Volume-5, Issue-9, September- 2016 • ISSN No 2277 - 8160 IF : 3.62 | IC Value 70.36

Original Research Paper Medical Science

Vitamin-Status in Patients Scheduled for Cardiac Surgery. A Prospective Single Centre Analysis

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ABSTRACT

BACKROUND: *This prospective single center study was designed to evaluate the prevalence of deficiency and postoperative level-course of vitaminD (25-hydroxyvitamin D=25(OH)D), E, C and A in cardiosurgical patients.*

METHODS: *Hundred high-risk patients scheduled for elective cardiac surgery were enrolled in this study between January 2010 and March 2013. Fasting serum samples were taken in five different perioperative time-points.*

RESULTS: *Fifty-nine percent of the patient had moderate to sever 25(OH)D deficiency (serum levels<29.9nmol/L), whereas the majority of the patients were presented with sufficient preoperative vitamin E (99%), C (88%) and A (98%) levels. Circulating levels of 25(OH)D below 29.9 nmol/L prior to surgery were associated with an increased in-hospital-mortality (OR=2.78; 95%CI=1.25-3.89, p:0.021) and prolonged intensive care unit stay (p:0.047).*

CONCLUSION: *Moderate to severe 25(OH)D deficiency is prevalent in high-risk patients scheduled for cardiac surgical and is associated with an increased in-hospital mortality and prolonged intensive care unit stay.*

Abstract Word Count: *150*

KEYWORDS : Cardiac Surgery, Intensive Care Unit, perioperative issues and risk profile.

INTRODUCTION

There is no doubt that cardiac surgery is facing the challenge of increasing patient age and comorbidities, both of which lead to a higher perioperative risk profile[1]. Hypovitaminosis is supposed to be prevalent in critically ill patients scheduled for surgery and therefore become a principle topic in surgical research[2].

A growing body of evidence suggests that a substantial proportion of low to middle-risk cardiosurgical patients have less than optimal serum vitamin D levels prior to surgery and that a low vitamin D status is a significant factor associated with the risk of major cardiac and cerebrovascular events in patients undergoing cardiac surgery[3-5].

This prospective single center study was designed to evaluate the prevalence of deficiency and postoperative level-course of vitamin D (25-hydroxyvitaminD=25(OH)D), E, C and A in high-risk patient scheduled for cardiac surgery. Furthermore we herein aimed to investigate the association of perioperative vitamin 25(OH)D, E, C and A levels with mortality and morbidity following cardiac surgery.

MATERIAL AND METHODS

Study population:A total of 100 consecutive high-risk patients scheduled for elective cardiac surgery in the Division of Thoracic and Cardiovascular Surgery of Johann Wolfgang Goethe University, Frankfurt Main, Germany were enrolled in this study from January 2010 through March 2013. The inclusion of the patients within the time stated ensured that patients were enrolled in the study over all four seasons. In order to calculate the risk-profile of our patient cohort logistic European System for Cardiac Operative Risk Evaluation (EuroSCORE) has been used. The exclusion criteria were: malignancy, systemic inflammatory disease, chronic renal failure (chronic renal failure = glomerular filtration rate < 60ml/min/1.73m^2) and failure to obtain consent. The local Ethics Committee approved the study protocol.

Blood sampling: Blood samples (10 ml) were required for determination of the levels of 25(OH)D, vitamin E, C and A. The blood samples were collected in five different time points: one day prior to surgery (T1), immediately after intensive care unit admission (T2), first (T3) second (T4) and 5th (T5) postoperative day.

Circulating 25(OH)D levels were analyzed by the autoanalyzer Liaison (DiaSorin, Stillwater, MN, USA) whereas serum levels of vitamin E, C and A were estimated using high performance liquid chromatography (HPLC).

According to published data following cut-off values for classifying vitamin 25(OH)D status have been used: moderate to severe deficiency (<29.9 nmol/L), mild deficiency (30-49.9 nmol/L), borderline status (50-74.9 nmol/L) and adequacy (75-100 nmol/L)[4,5,7] .The following reference values were used for further vitamin levels: vitamin E: 11.6-46.4µmol/l, vitamin C: 4-21mg/l and vitamin A: 1.05-2.45µmol/l.

Clinical variables: Patient demographic data and medical histories were collected prospectively. Four major event categories (in-hospital death, low cardiac output syndrome (LOS), postoperative myocardial infarction (pMI) and stroke) as well as seven other outcome parameters (length of ICU and in-hospital-stay, intubation time, pulmonary and wound infections, atrial fibrillation, and need for surgical revisions due to postoperative bleeding) were assessed prospectively.

Statistical analyses: Depending on the distribution of the data (Kolmogorov-Smirnov-Test), t-tests and paired t-tests or the Mann-Whitney Rank Sum and Wilcoxon signed rank tests were used to describe differences between groups and the measurements, respectively. Normal distribution was considered if probability values were > 0.05. Non-normally distributed data were logarithmically transformed before analysis. Values are expressed as the mean ± standard deviation or median.

Multiple logistic regression analysis was carried out to assess the independent relationship between perioperative vitamin values and four major event categories including in-hospital death, LOS, pMI and stroke. For evaluating the association of perioperative vitamin levels with the seven other outcome parameters including length of ICU and in-hospital-stay, intubation time, pulmonary and wound infections, atrial fibrillation, and need for surgical revisions due to postoperative bleeding, we used a two-factor analysis of covariance with the aforementioned patients and surgery characteristic as covariates.

A value of $p < 0.05$ was considered statistically significant. Statistical analysis of data was conducted with the SPSS system for statistics (SPSS 22.0 for Windows, SPSS Inc.).

RESULTS

Patient characteristics and operative procedures: From January 2010 through March 2013, 100 consecutive high-risk patients with a mean logistic EuroSCORE of 18.9±3.2%, scheduled for elective cardiac surgery in our department enrolled in this study. They consisted of 32 woman and 68 men with a mean age of 73±10 years and a mean BMI of 26.8 ± 4.3 Kg/m^2. Table 1 summarizes baseline characteristics and detailed operative procedures of the entire patient cohort.

Perioperative outcomes: In-hospital mortality was 7% (n=7). Two patients died due to sepsis and further two patients due to intestinal ischemia. Stroke and low cardiac output were responsible for death in one patient and two patients respectively. Table 2 illustrates perioperative data regarding mortality and morbidity in detail.

Preoperative Vitamin-levels: Only 2% of the study cohort had preoperatively (T1) adequate 25(OH)D values, whereas the majority of the patients presented with sufficient vitamin E (T1, 99%), C (T1, 88%) and A (T1:98%) levels. Fifty-nine percent of the patient had moderate to sever and 32% mild 25(OH)D deficiency. Seven percent were in borderline 25(OH)D status. Furthermore test results revealed that 48% of the patient cohort had vitamin A levels > 2,45 nmol/l (reference value vitamin A: 1.05-2.45µmol/l) prior to surgery, whereas none of the patients showed preoperatively overage serum levels of vitamin 25(OH)D, C and E.

Postoperative Vitamin-course: Figure 1 illustrates the postoperative course of vitamin 25(OH)D, E, C and A. Cardiac surgery led to a significant decrease of 25(OH)D- (T1 to T5, p: 0.041) and vitamin C serum levels (T1 to T2, p: 0.024). Female patients had lower mean serum levels of 25(OH)D preoperatively (p: 0.029) and in time point T4 (p: 0.035) and T5 (p: 0.038). Vitamin C serum levels reached at time point T3 the preoperative mean values of 8.82mg/l, whereas vitamin 25(OH) D, E and A could not reach preoperative mean values within the 5th (T5) postoperative day. Figure 2 illustrates the postoperative distribution of vitamin 25(OH)D, E, C and A regarding deficiency, sufficiency and overage.

Association of perioperative Vitamin-levels with mortality and morbidity: Circulating levels of 25(OH)D below 29.9 nmol/L (moderate to severe deficiency) prior to surgery were associated with an increased in-hospital-mortality (OR = 2.78; 95% CI = 1.25-3.89, p: 0.021) and prolonged intensive care unit stay (p:0.047). There was a trend towards prolonged ventilation in patients with moderate to sever 25(OH)D deficiency (p:0.062). Table 3 illustrates the association between preoperative vitamin 25(OH)D status and morbidity. Pre- and perioperative vitamin E, C and A serum levels was not significantly associated with an increased operative morbidity and mortality.

DISCUSSION

Vitamin D is classically known for its fundamental role in musculoskeletal metabolism[8]. However the expression of the calcitriol receptor and vitamin D metabolizing enzymes both in myocardiocytes and endothelial cells indicates a crucial role of vitamin D in cardiovascular system[9-11]. Thus vitamin D arrest considerable attention and become a hot topic in cardiothoracic research.

Based on our prospective single-center study, the vast majority of high-risk patients scheduled for cardiac surgery have less than optimal 25(OH)D levels. We found that more than half of the patients had serum 25(OH)D levels below 29.9nmol/l indicating a moderate to severe deficiency prior to cardiosurgical procedure. The incidence of moderate to sever 25(OH)D deficiency prior to cardiac surgery is reported in the literature to by as low as 15% and as high as 35% in patients with low to moderate risk profile[4,5]. As reported in a resent publication from Nakamura and associates one of the main risk factor for low circulating 25(OH)D levels is less sunlight exposure[12]. Thus the high-risk profile of our patient cohort as expressed by a mean logistic EuroSCORE of 18.9±3.2%, and 67% being in NYHA Class III to IV, indicating low sunlight exposure due to hospitalisation or inability of physical stress prior to surgery may be a possible explanation for the high incidence of circulating 25(OH)D levels below 29.9nmol/l in our series.

The high prevalence of 25(OH)D deficiency prior to surgery could not be reflected in preoperative serum levels of antioxidant vitamins estimated herein. The prevalence of deficiency was 12% for vitamin C and 1% and 2% for vitamin E and A respectively. Since, to the best of our knowledge, no available data are published dealing specifically with the prevalence of vitamin E, C and A deficiency in high-risk patients prior to cardiac surgery, only a limited comparison of our results to the literature can be facilitated. Yet our data regarding prevalence of vitamin C, E and A deficiency seems to be higher than the reported prevalence for outpatient population, which is referred to be 6% for vitamin C and almost absent for vitamins A (0%) and E (0.1%)[13, 14].

A major finding of the present investigation was that cardiac surgery led to a significant reduction of 25(OH)D and vitamin C serum levels. In contrast depletion of antioxidant agents vitamin E and A in response to cardiac operation could not be detected in our series. Our findings regarding the postoperative course of vitamin C, E and A support a previous small prospective single center study published from Ballmer et al back in 1995 indicating a serious depletion of vitamin c 24 hours after cardiac surgery and no significant postoperative changes of plasma concentration of vitamin E and A in a series of 18 consecutive low-risk patients[14]. According to Ballmer and associates the generation of reactive oxygen species and other cytotoxic substances such as cytokines following cardiac surgery may lead to a significant postoperative impairment of that principal antioxidant micronutrient that is vitamin C[14].

Recent studies reported a high incidence of adverse outcomes, including high mortality rates, in intensive care patients with deficient 25(OH)D levels[15,16]. Zittermann and associates demonstrated in a series of over 4000 patients not only that deficient 25(OH)D levels are very prevalent also in cardiac surgical patients but also that 25(OH) D deficiency prior to cardiac surgery is associated with an increased risk of major cardiac and cardiovascular events[5]. Our results of the multiple regression analysis are in general agreement with the publication of Zittermann and associates, indicating a relevant association between moderate to severe 25(OH)D deficiency prior to surgery and risk of in-hospital mortality as well as prolonged intensive care unit stay in high-risk patient scheduled for cardiac surgery[5].

CONCLUSION

In conclusion moderate to severe 25(OH)D deficiency is prevalent in high-risk patients scheduled for cardiac surgical and is associated with an increased in-hospital mortality and prolonged intensive care unit stay. Contrary to that finding a substantial proportion of high-risk patients investigated herein have optimal levels of vitamin C, E and A prior to surgery. According to our observations cardiac surgery cause a depletion of 25(OH)D and vitamin C serum levels in the early perioperative period.

Table 1. Baseline characteristics and operative procedures

Variables	No.	%
Mean ejection fraction		0.50 ± 0.05
Glomerular filtration rate (ml/min/1.73m^2)		75.8 ± 0.6
Smokers	17	17
Concomitant diagnosis		
Atrial Fibrillation	18	18
IDDM	30	30
Arterial Hypertension	80	80
Pulmonary Hypertension	27	27
Previous stroke	10	10
Coronary artery disease	65	65
Previous cardiac decompensation	39	39
Previous myoc. Infarction	21	21
Previous PCI	43	43
Peripheral vascular disease	18	18
COPD	29	29
Previous cardiac surgery	9	9

Type of surgery		
Isolated CABG	17	17
CABG and valve surgery	32	32
Isolated valve surgery	20	20
Double valve surgery	20	20
Triple valve surgery	6	6
Aortic surgery	5	5
Operative data		
Cross clamp time (min)	95.3 ± 32.1	
Bypass time (min)	143.5 ± 41.2	

CABG = coronary artery bypass grafting; COPD = chronic obstructive pulmonary disease; IDDM = insulin dependant diabetes mellitus; PCI = percutaneous coronary intervention.

Table 2. Perioperative data regarding mortality and morbidity

Variables	No.	%
Mean ventilation time (h)	10.4 ± 3.7	
Mean ICU stay (d)	3.2 ± 1.4	
Mean hospital stay (d)	12.7 ± 2.5	
Major events		
In-hospital death	7	7
LOS	10	10
PMI	3	3
Stroke	2	2
Further postoperative complications		
Pulmonary infections	14	14
Wound infections	7	7
Atrial fibrillation	36	36
Surgical reexploration for bleeding	9	9
Acute renal failure	12	12
Gastrointestinal complication	6	6

ICU = intensive care unit; LOS = low cardiac output syndrome; PMI = postoperative myocardial infarction.

Table 3: Association of preoperative vitamin 25(OH)D status and morbidity.

Variable / 25(OH)D	Moderate to sever deficiency <29.9 nmol/L (a)	Mild deficiency 30-49.9 nmol/L (b)	Borderline Status / Adequacy 50-100 nmol/L (c)	p-value (a / b)
Ventilation time (a)	17.9 ± 6.5	5.4 ± 3.1	5.8 ± 1.2	0.062
ICU-stay (c)	4.9 ± 2.8	1.8 ± 1.6	1.2 ± 1.1	0.047
In-hospital stay (c)	15.1 ± 3.5	11.2 ± 2.5	12.1 ± 3.1	0.078

Figure 1

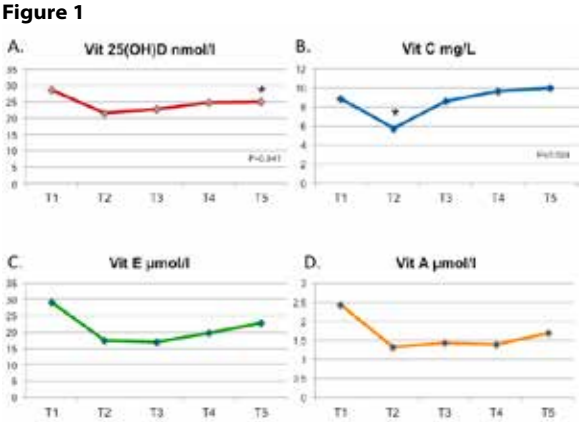

Figure 1: Figure 1 illustrates the postoperative course of vitamin 25(OH)D, E, C and A. Cardiac surgery led to a significant decrease of 25(OH)D- (T1 to T5, p: 0.041) and vitamin C serum levels (T1 to T2, p: 0.024).

Figure 2

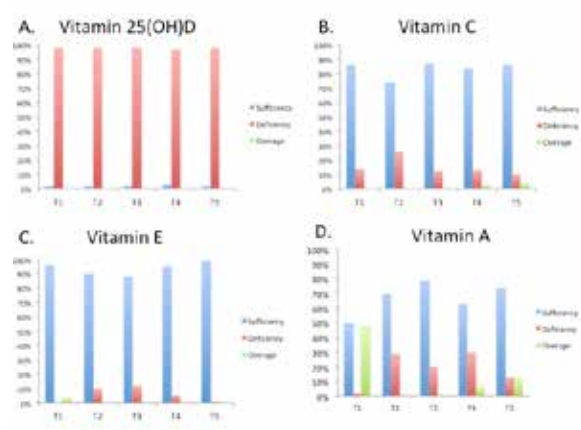

Figure 2: Figure 2 illustrates the postoperative distribution of vitamin 25(OH)D, E, C and A regarding deficiency, sufficiency and overage. Only 2% of the study cohort had preoperatively (T1) adequate 25(OH) D values, whereas the majority of the patients presented with sufficient vitamin E (T1, 99%), C (T1, 88%) and A (T1:98%) levels.

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