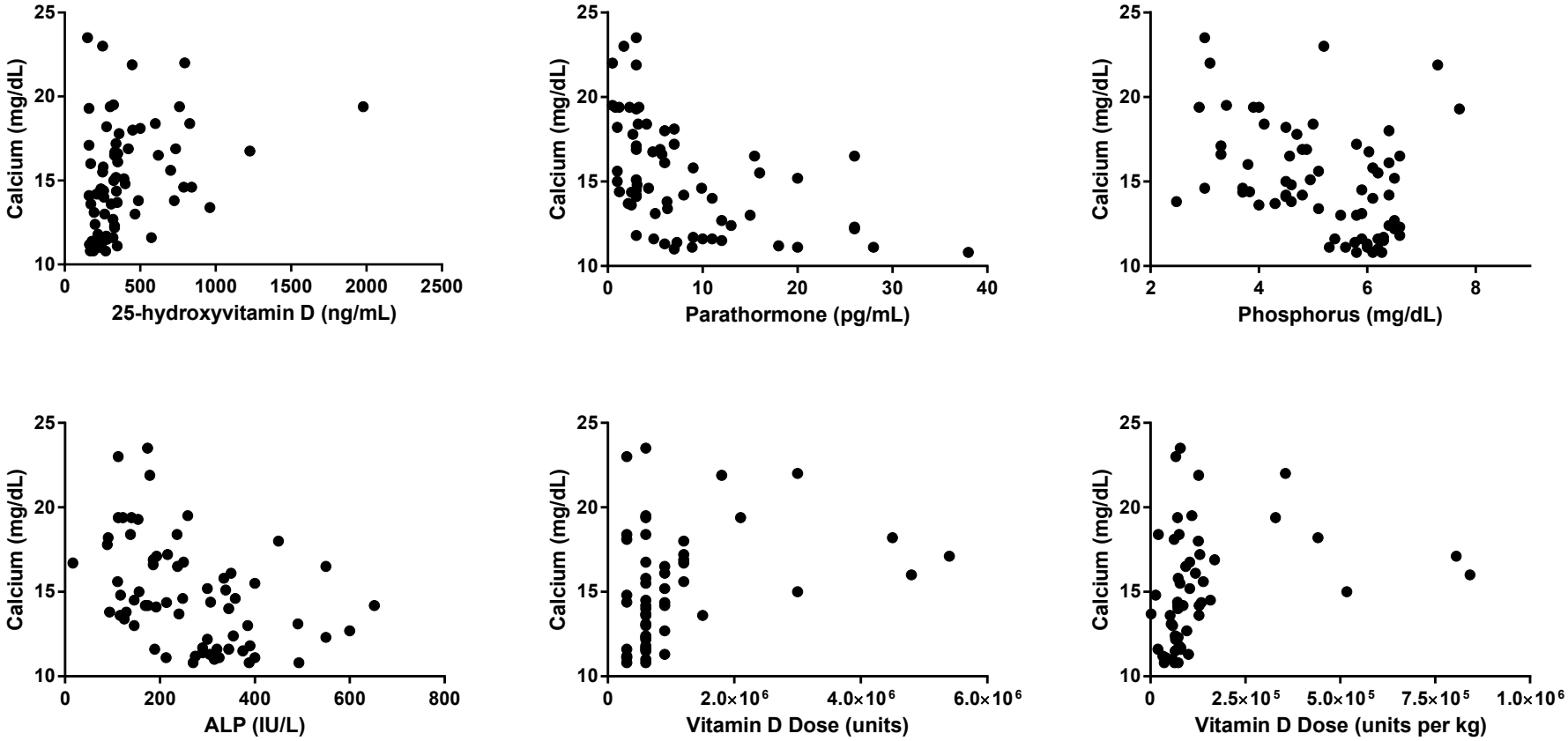

Figure 2. Box-whisker graphs of serum calcium and 25(OH)D levels among the groups (The horizontal lines within the boxes indicate the median, boundaries of the boxes indicate the 25th and 75th percentiles, and the whiskers indicate the highest and lowest values of the results).