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Prevalence and Predictors of Prilocaine Induced Abnormal Methemoglobinemia During Cardiac Device Implantation Procedure

Kardiyak Cihaz İmplantasyon Prosedürü Esnasında Prilokain Kaynaklı Anormal Methemoglobineminin Prevelansı ve Prediktörleri

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ABSTRACT

Aim: The aim was to determine the prevalence and predictors of prilocaine-induced methemoglobinemia during the cardiac implantable electronic device (CIED) implantation procedure.

Methods: One hundred patients who underwent CIED implantation procedures under local anesthesia with prilocaine were included in the study. Patients were divided into two groups according to the percentage of methemoglobin (MetHb) in arterial blood gas analysis. Data regarding patients, laboratory, and procedure-related factors were compared between the two groups.

Results: The mean age of the patients was 70.97 ± 11.54 years, and 42% were female. Based on the criterion of MetHb level above 3%, the prevalence of pathologic methemoglobinemia was 47%. Multivariate logistic regression analyses were performed to identify independent predictors for the development of prilocaine-induced abnormal methemoglobinemia. In multivariate analysis, the presence of low body mass index (BMI) and chronic obstructive pulmonary disease (COPD) (OR: 0.876; 95% CI 0.781-0.981; p=0.022 and OR: 5.170; 95% CI 1.535-17.411; p=0.008) independently predicted the development of abnormal methemoglobinemia.

Conclusion: Abnormal MetHb levels were found in almost half of patients who underwent the CIED implantation procedure after subcutaneous prilocaine injection. Methemoglobinemia may occur even at doses lower than the recommended maximum dose, especially in patients with low BMI and COPD.

Key Words: Methemoglobinemia, Prilocaine, Cardiac device, Anesthesia

ÖZ

Amaç: Kardiyak implante edilebilir elektronik cihaz (CIED) implantasyonu işlemi sırasında prilokainin neden olduğu methemoglobineminin prevalansını ve öngörücülerini belirlemeyi amaçladık.

Yöntem: Prilokain ile lokal anestezi altında CIED implantasyonu yapılan 100 hasta çalışmaya dahil edildi. Hastalar arteriyel kan gazı analizinde methemoglobin (MetHb) yüzdesine göre iki gruba ayrıldı. Hastalara ilişkin, laboratuvar ve prosedür ilişkili faktörlerle ilgili veriler iki grup arasında karşılaştırıldı.

Bulgular: Hastaların ortalama yaşı 70,97 ± 11,54 yıl olup, %42'si kadındı. MetHb düzeyinin %3'ün üzerinde olması kriterine göre patolojik methemoglobinemi prevalansı %47 idi. Prilokainin neden olduğu anormal methemoglobinemi gelişiminin bağımsız prediktörlerini belirlemek için çok değişkenli lojistik regresyon analizleri yapıldı. Çok değişkenli analizde düşük vücut kitle indeksi (VKİ) ve kronik obstrüktif akciğer hastalığı (KOAH) varlığı (OR: 0,876; 95% GA 0,781-0,981; p=0,022 ve OR: 5,170; 95% GA 1,535-) 17,411; p=0,008) bağımsız olarak anormal methemoglobinemi gelişimini öngördü.

Sonuç: Subkutan prilokain enjeksiyonu sonrası CIED implantasyon işlemi uygulanan hastaların neredeyse yarısında anormal methemoglobin düzeyleri bulundu. Özellikle düşük VKİ ve KOAH'lı hastalarda önerilen maksimum dozun altındaki dozlarda bile methemoglobinemi meydana gelebilir.

Anahtar Sözcükler: Methemoglobinemi, Prilokain, Kardiyak cihaz, Anestezi

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Introduction

Methemoglobinemia is a rare condition that is often neglected and potentially life-threatening if not treated promptly [1]. Hemoglobin (Hb) is an erythrocyte molecule that carries oxygen to tissues and contains iron in the ferrous (Fe+2) form. When Hb is oxidized to the ferric state (Fe+3), it is converted into methemoglobin (MetHb), which is unable to bind oxygen and thus the oxygen-carrying capacity of blood is reduced [2]. Due to the decrease in the oxygen transport capacity of the blood, the hemoglobin-oxygen dissociation curve shifts to the left. Functional anemia and tissue hypoxia result from excessive replacement of hemoglobin with methemoglobin. In response to oxidative stress, the body regularly produces MetHb at a rate of 3% daily [3]. This can be acquired due to certain anesthetics or inherited via mutations in the cytochrome-b5 reductase enzyme or the presence of hemoglobin defects [4]. The clinical presentation varies from cases with mild symptoms to severe cases [5]. The symptoms of methemoglobinemia are related to the MetHb level in the blood, and cyanosis may be observed when the MetHb value exceeds 10%; fatigue, dizziness, and dyspnea when it exceeds 30%; dysrhythmia, lethargy, syncope, seizures, and coma when it exceeds 50%; and values above 70% are fatal [4]. The severity of clinical presentation may vary depending on the MetHb percentage, the rate of increase in MetHb level, and the patient's underlying comorbidities.

In the last decade, the use of permanent pacemakers and implantable cardioverter defibrillators (ICD) has increased (20% vs. 44%) [6]. Unfortunately, serious complications such as pneumothorax, local or systemic infections, and venous thrombosis can occur with these procedures. In addition, another overlooked complication associated with local anesthetics, methemoglobinemia, can occur [7].

The most commonly used local anesthetic is prilocaine, a medium-long acting local anesthetic with a rapid onset of action compared to lidocaine but significantly reduced systemic toxicity [8-9]. Although prilocaine is considered to be a safer anesthetic agent than other local anesthetic agents, the extent of prilocaine-associated methemoglobinemia occurring during cardiac device implantation procedures is still unknown. Therefore, we aimed to determine the prevalence and predictors of abnormal methemoglobinemia due to prilocaine used for local anesthesia of the pectoral region prior to the cardiac implantable electronic device (CIED) implantation procedure.

Material and Methods

Study Population

This single-center, prospective, observational cross-sectional study was conducted at Antalya Education and Research Hospital, a 1270-bed tertiary health center in Turkey. All patients undergoing cardiac device implantation and using prilocaine between March and June in 2022 consecutively were enrolled.

Patients with any of the following conditions were excluded: age<18 years, hypersensitivity to local anesthesia, history of previous methemoglobinemia episode, exposure to local anesthetic in the last seven days, pneumothorax, hemothorax, fever in the past 24 hours, and development of tamponade during the procedure. After applying the exclusion criteria, 100 participants were included in the study.

Cardiac Device Implantation Protocol

The protocol used in our institution for anesthesia of the pectoral region prior to pacemaker implantation is based on the local application of prilocaine hydrochloride subcutaneously to the left or right pectoral region (8 mg/kg and a maximum total dose of 600 mg) (Priloc® 2%, Vem Pharmaceutical Company Tekirdag, Turkey). None of the patients were administered deep sedation or general anesthesia. All patients had blood pressure, cardiac rhythm monitoring, and O2 saturation with pulse oximetry monitored during the procedure. All patients had a PA chest radiography immediately and 24 hours after the procedure. Patient O2 saturations were recorded post-procedure using pulse oximetry. Patients were discharged 24 hours after the procedure with the necessary treatment and referrals if no adverse events occurred.

Arterial Blood Gas Analysis

Arterial blood samples for measurement of MetHb concentration were taken 60 min after injection of the local anesthetic. The collected sample was immediately analyzed with an ABL800 FLEX (Radiometer Medical, Denmark). The analyzer also has a co-oximetry module based on a multiwavelength spectrophotometric optical system that measures total hemoglobin concentration, O2 saturation, and Hb fractions such as oxyhemoglobin (O2Hb), deoxyhemoglobin (HHb), MetHb, and carboxyhemoglobin (COHb).

Previous studies showed that MetHb routinely forms in the body at a rate of 3% per day in response to oxidative stress [3]. Therefore, the patients in our study were divided into two groups according to MetHb content in arterial blood gas analysis: a group with MetHb content below 3% and a group with MetHb content above 3%.

Ethical Considerations

The study was approved with Protocol No:2022/23 Decision No:2/8 by the Ethics Committee of Antalya Education and Research Hospital. The study was conducted under the guidelines of the Declaration of Helsinki.

Statistical Analysis

Statistical analyses were conducted using SPSS version 24.0 (Statistical Package for the Social Sciences, v24.0). The distribution of the variables was assessed using both visual methods and the Kolmogorov-Smirnov test to determine normality. Descriptive statistics are presented as frequencies and percentages for categorical variables and as means with standard deviations (SD) or medians with interquartile ranges (IQR) for continuous variables, depending on the distribution of the data.

Comparisons between groups were performed using the Student's t-test for normally distributed continuous variables, and the Mann-Whitney U test for non-normally distributed continuous variables. Categorical variables were compared using the Chi-square test or Fisher's exact test, as appropriate. In univariate analyses, categorical variables were assessed using Chi-square or Fisher's exact tests, while independent-sample t-tests were used for continuous variables.

Multivariate analysis was performed using logistic regression to control for potential confounders. Variables found to be significant in univariate analyses, including Body Mass Index (BMI) and Chronic Obstructive Pulmonary Disease (COPD), were included in the logistic regression model. The results are presented as odds ratios (OR) with corresponding 95% confidence intervals (CI). Statistical significance was set at $p < 0.05$.

Results

A total of 100 patients who received subcutaneous prilocaine for pectoral local anesthesia prior to CIED implantation were included in the study. The mean age was 70.9±11.5 years (range: 35-94 years) and 42 (42%) were female. Based on the definition of methemoglobinemia above 3%, the prevalence was 47% (n=47). The mean Met-hb percentage in the methemoglobinemia group was 7.55±2.46%, while the mean Met-hb percentage in the group without methemoglobinemia was 2.60±0.79%.

Table 1 presents an overview of the baseline demographic data and laboratory findings of the study group. There were no significant differences in most variables between the two groups. However, an interesting aspect of the table is that the presence of COPD and low BMI ($p = 0.001$ and $p = 0.003$, respectively) were higher in the methemoglobinemia group. In addition, laboratory parameters were also similar between the groups (Table 1).

Basal parameters for transthoracic echocardiography (TTE), electrocardiography (ECG) and CIED procedure-related findings of the study group are presented in Table 2. The ECG and TTE parameters did not differ between the groups. In addition, the arterial blood gas parameters there was no significant difference was evident between the two groups, except for saturation gap (5.80 ± 2.68 vs. 3.50 ± 2.71, $p<0.001$) and MetHb % (7.55 ± 2 .46 vs. 2.60±0.39 <0.001). Also, the percentage of the patients with a methemoglobinemia level above 10% were 12%.

Figure 1 provides a summary of treatment strategies for patients with abnormal MetHb levels. While most patients received no treatment (n=24), supplemental oxygen therapy was

Table 1. Baseline demographics and laboratory findings of the study groups

	Presence of methemoglobinemia	Absence of methemoglobinemia	P value
Mean age, years	70,66±12,46	68,98±12,78	0,509*
Gender (male) ,n, (%)	28 (59.6%)	30 (56.6%)	0,764**
BMI	26,18±3,20	28,66±4,76	0,003*
Diabetes mellitus, n, (%)	14 (29.8%)	16 (30.2%)	0,965**
Hypertension, n, (%)	30 (63.8%)	29 (54.7%)	0,355**
Smoking, n, (%)	12 (25.5%)	12 (22.6%)	0,736**
CAD, n, (%)	21 (44.7%)	21 (39.6%)	0,609**
PAD, n, (%)	4 (8.5%)	2 (3.8%)	0,416**
Cerebrovascular disease, n, (%)	3 (6.4%)	2 (3.8%)	0,664**
COPD, n, (%)	16 (34.0%)	4 (7.5%)	0,001**
CRF, n, (%)	6 (12.8%)	2 (3,8%)	0,143**
Antiaggregant therapy, n, (%)	16 (34.0%)	23 (43.4%)	0,339**
Anticoagulant therapy, n, (%)	12 (25.5%)	16 (30.2%)	0,605**
Hemoglobin, g/dL	12,87±1,92	13,28±2,05	0,310*
Platelet count, (× 10^3 per µL)	225,11±79,50	248,69±72,04	0,123*
WBC, (× 10^3 per µL)	8,29±2,41	8,43±2,34	0,755*
Neutrophil to lymphocyte ratio	3,19±2,09	3,73±3,02	0,307*
MPV, (fl)	10,76±1,76	10,94±1,07	0,531*
Fasting blood glucose, mg/dL	122,98±48,77	116,17±42,23	0,456*
Creatinine, mg/dL	1,29±0,90	1,19±0,26	0,430*
HDL, mg/dl	49,60±12,92	47,89±13,97	0,529*
LDL, mg/dl	110,96±38,38	115,04±45,52	0,631*

*Independent Samples T Test, ** Chi-Square T

(BMİ: Body mass index; CAD: Coronary artery disease; PAD: Peripheral artery disease; COPD: chronic obstructive pulmonary disease CRF: Chronic renal failure; WBC: White blood cell; MPV: Mean platelet volume, HDL: High-density lipoprotein cholesterol, LDL: Low density lipoprotein cholesterol)

Table 2. Basal transthoracic echocardiography, electrocardiography parameters and findings related to the patients' implantation procedure

	Presence of methemoglobinemia	Absence of methemoglobinemia	P value
Pre-implantation rhythm	19 (40.4%)	26 (49.1%)	0,147*
- Atrial fibrillation, n (%)	7 (14.9%)	6 (11.3%)	
- Atrioventricular block, n (%)	12 (25.5%)	5 (9.4%)	
- Pacemaker rhythm, n (%)	9 (19,1%)	14 (26.4%)	
- Nodal rhythm, n (%)	0 (0.0%)	2 (3.8%)	
QRS duration, msn	114,47±31,61	123,85±44,09	0,221**
Ejection fraction,%	49,89±15,34	48,02±16,56	0,560**
Severe valve disease			0,654*
- No, n (%)	30 (63.8%)	34 (64.2%)	
- Mitral valve, n (%)	9 (19.1%)	13 (24.5%)	
- Aortic valve, n (%)	3 (6.4%)	1 (1.9%)	
- Tricuspid valve, n (%)	5 (10.6%)	5 (9.4%)	
- Pulmonary valve, n (%)	-	-	
Pacemaker type			0,863*
-DDDR	24 (51.1%)	24 (45.3%)	
-VVIR	4 (8.5%)	6 (11.3%)	
-ICD	10 (21.3%)	11 (20.8%)	
-Biventricular pacing	9 (19.1%)	11 (20.8%)	
-VDD	0 (0.0%)	1 (1.9%)	
Nitrate usage, n (%)	1 (2.1%)	2 (3.8%)	1,000*

* Chi-Square Test, **Independent Samples T Test

(DDDR: Dual Chamber, Rate-Modulated Pacemaker; VVIR: Ventricular Inhibited, Rate-Modulated Pacemaker; ICD: Implantable Cardioverter Defibrillator; VDD: Single Pass Ventricular Pacemaker with Atrial Sensing.)

sufficient in 22 patients. Only 1 patient required methylene blue therapy (1-2 mg/kg intravenously for 5 minutes). The mean methemoglobin levels of patients given oxygen therapy was 9%, while the mean methemoglobin level of the single patient that given methylene blue was 22%.

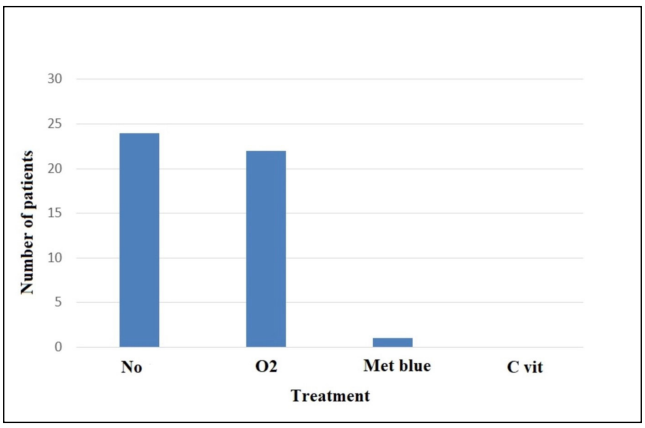

Figure 1: The treatment strategies applied to patients with abnormal methemoglobin levels

Univariate and multivariate logistic regression analyses were performed to identify independent "predictors for the development of prilocaine-induced abnormal methemoglobinemia prior to the CIED procedure (Table 3). Further statistical tests revealed low BMI [Odds ratio (OR): 0.876; 95% Confidence interval (CI) 0.781-0.981); p=0.022] and COPD (OR: 5.170; 95% CI 1.535-17.411; p=0.008) independently predicted the development of abnormal MetHb. In addition, according to logistic regression analysis, BMI and abnormal methemoglobinemia were negatively associated, and a unit numerical increase in BMI reduced the development of abnormal methemoglobinemia by 12.7%.

Table 3. Independent predictors associated with prilocaine-induced methemoglobinemia

95% C.I.for EXP(B)				
Variables	Odds Ratio	Lower bound	Upper bound	p-value
BMI	0,876	0,781	0,981	0,022
COPD	5,170	1,535	17,411	0,008

(CI: Confidence Interval, BMI: Body mass index; COPD: chronic obstructive pulmonary disease)

Discussion

This study found that almost half of the patients (47%) who received subcutaneous prilocaine had high levels of MetHb. To the best of our knowledge, this is the first study to prospectively analyze the effect of subcutaneous administration of prilocaine prior to the CIED procedure on blood methemoglobin levels and the occurrence of abnormal methemoglobinemia. Another key finding of our study was that low BMI and COPD were independent predictors for prilocaine-induced MetHb .

Four types of local anesthetic agents are major suspects for the development of acquired methemoglobinemia: prilocaine, benzocaine, lidocaine, and tetracaine. As local anesthetics are absorbed from the injection site, their concentration in the bloodstream increases, and dose-dependent suppression is observed in the peripheral and central nervous systems. Prilocaine, which is a medium-long-acting local anesthetic, has fewer side effects on the cardiovascular and central nervous systems than other local anesthetics [8]. Due to its large volume of distribution, the probability of systemic toxic reactions is very low [10]. Therefore, we prefer to use prilocaine as a local anesthetic during the CIED implantation procedure. However, a major disadvantage of prilocaine is the risk of MetHb development induced by its metabolites o-toluidine and nitrosotoluidine [11,12]. If prilocaine is metabolized by the liver (and possibly the kidneys), in contrast to other local anesthetics, o-toluidine is the primary product. A metabolite of prilocaine, o-toluidine, can oxidize the iron in hemoglobin from ferrous (Fe+2) to ferric (Fe+3). The resulting met-Hb prevents the release of oxygen from hemoglobin into tissues. Previous studies linked this condition to many clinical factors, including age, drug dosage, enzyme deficiencies, malnutrition, hospitalization, sepsis, and anemia [13].

The mechanism of MetHb formation after prilocaine administration was investigated in the literature. For example, Sadove et al. first reported a sudden change in blood color at the surgical site after using prilocaine on a patient. Spectroscopic analysis after the development of cyanosis in this healthy individual without any cardiovascular

disease revealed a significant increase in MetHb levels [14]. Later, Nolte et al. found a dose-response relationship for the development of methemoglobinemia and stated that a dosage of >600 mg was associated with a high risk of developing methemoglobinemia [15]. In addition, studies found that there were large variations in the development of methemoglobinemia among individuals and suggested that methemoglobinemia can develop in individuals with sensitivity, even at low doses. Kaiser et al. reported asymptomatic and acyanotic MetHb elevations in different individuals with the same dosage of prilocaine [16]. The maximum recommended dose of prilocaine for healthy adults is 8 mg/kg (600 mg) [17] or 6 mg/kg (400 mg) [18]. Some reports suggest that lower doses should be administered to children and patients with renal impairment [17,19]. In our study, we limited the dose of prilocaine to 8 mg/kg (total maximum dose of 600 mg). However, in multivariate logistic regression analysis performed in our study, abnormal methemoglobinemia levels were observed at a higher rate in people with low BMI. Low dose administration of prilocaine appears to be safer in individuals with multiple comorbidities.

Guay et al. reported that benzocaine caused the most cases of methemoglobinemia induced by local anesthetics, followed by prilocaine [19]. The incidence of symptomatic methemoglobinemia due to prilocaine requiring treatment in pediatric patients was reported to be 0.008% [20]. However, its incidence in teenagers or adults is uncertain. In our study, the abnormal MetHb level was 47%, which is too high. This finding was higher than previous studies conducted in different patient patterns. This discrepancy might be caused by the older, more frail, and comorbid individuals in our study cohort compared to those in prior studies. Another reason could be that prilocaine-induced methemoglobinemia can often present without symptoms. Indeed, although abnormal methemoglobinemia was observed in approximately 47% of patients in our study, only one patient was symptomatic and required treatment (1%).

Another result of our analysis showed that COPD diagnosis was an important predictor of abnormal methemoglobinemia. This finding is consistent with the literature, in case reports of anesthetic-associated methemoglobinemia COPD was the most common comorbid problem [21-23]. In patients with severe cardiopulmonary disease or multiple comorbidities such as anemia, even MetHb values below toxic levels can cause the development of symptoms [24]. In patients with a tendency to develop methemoglobinemia, much higher MetHb levels with severe symptoms can be observed with the same dose of prilocaine [24].

Contrary to theoretical knowledge, the risk of developing methemoglobinemia in patients with chronic renal failure is not as high as previously assumed. Wald-Oboussier et al. reported that prilocaine was safely administered to ten patients with chronic renal failure and anemia requiring hemodialysis. They reported that the patients' MetHb levels were similar to values measured in healthy individuals [25]. In addition, Tryba et al. reported that no side effects occurred when 600 mg prilocaine was administered to patients with renal failure or chronic anemia. Therefore, our results are consistent with the literature, in which univariate analysis revealed that chronic renal failure and anemia were not predictors for the development of abnormal methemoglobinemia in patients receiving local prilocaine injections.

In our study, 24 patients who developed abnormal methemoglobinemia were not given any treatment, while 22 were given supportive oxygen therapy. Intravenous methylene blue (1-2 mg/kg for 5 minutes) was given to one patient who developed symptoms. Initial treatment for methemoglobinemia starts with discontinuation of the relevant oxidant agent and symptomatic support. Supplemental oxygen should be initiated immediately and titrated as needed. According to guidelines, methylene blue (a starting dose of 1–2 mg/kg of 1% methylene blue to be repeated up to a dose of 5.5 mg/kg if there is no response after 30 min) is given to symptomatic patients with a MetHb level above 20% or asymptomatic patients with MetHb levels above 30% [4]. If the patient has underlying anemia and cardiac or pulmonary comorbidities, administration of methylene blue at lower MetHb levels should be considered. Ascorbic acid can be added as adjunctive therapy. Exchange transfusion or hyperbaric oxygen therapy should be administered to patients who

do not respond to first-line therapy.

Limitations

The present study includes a number of limitations; therefore, these findings should be regarded with caution. Firstly, while this is the first study examining prilocaine-associated MetHb in CIED patients, our study population was relatively small. Secondly, the study was conducted in a single heart center. The final limitation of this study is that MetHb was only tested with blood gas measurement, not evaluated with the Evelyn-Malloy assay, which is considered the most accurate test.

Our findings should be validated with multicenter studies involving greater patient populations. Nonetheless, this research has raised many questions that require further investigation.

Conclusion

In conclusion, given that approximately half of patients administered local anesthetic prior to the CIED procedure suffer from abnormal MetHb levels, cardiologists should be more sensitive to the use of prilocaine and the signs of methemoglobinemia in order to quickly and timely diagnose and prevent this condition. However, due to the large inter-individual variability between prilocaine dose and the rate of MetHb occurrence, an accurate and reliable assessment about the development of methemoglobinemia is not possible. Therefore, when using prilocaine as a local anesthetic, physicians should be aware that methemoglobinemia can occur at doses lower than the maximum recommended dose, particularly in patients with low BMI and COPD.

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