Trials

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Increase in calcidiol level is associated with improved sternal bone healing after cardiac surgery with sternotomy—REINFORCE-D trial results

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Abstract

Introduction Heart surgery is associated with a sternotomy in most patients. Low serum calcidiol level below 80 nmol/l carries the risk of bone loss as a risk factor in sternotomy healing.

Objectives The primary objective was to compare postoperative complications of sternotomy healing in two groups of patients treated with cholecalciferol or placebo. Secondary objectives were focused on the degree of sternal healing, length of hospitalization, number of days spent in ICU and mechanical ventilation, and number of repeated hospitalizations for sternotomy complications.

Methodology Monocentric, randomized, double-blind, placebo-controlled, prospective study was conducted from September 2016 to December 2020 at Na Homolce Hospital. Of the 216 originally recruited and randomized subjects, 141 completed the study. Seventy-two subjects were enrolled in the cholecalciferol arm, and sixty-nine subjects in the placebo arm. The detailed methodology has been published previously. The results are presented as a comparison between two groups: calcidiol above 80 nmol/l (saturated subjects) and the calcidiol lower or equal to 80 nmol/l (unsaturated subjects).

Results Statistics include 141 subjects. After a 6-month follow-up, CT imaging and calcidiol levels were performed. Primary objective: postoperative complications in sternotomy were not among the population under or above 80 nmol/l statistical difference ($p = 0.907$). Secondary objectives: monitored parameters did not differ between individual arms. But the key was the state of saturation with calcidiol (> 80 nmol/l), which was associated with a significantly lower risk of complete non-healed sternotomy ($p = 0.008$).

Conclusion Optimal calcidiol level (> 80 nmol/l) indicates a positive trend towards greater sternal healing. Cholecalciferol oral administration can be considered as a safe method how to achieve the required calcidiol concentration.

Trial registration EU Clinical Trials Register, EUDRA CT No: 2016–002606-39.

Keywords Vitamin D, Cholecalciferol, Cardiac surgery, Bone healing, Sternotomy, Calcidiol serum concentration

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Introduction

The majority of open-heart surgery patients undergo median sternotomy. From the pathophysiological point of view, sternotomy is considered fractured bone.

Sternotomy healing after cardiac surgery intervention is an arduous, complex, and multifactorial process dependent on many independent factors affecting not only the sternum but also surrounding soft tissues. Sternotomy healing complications are among the challenges in cardiac surgery. Complication rates for median sternotomy range from 0.5 to 5%; however, mortality rates from complications are variable (7–80%). Complications may affect the presternal (cellulitis, sinus tracts, abscess), sternal (osteomyelitis, dehiscence), or retrosternal (mediastinitis, hematoma, abscess) compartments [1]. According to previous studies, superficial complications occur in 1.1–6.7% of patients, whereas the incidence of deep sternal wound complications range from 0.1 to 3.7% [2–4]. In another single-center study involving 1279 subjects, 76 subjects (5.8%) developed sternal wound complications, superficial healing disorders occurred in 43 subjects (3.3%), while 33 subjects (2.5%) developed deep wound complications [5]. For the purposes of the present clinical trial, sternotomy healing complications (infective or non-infective) within the trial were defined as presternal complications (superficial soft tissues), sternal complications (sternal dehiscence or instability), and retrosternal complications (mediastinal tissues).

It has been hypothesized that low serum calcidiol concentration may affect sternotomy healing, as it can lead to sternal osteoporosis and impaired bone healing [6, 7]. Several osteoanabolic drugs (teriparatide, calcitonin) have been applied to enhance fracture healing in the setting of osteoporosis [8]. Although the majority of studies in animals support the beneficial effects of cholecalciferol on fracture healing, data from larger randomized trials are still lacking [9]. There is also some evidence of negative correlation between low calcidiol concentrations and poor wound healing; the healing of soft tissues adjacent to the sternum is directly dependent on sternal stability. There is also further evidence of the positive effect of vitamin D on superficial wound healing by systemic treatment [10].

According to a large German study (4418 cardiac surgery subjects), 38% of subjects had deficient serum calcidiol concentrations (below 30 nmol/L) and an additional 32.3% of subjects had an insufficient concentration (30–49.9 nmol/L). A positive correlation was also found between low calcidiol serum concentration and greater postoperative cardiovascular complications (higher number of ventilation days, higher number of cardiac and cerebrovascular events). Subjects with optimal calcidiol concentrations in the range of 75–100 nmol/L showed the lowest number of these events; however, only 7.3% of subjects achieved such serum concentrations. Subjects with insufficient concentrations of 50–74.9 nmol/L formed a borderline group 19.2%, where the number of these events was partially reduced but without statistical significance [11].

The optimal duration of sternum healing is the subject of debate. According to one study published in 2014, the sternum was not fully recovered after 3 nor after 6 months [12]. In the present clinical trial, a 6-month period for evaluation was selected due to the high probability of capturing any bone and soft tissue sternotomy healing complications during the trial using computed tomography.

Although the optimal serum calcidiol concentration for both skeletal and nonskeletal health is controversial, in the present trial, all non-placebo group subjects were treated with cholecalciferol individually to achieve serum calcidiol concentrations in the range of 75–100 nmol/L at the end of the trial. A cut-off value for target serum calcidiol concentration was set at 80 nmol/L for evaluation purposes.

Materials and methods

The REINFORCE – D clinical trial, registered on September 8, 2016, was performed at Na Homolce Hospital from 2016 to 2020 as a monocentric, randomized, double-blind, placebo-controlled, prospective trial. All details regarding trial design and methodology have been published previously [13].

The clinical trial protocol was approved by the ethics committee of Na Homolce Hospital and the local regulatory authority (SUKL). Informed consent was obtained from all individual participants included in the study.

Subjects

Male and female subjects aged 18 to 95 years who met the eligibility criteria and fulfilled the indication criteria for undergoing cardiac surgery with sternotomy were included in the trial. Exclusion and inclusion criteria, as well as prohibited concomitant medication and they are described in detail in the already published methodology [13]. Subjects were randomized at a 1:1 ratio (placebo or treated subject) by sealed randomization envelopes.

Trial medication

Unlabeled vials of the original medical product Vigantol® obtained from Merck Serono (Darmstadt, Germany) with cholecalciferol (active compound concentration 500 IU per drop) were used as an IMP (investigational medicinal product). Placebo was prepared as a compounded product at the Na Homolce Hospital pharmacy. The same vials as unlabeled Vigantol® were filled with

liquid saturated triglycerides in pharmaceutical quality obtained from Fagron (Olomouc, Czech Republic). The content of cholecalciferol was not verified, but it was considered as zero. Trial medication (placebo and IMP) was freshly compounded by the responsible hospital pharmacist on the day of randomization. A total of 340 vials of trial medication (placebo or IMP) were compounded.

Trial individualized medication dosing scheme

Specific cholecalciferol/placebo dosing was managed by a two-step scheme. The first step was an initial single bolus (50 drops) and the second step involved a maintenance dose schedule divided into three cohorts based on the initial (preoperative) calcidiol serum concentration. Each dose (expressed as drop count) was repeated once per week, administered by nurses on the cardiac surgery ward (inpatients) and thereafter by trial participants at home (outpatients). To improve outpatient drug dosing adherence, a special text message reminder system was introduced. The dosing scheme in detail is shown in Table 1; the total duration of therapy was 26 weeks. The rationale for this dosing regimen has been explained previously [12].

Laboratory, physical, and radiology examinations

All the examinations were planned throughout the entire trial and are completely described in methodology published previously. Laboratory examinations of serum calcium, phosphate, ALT, and ALP were performed from blood serum by using routine spectrophotometric biochemical analysis in all cardiac surgery subjects, not only trial participants. The 25-hydroxy vitamin D (=calcidiol) serum concentration was measured twice (preoperatively, postoperatively at the 6th month) in all trial subjects. The assay method was based on the principle of a competitive immunochemical reaction with chemiluminescent detection using the.

ADVIA Centaur XP analyzer (Siemens Healthineers; Forchheim, Germany).

Computed tomography (Somatom Definition Flash, Siemens Healthineers; Forchheim, Germany) with Safire interative reconstruction was performed on all subjects.

Statistical methods

Continuous variables were expressed as mean values ± standard deviation, categorical variables as absolute (relative) frequencies. Continuous variables were compared with Student's *t* test, categorical variables with the chi-square test, respectively with Fisher's exact test if the expected frequency of at least one of the 2×2 contingency tables was lower than five. Odds ratio analysis was used to evaluate primary and secondary objectives. A value of $p<0.05$ (two-sided test) was considered to be statistically significant. Statistical analyses were performed using Microsoft Excel 2016 and GraphPad Prism 9.5.1 statistical software.

Results

The results were divided to 2 main groups: efficacy data regarding primary and secondary outcomes, and safety data for safety outcomes.

A total of 216 trial subjects were recruited (Fig. 1), of which:

- 27 subjects withdrew during the trial for various reasons (lost interest, fear of further examination, hematophobia, withdrawal for unknown reason, cognitive deficit, non-compliance, health complications, operation canceled)
- 7 subjects retrospectively excluded due to missed exclusion criteria
- 41 subjects did not undergo the final examinations (after 6 months) and therefore were not included in the analysis.

A total of 141 subjects (mean age 66.4 ± 10.5 years, range 21–83; 31% female) completed clinical assessment and were included, of which 72 subjects were included in

Table 1 Individualized dosing with number of IMP drops given to specific cohorts

Initial calcidiol concentration	Initial bolus		Maintenance dose	
	Placebo	Cholecalciferol	Placebo	Cholecalciferol
1–24 nmol/L	0 IU 50 drops once before sternotomy	25,000 IU	0 IU 40 drops once a week after sternotomy	20,000 IU
25–49 nmol/L	0 IU 50 drops once before sternotomy	25,000 IU	0 IU 25 drops once a week after sternotomy	12,500 IU
50–75 nmol/L	0 IU 50 drops once before sternotomy	25,000 IU	0 IU 10 drops once a week after sternotomy	5000 IU

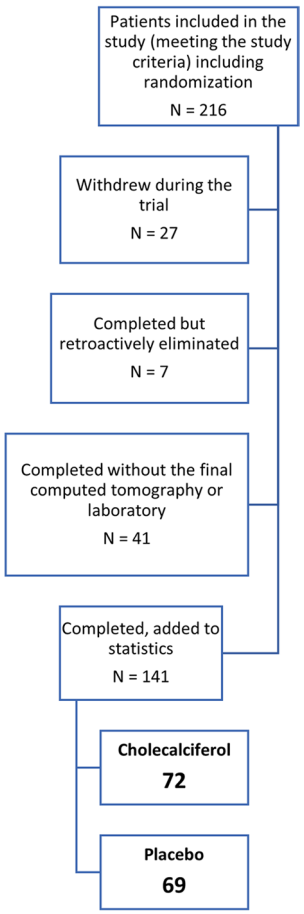

Fig. 1 Flow diagram of clinical trial subjects after recruitment

the cholecalciferol group and 69 subjects in the placebo group.

Comparison between baseline and target calcidiol serum concentration during the trial

As shown in Table 2, 32.9% of subjects in the placebo arm reached a target serum concentration of 80 nmol/L, while 33.8% of subjects in the cholecalciferol group were not able to achieve the target calcidiol concentration. A significant group-wise difference was demonstrated between those who were and were not able to achieve target calcidiol concentration ($p < 0.001$). It can be concluded that the dose regimens used during the trial were well designed.

We expressed all results based on whether the subject was "successfully saturated" by 25OH D (achieved final calcidiol concentration above 80 nmol/L) or "unsuccesfully saturated" by 25OH D (achieved final calcidiol concentration below or equal to 80 nmol/L) at the end of the trial, rather than based placebo or cholecalciferol cohort membership. This was considered a more objective manner of assessment.

Table 2 Distribution of saturated and unsaturated subjects by calcidiol (25OH D) in placebo or cholecalciferol groups

	25OH D > 80 nmol/L (*N* = 73)	**25OH D ≤ 80 nmol/L (*N* = 68)**	***p***
Placebo (*N* = 69)	24 (32.9)	45 (66.1)	< 0.001
Cholecalciferol (*N* = 72)	49 (67.1)	23 (33.8)	

Baseline demographic characteristics

As shown in Table 3, the average age of included participants was 66.41 ± 10.48 years, with men more often represented (68.1%). The average BMI of the whole trial group was 28.84 ± 5.32 kg/m^2, and the average initial calcidiol concentration was 48.68 ± 12.90 nmol/L. A significant difference between the saturated and unsaturated population was determined only for BMI (27.51 ± 4.88 vs. 30.29 ± 5.4 kg/m^2, $p = 0.001$). This finding can be interpreted such that subjects with lower BMI were able to easily achieve the target serum calcidiol concentration.

Primary and secondary outcome efficacy results

Primary and secondary outcome efficacy results

Primary efficacy outcome: sternotomy healing complications

Regarding the primary objective, the incidence of all postoperative sternotomy healing complications (presternal, sternal, and retrosternal), there was no significant difference in incidence between the saturated and unsaturated population (6.8% vs. 6.3%, OR = 1.079 (0.298; 3.906), $p = 0.907$). Data are shown in Table 4.

Table 3 Baseline demographic characteristics

	Total (*N* = 141)	**25OH D > 80 nmol/L (*N* = 73)**	**25OH D ≤ 80 nmol/L (*N* = 68)**	***p***
Age (years)	66.41 ± 10.48	67.82 ± 10.47	64.89 ± 10.29	0.099
Female sex *N* (%)	45 (31.9)	20 (27.4)	25 (36.8)	0.233
BMI (kg/m^2)	28.84 ± 5.32	27.51 ± 4.88	30.29 ± 5.4	0.001
Initial calcidiol level (nmol/L)	48.68 ± 12.90	48.01 ± 12.9	49.39 ± 12.86	0.527

Table 4 Primary and secondary efficacy outcomes in calcidiol saturated and unsaturated trial participants

		25OH D > 80 nmol/L (*N* = 73)	25OH D ≤ 80 nmol/L (*N* = 68)	OR (95% CI)	*p*
Primary objective	**Healing complications, *N* (%)**	5 (6.8)	5 (6.3)	1.079 (0.298; 3.906)	0.907
Secondary objectives	**Healing grade 0 *N* (%)**	10 (13.7)	22 (32.4)	0.332 (0.143; 0.768)	0.008
	Readmissions, *N* (%)	2 (2.7)	3 (4.4)	1.638 (0.265;10.118)	0.672
	Ventilator spent days, *N* (%)	1.03 ± 0.16	1.13 ± 1.08	NA	0.418
	ICU spent days *N* (%)	5.15 ± 1.86	4.75 ± 1.87	NA	0.208
	Days of pericardial effusions therapy, *N* (%)	0.52 ± 3.46	0.91 ± 5.28	NA	0.601
	Hospitalization days, *N* (%)	11.97 ± 8.82	10.21 ± 3.88	NA	0.127

Secondary efficacy outcomes

Sternal healing grade at the end of the trial

For objective sternal healing evaluation after CT examination, a validated healing grade scoring system with 6 degrees (0–5) was used. This scoring system was developed and published previously [11]. The subjects were divided into 2 groups: "not healed" (healing degree = 0) and "partially healed" plus "fully healed" (healing grade 1–5). As shown in Table 4, a significant difference in the incidence of total sternal complete of sternal healing was demonstrated between saturated and unsaturated participants at the end of the trial (13.7% vs. 32.4%, OR 0.332 (0.143; 0.768); $p = 0.008$). Significant differences were found in the average final calcidiol concentration (64.21 ± 25.51 nmol/L vs. 80.51 ± 23.83 nmol/L, $p = 0.002$) as well as the average change between final and initial calcidiol concentration (3.03 ± 14.58 vs. 25.1 ± 27.55 nmol/L, $p < 0.001$) between participants whose sternum showed no healing at the end of the trial and participants whose sternum was healed at least partially (degree 1–5; data shown in Table 5). To quantify the process of "sternal healing" in detail, we elected to use regression analysis. When comparing two linear regression curves describing the relationship between percentage of subject distribution in both groups and sternal healing grade, the healing process in the 25OH D > 80 nmol/L group was significantly ($p < 0.01$) faster than in the 25 OH D ≤ 80 nmol/L group, as shown in Fig. 2. The critical correlation coefficient value for 6 grades was R2 > 0.917.

Other secondary outcomes at the end of the trial

When comparing the average number of readmissions, number of days spent on ventilator, number of days spent in ICU, number of days of pericardial/pleural effusion treatment, and number of days spent in hospital, there were no significant differences in incidence between the saturated and unsaturated population at the end of the trial; the data are shown in Table 4.

Safety outcomes

Laboratory safety endpoints

No abnormalities in serum calcium, phosphate, and alkaline phosphatase (ALP) occurred throughout the entire trial, measured at time of hospitalization, at 6 weeks and 6 months after cardiac surgery.

Serious adverse events

No serious adverse events were noted.

Non-serious adverse events

Four subjects reported diarrhea several weeks after randomization. Their trial participation was concluded for preventive reasons. These subjects were unblinded; three subjects were from the cholecalciferol group and one was from the placebo group. No other side effects were noted.

Table 5 Average difference between final and initial calcidiol concentration and average final calcidiol concentration in patients healed to grade 0 and 1–5

	Healing grade 0 (*N* = 32)	Healing grade 1–5 (*N* = 109)	*p*
Average final calcidiol concentration (nmol/L)	64.21 ± 25.51	80.51 ± 23,83	0.002
Average difference between final and initial calcidiol concentration (nmol/L)	3.03 ± 14.58	25.1 ± 27.55	< 0.001

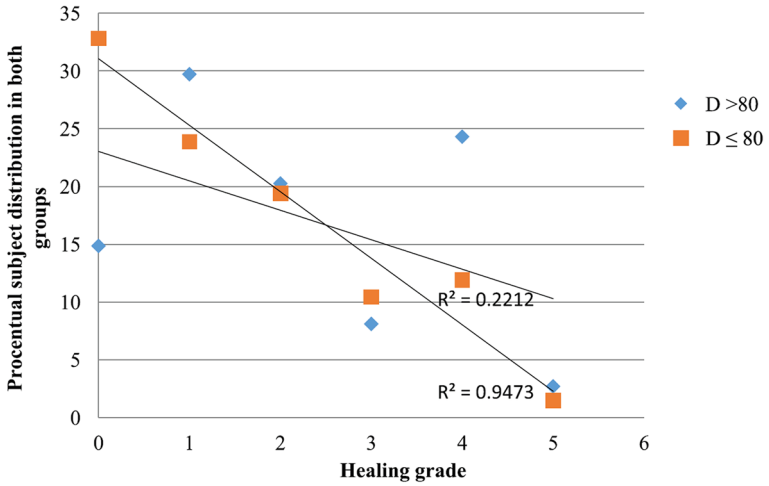

Fig. 2 Linear regression analysis—relationship between healing grade and percentual subject distribution in 25OH D > 80 nmol/L and 25 OH D ≤ 80 nmol/L groups

Discussion

This prospective, randomized, double-blind trial opened new point of view to the cardiac surgery with sternotomy risk factors and their individualized prevention.

Since the trial began, there have been other trials concerned with the same topic [14, 15]. One trial by radiology specialists from Turkey was very similarly designed [16]. They observed subjects in cohorts with different calcidiol deficiencies and examined them by CT after 3 and 6 months. Their findings were very similar to ours with subjects without optimal increase of calcidiol (as shown in Fig. 2).

Optimal timepoint for sternotomy healing evaluation

An important finding was that in the majority of subjects the sternum was not fully healed after 6 months regardless of calcidiol concentration. The status of the sternum at this postoperative time point has also been confirmed by other published data [17, 18]. Therefore, it can be concluded that the length of this trial was optimally set, as it was possible to compare subjects with a significant increase in calcidiol concentration (mostly subjects administered cholecalciferol) and subjects without an increase (majority of subjects administered placebo) in the context of sternotomy healing, which was ongoing.

Calcidiol saturability evaluation after individualized dosing regimen within the trial

As depicted in Table 2, a statistically significant difference in placebo and cholecalciferol groups was demonstrated between those who were and were not able to achieve the target calcidiol concentration ($p < 0.001$). As shown in Table 3, we may also conclude that calcidiol saturability of the prospectively planned cholecalciferol dosing regimen, which has been described previously [13], was successful and our findings are in concordance with other publications and clinical guidelines [13]. It is clear from our data that increased baseline serum calcidiol concentration was crucial in decreasing the probability of sternal healing failure after 6 months (healing grade 0). Individualization of cholecalciferol dosing appeared to be a very effective tool to increase serum calcidiol level. This regimen is likely transferable mostly in countries and regions with a similar geographical latitude and a similar number of sunny days annually. Although the majority of subjects (67.1%) in the cholecalciferol group successfully achieved a target calcidiol concentration above 80 nmol/L, 33.8% of subjects taking the same medication were unable to achieve this "cut-off" concentration at the end of the trial. These subjects (33.8%) may have been non-adherent to their medication regimens, or they may have had problems with vitamin D absorption or its intrinsic conversion to calcidiol (for example vitamin D 25-hydroxylase deficiency). Of note, subjects with lower BMI (27.51 ± 4.88) were able to achieve the target serum calcidiol concentration as opposed to subjects with higher BMI (30.29 ± 5.4). This may be explained by two main factors: obese subjects have a greater amount of adipose tissue (larger deposition for lipophilic vitamins) and less often follow medical recommendations, especially regarding lifestyle changes [19]. Conversely, 32.9% of trial participants that received placebo were able to achieve the target calcidiol concentration above 80 nmol/L. This finding may be explained by intentional/non-intentional dietary vitamin D administration (although subjects were

instructed with respect to dietary vitamin D intake) and varying duration of sun exposure. The number of days spent in the sun, when at least half of the body is exposed to sunlight, and the number of days with a cough were included in the patient questionnaire, but the yield from this data was very poor.

Dosing frequency considerations

Another factor affecting both subject groups was the dosing frequency of trial medication. It has been shown that supplementation with vitamin D can be achieved equally well with daily, weekly, or monthly dosing frequencies [20]. Weekly dosing may be less effective due to a higher probability to forget the dose than daily dosing, which is more regular. On the contrary, weekly dosing may be better tolerated than monthly dosing regarding adverse gastrointestinal side effects (30 times higher individual dose than in regular daily dose). In the present trial, a weekly dosing regimen was used and supported by text message reminders to the mobile phones of all trial participants.

Target calcidiol cut-off value

The target calcidiol cut-off value 80 nmol/L is a point for debate. As mentioned above, the primary premise was that optimal calcidiol serum concentration should range between 75 and 125 nmol/L for bone health. We therefore elected to set the cut-off value at a serum concentration 80 nmol/L, to eliminate borderline trial subjects.

Demographic characteristics in trial groups

The trial population was very homogenous initially. There were no statistically significant differences in age, sex, and initial calcidiol serum concentration. The only difference detected was in body mass index, which may explain the decreased probability of achieving the target calcidiol concentration. Calcidiol is a lipophilic molecule with adipose tissue distribution in lower serum concentrations.

Primary efficacy outcomes

To summarize the findings regarding primary efficacy outcomes, we must first declare that it was not possible to include the originally planned 600 subjects (see published methodology for power analysis). Unfortunately, there were not enough suitable subjects that met the entry criteria or would be capable of participating in the trial. Moreover, the epidemiological situation with coronavirus SARS-CoV-19 and the subsequent limitations in elective surgical procedures also played a negative role in trial enrollment. We were therefore not able to include the number of subjects planned by power analysis before the trial, and thus there were only a very small number of subjects with postoperative complications, which led to a non-countable result regarding the primary endpoint. The statistical power of the study was low due to the very small number of subjects in both trial groups.

Secondary efficacy outcomes

In Table 4, a significant difference in the incidence of complete sternal dehiscence was demonstrated between saturated and unsaturated participants at the end of the trial (13.7% vs. 32.4%, OR 0.332 (0.143; 0.768); $p=0.008$). A *t*-test demonstrated significant differences in average final calcidiol concentration (64.21 ± 25.51 nmol/L vs. 80.51 ± 23.83 nmol/L, $p=0.002$) as well as in average change between final and initial calcidiol concentration (3.03 ± 14.58 vs. 25.1 ± 27.55 nmol/L, $p<0.001$) between participants whose sternum completely failed to heal at the end of the trial and participants whose sternum healed at least partially (degree 1–5; data shown in Table 5). As shown in Fig. 2, a positive correlation was found between "sufficiently saturated" subjects by calcidiol and better healing score (relationship between the distribution of subjects with healing grades). With these findings, it can be concluded that vitamin D and its deposition (in the form of calcidiol) is remarkable and should not be underestimated in subjects undergoing cardiac surgery procedures, especially those requiring median sternotomy. In contrast to previous findings, it is unquestionable that there are many more important factors that affect sternotomy healing, which cannot be prevented nor influenced. These aspects may include individual clinical characteristics, the scope of the surgical procedure, the skill and experience of the cardiac surgeon, patient adherence/tolerance to the whole perioperative and postoperative regimen, operative materials, special devices, and postoperative complications (intrinsic, external). All of these factors can affect fusion of the sternum and the status of serum calcidiol concentration.

Regarding other secondary endpoints (total number of ventilatory days, days spent in ICU, total hospitalization length, readmissions, and days of therapy for pericardial effusion), the difference between groups with lower and higher calcidiol was not statistically significant. However, this was biased by factors not directly related to standard medical care (Czech health-care insurance conditions regarding health care reimbursement, operational conditions in ICU units and semi-intensive care units, hospital record limits [it was possible to collect data rounded to whole days, not hours]). Another factor was low statistical power due to the very small number of subjects.

Conclusion

Cholecalciferol oral administration is a very safe method on how to achieve the required calcidiol concentration. Vitamin D3, even though dosed in higher amounts, showed to be safe except for few adverse gastrointestinal

effects that might be preventable by changing the dosing frequency or switching to another drug formulation. Optimal calcidiol concentration may lead to improved sternal healing after sternotomy.

Trial steering committee, interim clinical trial reports, clinical trial protocol amendments, and patient Public Involvement

The Trial Steering Committee consisted of two physicians, one pharmacist, a main project manager, and one biochemist. This committee met once a month for auditing trial conduct during the entire trial. Rules for the clinical trial termination within the trial were described in our previous methodology paper (SPIRIT Checklist {21b}). The Trial Steering Committee did not have to decide on trial discontinuation due to inconvenient trial interim findings. No extra Data Monitoring Committee was established as this was a low-risk intervention (SPIRIT Checklist {23}). The Ethic Committee and the Czech Institute for Drug Control (SUKL) were regularly (once a year) informed by interim clinical trial reports. No protocol amendments were necessary after the initial SUKL clinical trial approval (SPIRIT Checklist {25}). There was no patient group or patient organization involvement in the design of the protocol because vitamin D supplementation is considered as low-risk therapeutical intervention.

Abbreviations

25OH D	25-Hydroxycholecalciferol
ALP	Alkalic phosphatase
ALT	Alkalic transaminase
BMI	Body mass index
CT	Computed tomography
ICU	Intensive care unit
IMP	Investigational medicinal product
IU	International unit
SMS	Short message service

Acknowledgements

We would like to thank all the nurses who cared for the clinical trial participants, namely Karin Grégrová, Renata Urbanová, Jana Vobrubová, Leona Hurníková, Aneta Ungrová, DiS and Bc. Naďa Marešová; Michala Pokusová, PharmD. as hospital pharmacist who compounded the IMP; Ing. Jana Tamášová from Department of Medical Physics, Na Homolce Hospital who calculated the radiation doses during the CT examination; Ing. Vlasta Dudková who analyzed calcidiol levels. We would like to thank our statistician, Mgr. Jelena Skibová. Special thank in memoriam belongs to our main statistician Prof. Dr. Jana Zvárová, Dr.Sc, who passed away during the final preparations for the trial.

Authors' contributions

All authors are responsible for the work described in this paper. DČ, ES, IS, and MH were involved in the conception, design, or planning of the study. DČ, MČ, BM, ED, and MM were involved in the analysis of data. DČ, MČ, MM, and MH interpreted the study results.

Funding

This study was supported by the Ministry of Health, Czech Republic—conceptual development of Na Homolce Hospital research organization (NNH, 00024883 – IG No 168602, IG No 168601) and by the projects SVV 260 638 and SVV 260 764 – Specific university research projects of 1st Faculty of Medicine research organization.

Availability of data and materials

Any data required to support the protocol can be supplied on request. MC and DC will have access to the final trial dataset.

Declarations

Ethics approval and consent to participate

The clinical trial was reviewed by the Na Homolce Hospital's Local Ethics Committee prior to regulatory authority approval. The Ethics Committee approval from November 2, 2016, is an integral part of the clinical trial documentation. Trial participant signatures on the informed consent form are necessary before recruitment to the clinical trial.

Consent for publication

Informed consent materials are attached as supplementary materials. No identifiable clinical details of participants are presented in this current article or will be presented in the subsequent publication of trial results.

Competing interests

The authors have no conflict of interest. This clinical trial is founded by Na Homolce Hospital and Ministry of Health of the Czech Republic. There is no influence on the pharmaceutical industry.

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Received: 16 July 2024 Accepted: 26 February 2025
Published online: 23 June 2025

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