






The relationship between vitamin D serum concentration and common inflammatory biomarkers in the early postoperative period in infants with congenital heart defects operated on with extracorporeal circulation: preliminary results

Zależność pomiędzy stężeniem witaminy D w osoczu oraz rutynowymi wykładnikami stanu zapalnego we wczesnym okresie pooperacyjnym u niemowląt poddanych operacji wrodzonych wad serca z zastosowaniem krążenia pozaustrojowego – wyniki wstępne

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Abstract

Introduction. Children operated on congenital heart defects (CHD) with the use of extracorporeal circulation (ECC) experience various forms of systemic inflammatory response syndrome (SIRS) which can be measured by routine inflammatory biomarkers (C-reactive protein [CRP], procalcitonin). According to literature, vitamin D serum concentration in multiple potential ways may be related to the inflammatory response activation in the acute phase of SIRS in infants operated on CHD with the use of ECC.

Material and methods. The study group consisted of 20 infants (mean age = 7.35 months; standard deviation = 2.76) with CHD underwent cardiac surgery with the use of ECC in one cardiac unit. Serum concentration of vitamin D (in 2 forms: 25(OH)D₃ and 1.25(OH)₂D₃), as well as inflammatory biomarkers were measured three times: a day before surgery, on the 2nd day after the operation, and finally – in the 6th postoperative day. All participants received standard vitamin D supplementation (500 IU) orally within first week after birth as well as just after the return to oral feeding after cardiac surgery (1st postoperative day). The specimens were analysed in the local laboratory. The obtained data were analysed statistically. To assess vitamin D sufficiency the standard, recommended thresholds were used.

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Results. All patients had sufficient level of vitamin D before the surgery. Patients with any clinical sign of infection (including elevated inflammatory biomarkers) were excluded. On the 2nd postoperative day, when the peak level of CRP (median [m] = 131.59 mg/L) was observed, the 1.25(OH)₂D₃ fell to insufficiency (m = 66.10 ng/mL). In the 6th postoperative day CRP was observed in the nearly normal ranges, while vitamin D returned to preoperative sufficiency levels.

Conclusions. The study's preliminary results show that the dynamics of early postoperative inflammatory markers level increase correlates with early postoperative serum vitamin D concentration drop below the therapeutic level. Our results eligible further studies to determine new universal protocols of preoperative, and perioperative vitamin D administration to prevent from vitamin D deficiency in children operated on for CHD in infancy.

Key words: vitamin D, systemic inflammatory response syndrome, paediatrics, paediatric cardiac surgery, congenital heart defects

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Introduction

The global development of prenatal diagnostics caused the birth prevalence of congenital heart defects (CHDs) to reach 9.410 in 1000 births between 2010 and 2017, with untreated CHD resulting in the greatest mortality during the first year of life [1, 2]. A significant proportion of these paediatric patients require one or more corrective procedures over their lifetime with the use of extracorporeal circulation (ECC). The ECC provokes the inflammatory response due to ischemic/reperfusion injury, haemodilution etc. [3]. Therefore, systemic inflammatory reaction syndrome (SIRS) is frequently observed in children after open heart surgery, which has been associated with both ECC and surgical trauma. The pathophysiology of SIRS involves a cytokine-mediated general capillary leakage followed by intravascular volume depletion, haemodilution, generalized oedema, circulatory compromise and altered microcirculation. Postoperative SIRS can be measured by routine biomarkers such as C-reactive protein (CRP), procalcitonin or leukocytosis [4].

Despite the powerful strategies to prevent it, SIRS increases the risk of multiple organ dysfunction syndrome and further postoperative complications. Any means of preventing or controlling these complications may improve the condition of high-risk paediatric patients, promote recovery, and decrease mortality [4, 5].

Vitamin D supplementation and control

Vitamin D is routinely measured in 2 forms: 25-hydroxy vitamin D (25(OH)D₃) and its active metabolite 1.25-dihydroxy vitamin D (1.25(OH)₂D₃). The metabolite has the highest affinity to vitamin D receptors and is mainly responsible for calcium homeostasis. Except for the mineral metabolism function, recent studies indicate that the vitamin D receptors responsible for vitamin D physiologic effects

exertion are expressed in most of the body tissues providing a wide field for research on its potential in the prevention, or even treatment, in a variety of extra-skeletal conditions [6]. Nevertheless, the 25(OH)D₃ is the compound that is optimally suited for assessing vitamin D status in most patients, due to its relatively high serum concentration and long half-life [5, 6].

Standard vitamin D supplementation recommended in the general population includes 400 IU/day from the first days of life, regardless of the way of feeding for the neonates and infants aged 0–6 months and 400–600 IU/day, depending on the daily amount of vitamin D taken with food for the infants aged 6–12 months according to the recommendations of the Polish Society of Paediatric Endocrinology and Diabetes [7]. The generally accepted thresholds for defining 'desired' vitamin D sufficiency is 75 nmol/L (30 ng/mL), with deficiency defined as below 50 nmol/L (20 ng/mL), and severe deficiency at 25 to 30 nmol/L (10–12 ng/mL) [5].

The vitamin D supplements are usually administered by the parents or tutors, who control both the way, and the frequency of supplementation. There are several vitamin D supplements available over-the-counter, including generic products, with different active constituents' concentrations. Those variable factors make monitoring of the vitamin D correct administration, dosage, and serum concentration in infants with elective cardiac surgery not easy, although it could have an impact on the postoperative pathophysiology.

Possible role of the vitamin D in cardiac surgery

The current body of knowledge supports the hypothesis that vitamin D is critical for different common conditions including autoimmune and neurological diseases, pregnancy complications, cancer as well as cardiovascular disorders and various types of infections [6]. Higher vitamin D concentrations in adult patients are associated

with significantly fewer postoperative organ dysfunctions, decreased procalcitonin levels, fewer nosocomial infections, and less frequent death and/or prolonged hospital stay [8].

Kruit et al. [9] based on a cohort study proved an inverse correlation between 25(OH)D₃ and CRP, especially pronounced in elderly patients with inflammatory diseases. In the literature it is also strongly hypothesized that vitamin D insufficiency can be associated with increased morbidity and mortality in critically ill patients and that it may be a consequence of the critical illness itself, probably intensifying the adverse effects [10]. The analysis of the critically paediatric patients in a large multicentre intensive care unit reported a 70% vitamin D deficiency rate, suggesting the association between low vitamin level and their clinical course [11]. *In vitro* studies have suggested that vitamin D suppresses proinflammatory cytokines and increases anti-inflammatory cytokines [12].

Studies focused on adult cardiovascular patients point to vitamin D deficiency as a risk factor for acute coronary syndromes and other critical conditions associated with cardiovascular disease [13, 14].

According to case reports/series paediatric patients operated on CHD with the use of ECC often experience calcium serum level alterations and cardiogenic shock with vitamin D serum level decrease. Graham et al. [15] confirmed these observations with a secondary analysis of blood specimens (samples taken before skin incision, at the cessation of ECC and 24 hours postoperatively), reporting that 84% of neonates with CHD were vitamin D deficient postoperatively, while lower vitamin D levels were associated with increased inotropic support. Ye et al. [16] suggested that children with vitamin D deficiency before the surgery need increased postoperative inotropic support. Vitamin D supplementation in outpatient paediatric congenital heart failure (HF) showed improved cardiac function with a higher daily dose of vitamin D [17].

The current knowledge suggests that the biological role of vitamin D and the impact on heart function rely on multiple potential mechanisms such as reduced inflammation, lower risk of infections, improved cardiac function and faster postoperative recovery, which justify the need to control and finally provide its optimal serum concentration in every phase of surgical cardiac treatment.

Aim of the study

The aim of the study was the analysis of vitamin D serum concentration and common inflammatory biomarkers levels in the early postoperative period in infants with congenital heart defects operated on with the use of extracorporeal circulation.

Material and methods

Clinical data were collected prospectively from 30 consecutive paediatric patients referred for surgery to one department of paediatric cardiac surgery. All children referred for cardiac surgery with the use of ECC were carefully examined preoperatively, with regular clinical tests including serum vitamin D level tests (measured in two forms: 25(OH)D₃ and 1.25(OH)₂D₃). Routine preoperative exams and laboratory tests were performed. The patients referred for surgical procedures were free of any clinical or laboratory signs of infection.

Finally, after a meticulous analysis of the data obtained, the group of 20 children were enrolled on further analysis. Infants with incomplete data or additional comorbidity that could affect their clinical management were excluded from the study.

The patients were involved in the study group according to inclusion and exclusion criteria. The informed parental consent were obtained before the inclusion in the study group.

The inclusion criteria were:

- age between 30 days–12 months;
- congenital heart defects surgery with ECC in one paediatric cardiac surgery department;
- standard vitamin D₃ supplementation from the first week after birth according to the recommendations of the Polish Society of Paediatric Endocrinology and Diabetes [7];
- every clinical symptom of potential infections was identified and excluded.

The exclusion criteria were:

- cardiac or gastrointestinal disease prevented feeding or drug administration before the surgery, to the day before the operation;
- confirmed or suspected William's syndrome – a genetic disorder with symptoms including cardiovascular problems and elevated blood calcium;
- born at gestational age less than 32 weeks.

The eligibility criteria were justified because infants born before 32 weeks gestational age have a significantly increased risk of nephrocalcinosis, while patients with Williams syndrome have a genetic susceptibility to hypercalcemia, and current guidelines do not recommend vitamin D supplementation [7, 18, 19].

Study group

The group consisted of 20 infants (age: 4–7 months; mean age = 7.35 months; SD = 2.76; 6 females [30%], 14 males [70%] with mean body mass 7.33 kg; SD = 1.86 kg) with CHD (Table 1) who underwent a moderate hypothermic ECC cardiac surgical correction of congenital heart defects

Table 1. Heart defects were presented, and clinical analysis and drugs were administered within the study group

Heart defects	Number (percentage)
Ventricular septal defect	10 (50)
Tetralogy of Fallot	4 (20)
Atrioventricular septal defect	3 (15)
Single ventricle	1 (5)
Atrial septal defect, pulmonary stenosis	1 (5)
Criss-cross heart, transposition of the great arteries, pulmonary stenosis	1 (5)
Clinical analysis	Number (percentage)
Cyanosis	7 (35) and 4 (20) patients after pulmonary artery banding
Heart failure	12 (60)
Respiratory failure	14 (70)
Genetic disorders	Down syndrome – 3 (15) Phenylketonuria – 1 (5)
Other	Obesity – 1 (5) Urinary tract defect – 1 (5) Glucose intolerance – 1 (5) Premature infant (born 32 < and > 37 weeks gestational age) – 1 (5)
Drugs administered (preoperatively)	Number (percentage)
Spironolactone	7 (35)
Lisinopril	5 (25)
Propranolol	3 (15)
Acetylsalicylic acid	2 (10)
Bisoprolol	1 (5)
Levothyroxine	1 (5)

in one cardiac unit. The study group included also clinical course analysis and preoperative drug administration distinction (Table 1).

Procedure

All the cardiac surgeries with ECC were done with standard general anaesthesia. All patients received a standard perioperative institutional antibiotics prophylaxis (cefazolin). Moderate hypothermia (28–32 °C) during ECC and cardiac arrest with standard single-dose antegrade cold crystalloid cardioplegia (Custodiol) was used. For deep hypothermia,

a deep hypothermic circulatory arrest strategy was used, as routinely. Haematocrit values were kept above 30% during the ECC in rewarming period with continuous hemofiltration commenced in the circuit. No steroids were given routinely. The protocol of postoperative biochemical analysis was followed in every consecutive patient referred for cardiac surgery, all tests were performed in the institutional laboratory.

Blood samples were collected on the day before surgery, and on the second and sixth postoperative days as part of the routine laboratory control during the perioperative period. The samples were collected at the same time (6 AM) as a part of the morning examination panel, without the need for any additional blood collection. Serum CRP concentration was measured using a turbidimetric immunoassay (Modular Roche A PB 06-76). The normal range of CRP serum concentration was below 5 mg/L.

Vitamin D serum concentrations were measured three times: a day before surgery, on the second day after the operation and on the 6th postoperative day (PRE-OP, POD2 and POD6, respectively). All infants received a standard dose of vitamin D supplementation according to the recommendations from the first week after birth. Every patient received a standard dose of vitamin D on the first postoperative day, just after the return to oral feeding. All specimens for vitamin D analysis were collected and analysed in the local laboratory at the institution. Standard institutional thresholds for defining 25(OH) D₃ sufficiency and deficit were used compared with the sufficiency thresholds from the literature (Table 2). For 1.25(OH)₂D₃ status an institutional sufficiency range of 15.02–90.10 (ng/mL) was used. Clinical course analysis was also performed on every subject, with the identification of prolonged administration of catecholamines and antibiotics. The symptoms of HF, cyanosis, metabolic demands, organ insufficiency, drugs and genetic abnormalities were analysed as they can potentially cause susceptibility to vitamin D level fluctuations.

The data were simultaneously collected, while the analysis was performed after complete data collection and retrospective verification. The statistical analysis was performed after the final data collection.

Ethical considerations

The presented single-institutional prospective preliminary study was performed according to the rules and guidelines of the local Ethic Examining Committee of Human Research (Decision of Approval: NKBBN 178/2012 dated: May 14, 2012 – continuation of the ongoing study on inflammatory biomarkers) and the procedures followed the ethical standards of the Helsinki Declaration of 1975.

Table 2. The standard institutional laboratory thresholds for 25-hydroxy vitamin D (25(OH)D) sufficiency

Standard institutional 25-hydroxy vitamin D (25(OH)D) sufficiency thresholds	Range [ng/mL]	25-hydroxy vitamin D (25(OH)D) thresholds proposed by McNally et al. [5]	Range [ng/mL]
Low	20–30	Severe deficiency	10–12
Optimal	30–50	Deficiency	~ 20
High	50–100	Sufficiency	> 30
Potentially toxic	100–150		
Toxic	> 150		

Table 3. Median and mean values of serum concentration of 25(OH)D₃ and 1.25(OH)₂D₃ and C-reactive protein (CRP) concentration values in 3 measures: PRE-OP, POD2 and POD6

Serum concentration/day of measurement	PRE-OP	POD2	POD6
25(OH)D ₃ [ng/mL]	Median = 36.33	Median = 27.79	Median = 35.03
	Q1 = 25.90	Q1 = 23.35	Q1 = 30.4
	Q3 = 49.15	Q3 = 31.80	Q3 = 39.3
	IQR = 23.25	IQR = 8.45	IQR = 8.9
1.25(OH) ₂ D ₃ [ng/mL]	Median = 109.31	Median = 66.10	Median = 72.54
	Q1 = 57.15	Q1 = 56.22	Q1 = 55.70
	Q3 = 150	Q3 = 86.45	Q3 = 77.9
	IQR = 92.85	IQR = 30.23	IQR = 22.2
CRP [mg/L]	Mean ≤ 5	Median = 131.59	Mean ≤ 20
	Median ≤ 5	Q1 = 65,5	Median ≤ 5
		Q3 = 199	
		IQR = 133.5	

Statistical analysis methods

Statistical analysis was performed using SPSS v. 26.0 (SPSS Inc., USA). Continuous variables were presented as medians with quartiles and means with standard deviations. The data sets that did not follow a normal distribution were analysed with the nonparametric Wilcoxon test. The correlation between the data was assessed with Spearman's coefficient. Also, the coefficient of determination was set to graphically present the correlation. Statistical significance was assumed for p values of less than 0.05.

Results

All patients had a sufficient level of both 25(OH)D₃ (median = 36.33 ng/mL [Q1 = 25.90; Q3 = 49.15; IQR = 23.25]) and 1.25(OH)₂D₃ (median = 109.31 ng/mL [Q1 = 57.15; Q3 = 150; IQR = 92.85]). The inflammatory biomarkers were within normal range before the surgery (Table 3, Figure 1).

In the second postoperative day the 25(OH)D₃ serum concentration fall to severe insufficiency (median = 27.79 ng/mL [Q1 = 23.35; Q3 = 31.80; IQR = 8.45]) and its active metabolite 1.25(OH)₂D₃ falls significantly (median = 66.10 ng/mL [Q1 = 56.22; Q3 = 86.45; IQR = 30.23]) (Table 3, Figure 1).

In the 6th postoperative day 25(OH)D₃ levels returned to preoperative sufficiency (median = 35.03 ng/mL [Q1 = 30.4; Q3 = 39.3; IQR = 8.9]) and 1.25(OH)₂D₃ serum concentration significantly increased (median = 72.54 ng/mL [Q1 = 55.70; Q3 = 77.9; IQR = 22.2]) (Table 3, Figure 1).

Statistical analysis

There was a significant difference between vitamin 25(OH)D₃ measured PRE-OP and POD2, as well as POD2 and POD6 and for 1.25(OH)₂D₃ measured PRE-OP and POD2 (Table 4). Spearman's correlation coefficients showed a negative correlation between the CRP levels and 25-hydroxy vitamin D concentrations and between CRP levels and 1.25-dihydroxy

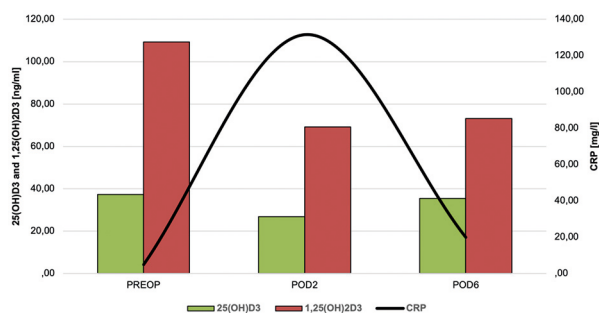


Figure 1. The median serum concentration of 25(OH)D₃ and 1,25(OH)₂D₃ in relationship with median C-reactive protein (CRP) values in 3 measures: PRE-OP, POD2 and POD6

vitamin D concentrations in the second postoperative day measurements (Table 5).

The p-values showed a statistically significant decrease between 25(OH)D₃ values measured PRE-OP and POD2 and an increase in POD2 and POD6. What is more, the increase between 1,25(OH)₂D₃ measured PRE-OP and POD2 was also statistically significant, contrary to the non-significant difference between 1,25(OH)₂D₃ decrease between POD2 and POD3. The coefficients of determination low values show that the independent values cannot be always explained by the dependent values.

Table 4. P-values between 25(OH)D₃ and 1,25(OH)₂D₃ measurements in PRE-OP vs. POD2 and POD2 vs. POD6

P-values between 25(OH)D ₃ and 1,25(OH) ₂ D ₃ measurements in PRE-OP vs. POD2 and POD2 vs. POD6		
	PRE-OP vs. POD2	POD2 vs. POD6
25(OH)D ₃	p < 0.001	p < 0.001
1,25(OH) ₂ D ₃	p = 0.019	p = 0.616

Table 5. Spearman's correlation coefficient and coefficient of determination values

Spearman's correlation coefficient and coefficient of determination values between CRP concentration and 25(OH)D ₃ concentrations and between CRP levels and 1,25(OH) ₂ D ₃ in the POD2				
		25(OH)D ₃	1,25(OH) ₂ D ₃	
CRP	Spearman's correlation coefficient		Spearman's correlation coefficient	Coefficient of determination
		-0.196	-0.226	R ² = 0.004
	Coefficient of determination	R ² < 0.001		

CRP – C-reactive protein

Discussion

Our preliminary results showed significant perioperative changes in serum vitamin D levels and a negative correlation between CRP levels (commonly used as a marker of SIRS) and vitamin D levels in 20 infants undergoing cardiac surgery with ECC and receiving standard preoperative vitamin D supplementation.

Abou Zahr et al. [20] also showed a statistically significant decrease in vitamin D levels immediately and 24 hours after ECC use during paediatric cardiac surgery. The report also claims no significant change in the vitamin D binding protein in the measured probes justifying the omission of this factor in the presented preliminary report.

The presented preliminary report focused on two forms of vitamin D: 25-hydroxyvitamin D and 1,25-dihydroxy vitamin D, available in the local laboratory. The vitamin D sufficiency was determined by standard institutional thresholds which are not dedicated to, and not adjusted to paediatric patients and differ from the thresholds proposed in the literature. The generally accepted thresholds for vitamin D sufficiency differed between literature [5] and available institutional laboratories. Further studies on vitamin D serum concentration in paediatric patients should be conducted to determine adjusted thresholds and to enable better vitamin D level monitoring.

According to Boehne et. al. [4], the period between 24–72 hours is the most probable period of SIRS incidence after paediatric cardiac surgery with the use of ECC. Yet another study claims that around 20% of SIRS may happen up to 5 days after the surgery [21]. To focus on the postoperative SIRS pathophysiology, the time of the collection of blood samples for vitamin D and inflammatory biomarkers measurements was set to 2 and 6 days after the surgery. The postoperative measurements were put in comparison to preoperative, unimpaired, inflammatory patients' status. On the 6th day a normalized inflammatory status was expected – confirmed by the inflammatory biomarkers. The patients that did not fulfil the inclusion criteria and developed any additional postoperative complications were excluded from the study group. On the other hand, their vitamin D status could differ from the patients included in the study, probably presenting a deeper deficiency level, which emphasizes the need to establish whether vitamin D deficiency could be associated with final clinical outcomes.

The inverse correlation between 25(OH)D₃ and CRP had been previously studied in elderly patients with inflammatory diseases and showed a negative correlation between those [9]. The vitamin D status after cardiac surgeries with ECC in children was also compared to the albumin level as the patients' homeostasis monitoring factor, not showing any significant correlation [20].

The study group in this preliminary report was also heterogeneous. The paediatric patients with CHD have

presented with different types of CHD and concomitant disorders as the symptoms of HF, cyanosis, metabolic demands, organ insufficiency, drugs administered, genetic abnormalities etc. Although all the patients underwent cardiac surgery procedures with the use of ECC, their general condition, type and severity of surgery performed, and the time of the ECC and hypothermia applied differed. Next, the SIRS may lead to different organs disturbance, or failure altering other metabolic pathways [4]. All these factors could potentially cause susceptibility to vitamin D serum concentration fluctuations during the postoperative period and result in alterations to raw and statistical data for this preliminary report.

Furthermore, the interquartile ranges values may doubt the exact results' applicability, especially for the values of the $1.25(\text{OH})_2\text{D}_3$ vitamin D active metabolite. The interquartile range (IQR) values for all $25(\text{OH})\text{D}_3$ serum concentrations measured were similar, low values ($\text{IQR}_{\text{max}} = 23.25$ and $\text{IQR}_{\text{min}} = 8.45$), whereas for both $1.25(\text{OH})_2\text{D}_3$ and CRP measurement the IQR was significantly higher ($1.25(\text{OH})_2\text{D}_3$ $\text{IQR}_{\text{max}} = 92.85$; CRP IQR = 133.50) showing a notable spread of the data. The statistical analysis suggests that there may be different dynamics between $25(\text{OH})\text{D}_3$ and $1.25(\text{OH})_2\text{D}_3$ in the perioperative period and emphasizes the need to research a significantly larger study group to obtain more comparable results.

For the time of this preliminary study being conducted, the paediatric cardiac surgery population is supplemented with the standard doses of vitamin D recommended for the general population by the Polish Society of Paediatric Endocrinology and Diabetes. Further studies of presented relationships between the postoperative SIRS and vitamin D serum level could determine whether the perioperative vitamin D level maintenance could have a therapeutic effect and a benefit for demanding paediatric patients undergoing cardiac surgery in early infancy. And, as the clinical postoperative outcomes may in many ways depend on vitamin D status, what kind of vitamin D supplementation should be applied to paediatric cardiac surgery patients.

Limitations of the study

There are several limitations to be mentioned regarding this study. The presented report is a prospective, one-centre

observational study of a small group of children referred for cardiosurgical operation in ECC without randomization. Preoperatively vitamin D was administered by parents at home, therefore one could not exclude some individual differences as an effect of suboptimal, negligent drug regimens, or even the difference in the quality of pharmacy-delivered vitamin D drops. Although the perioperative antibiotic prophylaxis algorithm was homogenous, during the observation period the range of operative trauma might differ in selected groups of patients. Therefore, the differences in values of CRP and leukocytosis in the early postoperative period might exist, although reproductive characteristics of biomarkers trends were observed. In addition, particular operative strategies at the study institution, as well as postoperative care of paediatric patients after cardiac surgery with ECC may differ from other centres. There is no doubt that further studies are needed.

Conclusions

Standard vitamin D supplementation in children with CHD referred for cardiac surgical treatment with means of surgery with ECC does not prevent perioperative serum vitamin D level drop and its potential clinical consequences.

The dynamics of early postoperative inflammatory markers level increase correlates with early postoperative serum vitamin D concentration drop below the therapeutic level.

The observation and preliminary results eligible further studies to determine new universal protocols of preoperative, and perioperative vitamin D administration to prevent vitamin D deficiency in children operated on for CHD in infancy.

Conflict of interest

None declared.

Funding

None

Streszczenie

Wstęp. Operacje kardiologiczne u dzieci wykonywane z powodu wrodzonych wad serca (CHD, *congenital heart defects*) w krążeniu pozaustrojowym (ECC, *extracorporeal circulation*) prowadzą do różnych postaci zespołu ogólnoustrojowej reakcji zapalnej (SIRS, *systemic inflammatory response syndrome*) mierzonej rutynowymi biomarkerami (białko C-reaktywne [CRP, *C-reactive protein*], prokalcytonina). Stężenie witaminy D w wielu potencjalnych mechanizmach może być związane z poziomem aktywacji odpowiedzi zapalnej w ostrej fazie SIRS po ECC u operowanych niemowląt z CHD.

Materiał i metody. Badaniem objęto grupę 20 niemowląt (wiek: 4–7 miesięcy) z CHD, które poddano kardiochirurgicznej korekcji wrodzonych wad serca metodą w krążeniu pozaustrojowym w umiarkowanej hipotermii na jednym oddziale kardiochirurgicznym. Stężenie witaminy D (w dwóch postaciach: 25(OH)D₃ i 1,25(OH)₂D₃) oraz CRP i leukocytozy mierzono trzykrotnie: dzień przed operacją, w 2. dobie po operacji i ostatecznie – w 6. dobie pooperacyjnej. Wszystkie niemowlęta otrzymywały standardową dawkę suplementacji witaminą D (500 IU doustnie) w 1. tygodniu po urodzeniu, a także w 1. dobie pooperacyjnej tuż po powrocie do karmienia doustnego. Wszystkie próbki zostały pobrane, poddane analizie laboratoryjnej, a uzyskane dane poddano analizie statystycznej. Zastosowano standardowo przyjęte progi definiujące niedobór witaminy D.

Wyniki. Stężenie witaminy D w osoczu u wszystkich pacjentów przed operacją, jak również stężenie biomarkerów zapalnych mieściły się w zakresie normy. Jakikolwiek objawy kliniczne potencjalnej infekcji zostały zidentyfikowane i wykluczone. W 2. dobie pooperacyjnej, kiedy obserwowano szczytowy poziom stężenia CRP, aktywny metabolit witaminy D spadł do poziomu ciężkiego niedoboru. W 6. dobie pooperacyjnej stężenie CRP było w zakresie zbliżonym do prawidłowego, a poziom witaminy D powrócił do stanu sprzed operacji.

Wnioski. Wstępne wyniki wykazały odwrotną korelację pomiędzy parametrami SIRS a poziomem witaminy D u niemowląt przy standardowej suplementacji przedoperacyjnej. Dalsze badania przedstawionych zależności mogłyby określić, czy okołoperacyjna suplementacja witaminą D może mieć efekt terapeutyczny i przynieść korzyść pacjentom pediatrycznym poddawanych zabiegom kardiochirurgicznym we wczesnym okresie niemowlęcym.

Słowa kluczowe: witamina D, zespół ogólnoustrojowej reakcji zapalnej, pediatria, kardiochirurgia dziecięca, wrodzone wady serca

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References

- Liu Y, Chen S, Zühlke L, et al. Global birth prevalence of congenital heart defects 1970-2017: updated systematic review and meta-analysis of 260 studies. *Int J Epidemiol.* 2019; 48(2): 455–463, doi: [10.1093/ije/dyz009](https://doi.org/10.1093/ije/dyz009), indexed in Pubmed: [30783674](https://pubmed.ncbi.nlm.nih.gov/30783674/).
- Best KE, Rankin J. Long-term survival of individuals born with congenital heart disease: a systematic review and meta-analysis. *J Am Heart Assoc.* 2016; 5(6): e002846, doi: [10.1161/JAHA.115.002846](https://doi.org/10.1161/JAHA.115.002846), indexed in Pubmed: [27312802](https://pubmed.ncbi.nlm.nih.gov/27312802/).
- Ziyaeifard M, Alizadehasl A, Massoumi G. Modified ultrafiltration during cardiopulmonary bypass and postoperative course of pediatric cardiac surgery. *Res Cardiovasc Med.* 2014; 3(2): e17830, doi: [10.5812/cardiovascmed.17830](https://doi.org/10.5812/cardiovascmed.17830), indexed in Pubmed: [25478538](https://pubmed.ncbi.nlm.nih.gov/25478538/).
- Boehne M, Sasse M, Karch A, et al. Systemic inflammatory response syndrome after pediatric congenital heart surgery: Incidence, risk factors, and clinical outcome. *J Card Surg.* 2017; 32(2): 116–125, doi: [10.1111/jocs.12879](https://doi.org/10.1111/jocs.12879), indexed in Pubmed: [27928843](https://pubmed.ncbi.nlm.nih.gov/27928843/).
- McNally JD, O'Hearn K, Lawson ML, et al. Prevention of vitamin D deficiency in children following cardiac surgery: study protocol for a randomized controlled trial. *Trials.* 2015; 16: 402, doi: [10.1186/s13063-015-0922-8](https://doi.org/10.1186/s13063-015-0922-8), indexed in Pubmed: [26353829](https://pubmed.ncbi.nlm.nih.gov/26353829/).
- Pilz S, Zittermann A, Trummer C, et al. Vitamin D testing and treatment: a narrative review of current evidence. *Endocr Connect.* 2019; 8(2): R27–R43, doi: [10.1530/EC-18-0432](https://doi.org/10.1530/EC-18-0432), indexed in Pubmed: [30650061](https://pubmed.ncbi.nlm.nih.gov/30650061/).
- Rusińska A, Płudowski P, Walczak M, et al. Vitamin D supplementation guidelines for general population and groups at risk of vitamin D deficiency in Poland – recommendations of the Polish Society of Pediatric Endocrinology and Diabetes and the Expert Panel with Participation of National Specialist Consultants and Representatives of Scientific Societies – 2018 update. *Front Endocrinol (Lausanne).* 2018; 9: 246, doi: [10.3389/fendo.2018.00246](https://doi.org/10.3389/fendo.2018.00246), indexed in Pubmed: [29904370](https://pubmed.ncbi.nlm.nih.gov/29904370/).
- Ney J, Heyland DK, Amrein K, et al. The relevance of 25-hydroxyvitamin D and 1,25-dihydroxyvitamin D concentration for postoperative infections and postoperative organ dysfunctions in cardiac surgery patients: The eVIDenCe study. *Clin Nutr.* 2019; 38(6): 2756–2762, doi: [10.1016/j.clnu.2018.11.033](https://doi.org/10.1016/j.clnu.2018.11.033), indexed in Pubmed: [30583965](https://pubmed.ncbi.nlm.nih.gov/30583965/).
- Kruit A, Zanen P. The association between vitamin D and C-reactive protein levels in patients with inflammatory and non-inflammatory diseases. *Clin Biochem.* 2016; 49(7-8): 534–537, doi: [10.1016/j.clinbiochem.2016.01.002](https://doi.org/10.1016/j.clinbiochem.2016.01.002), indexed in Pubmed: [26778547](https://pubmed.ncbi.nlm.nih.gov/26778547/).
- Autier P, Mullie P, Macacu A, et al. Effect of vitamin D supplementation on non-skeletal disorders: a systematic review of meta-analyses and randomised trials. *Lancet Diabetes Endocrinol.* 2017; 5(12): 986–1004, doi: [10.1016/S2213-8587\(17\)30357-1](https://doi.org/10.1016/S2213-8587(17)30357-1), indexed in Pubmed: [29102433](https://pubmed.ncbi.nlm.nih.gov/29102433/).
- McNally JD, Menon K, Chakraborty P, et al. The association of vitamin D status with pediatric critical illness. *Pediatrics.* 2012; 130(3): 429–436, doi: [10.1542/peds.2011-3059](https://doi.org/10.1542/peds.2011-3059), indexed in Pubmed: [22869837](https://pubmed.ncbi.nlm.nih.gov/22869837/).
- Schleithoff SS, Zittermann A, Tenderich G, et al. Vitamin D supplementation improves cytokine profiles in patients with congestive heart failure: a double-blind, randomized, placebo-controlled trial. *Am J Clin Nutr.* 2006; 83(4): 754–759, doi: [10.1093/ajcn/83.4.754](https://doi.org/10.1093/ajcn/83.4.754), indexed in Pubmed: [16600924](https://pubmed.ncbi.nlm.nih.gov/16600924/).
- Dziedzic EA, Gąsior JS, Pawłowski M, et al. Vitamin D level is associated with severity of coronary artery atherosclerosis and incidence of acute coronary syndromes in non-diabetic cardiac patients. *Arch Med Sci.* 2019; 15(2): 359–368, doi: [10.5114/aoms.2019.83291](https://doi.org/10.5114/aoms.2019.83291), indexed in Pubmed: [30899288](https://pubmed.ncbi.nlm.nih.gov/30899288/).

14. Izzo M, Carrizzo A, Izzo C, et al. Vitamin D: not just bone metabolism but a key player in cardiovascular diseases. *Life (Basel)*. 2021; 11(5): 452, doi: [10.3390/life11050452](https://doi.org/10.3390/life11050452), indexed in Pubmed: [34070202](https://pubmed.ncbi.nlm.nih.gov/34070202/).
15. Graham EM, Taylor SN, Zybiewski SC, et al. Vitamin D status in neonates undergoing cardiac operations: relationship to cardiopulmonary bypass and association with outcomes. *J Pediatr*. 2013; 162(4): 823–826, doi: [10.1016/j.jpeds.2012.10.013](https://doi.org/10.1016/j.jpeds.2012.10.013), indexed in Pubmed: [23149171](https://pubmed.ncbi.nlm.nih.gov/23149171/).
16. Ye X, Dong S, Deng Y, et al. Preoperative vitamin D deficiency is associated with higher vasoactive-inotropic scores following pediatric cardiac surgery in Chinese children. *Front Pediatr*. 2021; 9: 671289, doi: [10.3389/fped.2021.671289](https://doi.org/10.3389/fped.2021.671289), indexed in Pubmed: [34395337](https://pubmed.ncbi.nlm.nih.gov/34395337/).
17. Shedeed SA. Vitamin D supplementation in infants with chronic congestive heart failure. *Pediatr Cardiol*. 2012; 33(5): 713–719, doi: [10.1007/s00246-012-0199-6](https://doi.org/10.1007/s00246-012-0199-6), indexed in Pubmed: [22349668](https://pubmed.ncbi.nlm.nih.gov/22349668/).
18. Chang HY, Hsu CH, Tsai JD, et al. Renal calcification in very low birth weight infants. *Pediatr Neonatol*. 2011; 52(3): 145–149, doi: [10.1016/j.pedneo.2011.03.004](https://doi.org/10.1016/j.pedneo.2011.03.004), indexed in Pubmed: [21703556](https://pubmed.ncbi.nlm.nih.gov/21703556/).
19. Schlingmann KP, Kaufmann M, Weber S, et al. Mutations in CYP24A1 and idiopathic infantile hypercalcemia. *N Engl J Med*. 2011; 365(5): 410–421, doi: [10.1056/NEJMoa1103864](https://doi.org/10.1056/NEJMoa1103864), indexed in Pubmed: [21675912](https://pubmed.ncbi.nlm.nih.gov/21675912/).
20. Abou Zahr R, Faustino EV, Carpenter T, et al. Vitamin D status after cardiopulmonary bypass in children with congenital heart disease. *J Intensive Care Med*. 2017; 32(8): 508–513, doi: [10.1177/0885066616652077](https://doi.org/10.1177/0885066616652077), indexed in Pubmed: [27251108](https://pubmed.ncbi.nlm.nih.gov/27251108/).
21. Soares LC, Ribas D, Spring R, et al. [Clinical profile of systemic inflammatory response after pediatric cardiac surgery with cardiopulmonary bypass]. *Arq Bras Cardiol*. 2010; 94(1): 127–133, doi: [10.1590/s0066-782x2010000100019](https://doi.org/10.1590/s0066-782x2010000100019), indexed in Pubmed: [20414536](https://pubmed.ncbi.nlm.nih.gov/20414536/).