An effect of single high dose of vitamin D3 on the risk of nosocomial infections, hospitalization time and mortality in hospitalized elderly population. A preliminary report

Ocena wpływu jednorazowego podania wysokiej dawki witaminy D3 w populacji osób starszych na przebieg hospitalizacji ze szczególnym uwzględnieniem ryzyka zakażeń wewnątrzszpitalnych, czasu hospitalizacji i śmiertelności. Doniesienie wstępne

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Keywords:
• vitamin D
• serum 25(OH)D
• hospital-acquired infection
• elderly population

Abstract

Introduction: Observational studies indicate a significant impact of serum 25(OH)D concentration on incidence of hospital-acquired infections. However, we did not find any interventional study assessing the effect of vitamin D3 administration at the admission on the course of further hospitalization in internal medicine departments.

Objective of the paper: Investigation of the impact of one-time high-dose vitamin D3 administration in elderly patients on the day of urgent admission to the hospital, on hospital-acquired infections.

Materials and methods: A randomized, two-arms, open pilot study in 97 adults aged 60-100. A study group was given a single dose of 60,000 IU vitamin D3 and a control group was not subject to any intervention. Serum 25(OH)D and calcium were measured at the baseline and after 7 days.

Results: 77.32% of studied patients were vitamin deficient, and among those, in 28.87% severe vitamin D deficiency was found. After single administration of 60,000 IU of vitamin D3, only 4 patients achieved recommended serum 25(OH)D concentration. The highest increase in serum 25(OH)D was observed in patients with severe deficiency. Numbers of observed nosocomial infections such as flu, hospital-acquired pneumonia or Klebsiella pneumoniae MBL+ infection did not differ significantly between study and control group, however there was a trend close to significance for lower incidence of Clostridium difficile infection in the vitamin D3 group.

Conclusions: Preliminary results of the presented research indicate possible protective effect of single high dose of vitamin D3 against Clostridium difficile infection during hospitalization. Further research on larger group of patients, using higher dose of vitamin D3 is necessary.

Słowa kluczowe:
• witamina D
• stężenie 25(OH)D w surowicy
• zakażenia wewnątrzszpitalne
• populacja osób starszych

Streszczenie

Wstęp: Doniesienia naukowe ostatnich lat wskazują na istotny wpływ stężenia 25(OH)D na występowanie zakażeń wewnątrzszpitalnych. Do tej pory nie przeprowadzono interwencyjnego badania z podaniem witaminy D3 przy przyjęciu do szpitala i oceny wpływu takiego postępowania na przebieg hospitalizacji w oddziałach internistycznych.

Cel pracy: Celem pracy jest zbadanie wpływu jednorazowego podania wysokiej dawki witaminy D3 w momencie przyjęcia do szpitala z pełnymi wskazaniami internistycznymi na przebieg hospitalizacji, ze szczególnym uwzględnieniem zakażeń wewnątrzszpitalnych.
Introduction
Understanding the pathways of action and metabolism of vitamin D led to the discovery of 1,25(OH)2D (calcitriol) as a steroid hormone. Calcitriol and vitamin D receptor (VDR) form a universal transcriptional complex controlling about 3% of human genome (1). Among the non-classical effects of vitamin D the immunomodulation seems to be especially important.

The expression of vitamin D receptors (VDR) was discovered in all immune system cells: monocytes, macrophages, lymphocytes T and B, antigen-presenting cells (2). Vitamin D affects innate immunity by stimulation of macrophages to produce antimicrobial peptides — cathelicidins and defensins, acting bactericidal, antifungal and antiviral (3). The first reports on the beneficial effects of vitamin D on the immune system concerned tuberculosis treatment. It is currently known that this effect also applies to other bacterial and viral infections.

The increasing incidence of hospital-acquired infections (5-10% of hospitalized patients), especially Clostridium difficile, Klebsiella pneumoniae MBL/NDM and multi-resistant strains of other bacteria is a major problem in all hospitals, also common in countries with the highest standards of medical care (4). Nosocomial infections results in prolonged hospitalization time, necessity of isolation infected patients, usage of multiple antibiotics and increased mortality, as well as significant increase in direct medical costs. In the light of the above, the growing interest in the impact of the supply of vitamin D on the incidence of hospital infections is becoming understandable.

A retrospective cohort study of Quarishi et al. showed a 3-fold higher risk of Clostridium difficile infection in patients with serum 25(OH)D <10 ng/ml compared to patients with level >30 ng/ml (5). A similar relationship was demonstrated in a study of patients with inflammatory bowel disease: a group with Clostridium difficile infection had significantly lower levels of serum 25(OH)D (6). Moreover, the results of trials indicate that the serum 25(OH)D may be an important factor in predicting the severity of infection and may influence the risk of its recurrence (7, 8). Some of the reports indicate a significant effect of 25(OH)D concentration on hospital-acquired blood infections. A retrospective analysis of 2,135 patients with positive blood cultures showed 2.3-fold increase in risk of this type of infection in patients with serum 25(OH)D <10 ng/ml (9). According to recent studies, the proper supply of vitamin D3 plays a key role in preventing influenza virus infection. In a multicentre randomized study of children infected with influenza virus, patients who received a high dose of vitamin D3 had statistically significantly shorter duration of fever and cough (10). However, there are no reports regarding the effect of the vitamin D3 supply on the risk of Klebsiella pneumoniae MBL/NDM infection.

Hospital interventional studies using a high dose of vitamin D3 have been carried out only in critically ill patients in intensive care units (11, 12). A study of Quraishi et al. showed that a single administration of 400,000 IU vitamin D3 is an effective intervention to quickly improve serum 25(OH)D. The increase in serum 25(OH)D positively correlated with the serum cathelicidin — a peptide with bactericidal and antiviral properties. Amrein et al. showed that administration of a single dose of 540,000 IU vitamin D3 did not affect the length of hospitalization and 6-month mortality, while significantly lower hospital mortality was observed in people with severe 25(OH)D deficiency (<12 ng/ml), compared with placebo group. No hypercalcemia events were observed in either study. Nevertheless, the safety of giving a single high dose of vitamin D3 is being questioned. In the study of Sanders et al. annual administration of a single dose of 500,000 IU in the elderly women significantly increased risk of falls and fractures (13). This relationship has not been demonstrated in studies with a lower dose of vitamin D3, such as a New Zealand trial with 5108 adults aged 50-84 (100,000 IU/month), for a median of 3.3 years and British study of 2686 seniors (100,000 IU/4 months for 5 years) (14, 15, 16). Only in study of HA. Bischoff-Ferrari et al. with 200 participants, a vitamin D3 bolus of 60,000 IU/month for 1 year increased risk of falls compared with the group receiving 24,000 IU (17).

The study of S. De Niet et al. comparing daily supplementation of 2000 IU with a dose of 50,000 IU per month, showed that a high one-time dose results in more effective and faster normalization of 25(OH)D with a significant increase observed from the second day after drug administration (18).

Material and methods
The randomized, two-arms, open pilot study which was conducted in internal departments of Bielański Hospital in Warsaw.

Study population was made out of 97 caucasian, male and female patients, aged from 60 to 100 years old, admitted to internal departments on an emergency basis in Bielański Hospital from January to June 2019. The exclusion criteria were: hypercalcaemia, nephrolithiasis, serum
creatinine level >1.5 mg/dL (women) or 2.0 mg/dL (men), due to differences in muscle mass and documented vitamin D metabolism disorders such as sarcoidosis, parathyroid disease or genetic defects. Subjects were not allowed to take any other medications or supplements containing vitamin D₃. Patients were randomized in two groups: study group – 45 subjects, receiving 60,000 IU of vitamin D₃ (two tablets for oral use containing 30,000 IU of vitamin D₃), and control group – 52 subjects. All participants provided written informed consent. The study was approved by Ethics Committee in Centre of Postgraduate Medical Education (Warsaw, Poland).

Laboratory tests

Blood samples for determination of 25(OH)D, calcium and creatinine was collected at admission and after 7 days. Serum 25(OH)D was determined by the CLIA chemiluminescence method, using the LIAISON DiaSorin analyser as "Total 25(OH)D", a combined determination of 25(OH)D₂ and 25(OH)D₃.

Serum total and ionized calcium and serum creatinine were measured by routine automated method (Roche autoanalyser). All the analyses were performed at the laboratories of Bielański Hospital in Warsaw.

Statistical analysis

Statistical analysis was performed with the use of following software: Microsoft Excel (Microsoft Corporation, Redmond, Washington, United States) and STATISTICA 13.3. (TIBCO Software Inc., Palo Alto, California, United States). Descriptive data was presented as numbers, percentages, and means with standard deviations and medians. P-value (p) <0.05 was considered statistically significant.

None of the analyzed numerical parameters showed a normal distribution, which was checked with the use of Shapiro-Wilk test (for all p <0.05). On this basis, only non-parametrical test were applied. Mann-Whitney U test was used to compare two independent samples. The strength of association between two events was determined using the Chi-squared test. Wilcoxon signed-rank was used for the detection of differences between dependent variables. Additionally, correlations between 25(OH)D level and its increase after a single high dose in the study group were expressed using the Spearman’s coefficient.

Results

Patients from the study (n = 45) and control group (n = 52) did not differ significantly at the baseline (Table 1).

Table 1. Baseline characteristics of study participants.

| Variable                  | Vitamin D₃ (n = 45) | Control group (n = 52) | p-value |
|---------------------------|---------------------|------------------------|---------|
| Age                       |                     |                        |         |
| Mean (±standard deviation [SD]) | 75.44 (±8.94)   | 74.83 (±9.88)          | 0.745   |
| Range                     | 61-100              | 60-99                  |         |
| Sex                       |                     |                        |         |
| Female                    | 44.44% (n = 20)     | 46.15% (n = 24)        | 0.866   |
| Male                      | 55.55% (n = 25)     | 53.85% (n = 28)        |         |
| Ionized calcium [mmol/l]  |                     |                        |         |
| Mean (±SD)                | 1.14 (±0.05)        | 1.14 (±0.08)           | 0.933   |
| Range                     | 1.04-1.21           | 0.93-1.30              |         |
| 25 hydroxyvitamin D on admission [ng/ml] |           |                        |         |
| ≥30                       | 22.22% (n = 10)     | 23.06% (n = 12)        | 0.811   |
| ≥20 and <30               | 11.11% (n = 5)      | 17.31% (n = 9)         |         |
| ≥10 and <20               | 42.22% (n = 19)     | 26.92% (n = 14)        |         |
| <10                       | 24.44% (n = 11)     | 32.69% (n = 17)        |         |
| Creatinine [mg/dl]        |                     |                        |         |
| Mean (±SD)                | 0.89 (±0.31)        | 0.87 (±0.39)           | 0.421   |
| Range                     | 0.37-2.00           | 0.17-1.99              |         |
| Antibiotic therapy prior to admission | 68.89% (n = 31) | 63.46% (n = 33)        | 0.321   |
| Admitting diagnosis       |                     |                        |         |
| Heart failure             | 22.22% (n = 10)     | 25% (n = 13)           |         |
| Arrhythmias               | 6.66% (n = 3)       | 11.54% (n = 6)         |         |
| Pneumonia                 | 33.33% (n = 15)     | 30.77% (n = 16)        |         |
| Exacerbation COPD         | 15.55% (n = 7)      | 11.54% (n = 6)         |         |
| Urinary tract infection   | 8.88% (n = 4)       | 11.54% (n = 6)         |         |
| Anaemia                   | 6.66% (n = 3)       | 13.46% (n = 7)         |         |
| Diabetes                  | 15.55% (n = 7)      | 15.38% (n = 8)         |         |
| Hyponatremia              | 4.44% (n = 2)       | 7.69% (n = 4)          |         |
| Malignant disease         | 11.11% (n = 5)      | 11.54% (n = 6)         |         |
| Other infections          | 4.44% (n = 2)       | 7.69% (n = 4)          |         |
Initial serum 25(OH)D concentrations were similar in both groups [in study group: mean 19.85 (±15.21), in control group: 18.70 (±12.64); p = 0.811]. Vitamin D₃ deficiency [serum 25(OH)D <30 ng/mL] was found in 77.32% (n = 75) of subjects in the whole study group: 35 out of 45 patients from study group (77.78%) and 40 out of 52 patients from control group (76.92%); (p = 0.920).

A statistically significant increase in serum 25(OH)D was observed after 7 days from baseline in the study group (p <0.01) (Figure 1.).

The observed increase in serum 25(OH)D in study group was inversely correlated with baseline 25(OH)D levels (r = -0.32; p <0.05) (Table 2).

In study group, only 4 out of 35 (11.43%) patients with baseline deficiency reached recommended serum 25(OH)D (>30 ng/mL) on seventh day after oral administration of 60,000 IU of vitamin D₃.

In the whole group, 11 out of 97 (11.34%) patients underwent hospital infections, however there were no significant differences between the study and control groups (p = 0.479). However, Clostridium difficile infections were less common in the vitamin D₃ group than in control group [0.22% (n = 1 out of 45) vs 11.54% (n = 6 out of 52)], difference on the verge of statistical significance (p = 0.08).

The number of other nosocomial infections (influenza, hospital-acquired pneumonia, MBL-positive Klebsiella pneumoniae infection) did not significantly differ between groups.

Time of hospitalization was similar in both groups (in treatment group median 8 days; in control group median 9 days; p = 0.291). There were 7 in-hospital deaths, 2 in the vitamin D₃ group and 5 in the control group.

### Discussion

Increasing problem of nosocomial infections, associated with the enormous medical costs is one of the most pressing challenges of modern medicine. Consequently it is exceedingly important to study all factors which can have impact on reducing the risk of prevalence of these type of infections. The latest research articles indicate that one of those factors may be maintaining proper levels of 25(OH)D. That is why we deemed it promising to conduct intervention study by administrating one high dose of vitamin D₃ after admission to Internal Medicine ward with evaluation of course of hospitalization in terms of nosocomial infections. The pilot

![Figure 1. Increase in serum 25(OH)D after single high dose in the study group.](image)

| Baseline 25(OH)D [ng/ml] | Percent and number of patients | Mean increase (±SD) |
|--------------------------|--------------------------------|---------------------|
| <10                      | 24.44% (n = 11)                | 10.57 (±4.86)       |
| ≥10 and <20              | 42.22% (n = 19)                | 9.57 (±4.51)        |
| ≥20 and <30              | 11.11% (n = 5)                 | 7.08 (±4.95)        |
| ≥30                      | 22.22% (n = 10)                | 6.23 (±6.50)        |
study included 97 patients. In 79% of those patients serum 25(OH)D was below 30 ng/ml, and among those in 28% was below 10 ng/ml. This result confirms past data on the prevalence of vitamin D deficiency in Poland (19). Single oral dose of 60,000 IU of vitamin D3 resulted after seven days in significant increase in serum 25(OH)D. An increase in serum 25(OH)D concentration was significantly higher in the group of subjects with the lowest concentrations at the baseline compared with group with normal basal serum 25(OH)D. Consequently it proves that liver 25-hydroxylase works more efficiently in lower level of substrate. Only 4 participants of the researched group achieved optimal serum 25(OH)D concentration (>30 ng/mL) after single administration of 60,000 IU of vitamin D3. According to recent studies such concentration is needed to achieve full pleiotropic effect of vitamin D3. In terms of nosocomial infections, the prevalence of Clostridium difficile was less common in experimental group, tridium difficile was less common in experimental group, and to include an earlier vitamin D supplementation as a criterion for exclusion from the study was below 10 ng/ml. This result confirms past data on the prevalence of Clostridium difficile-associated diarrhea. Therap Adv Gastroenterol 2014 Jan; 7(1):14-19.

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