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Factors Associated with Phlebitis in Amiodarone Administration by Changing the Infusion Site*

İnfüzyon Yeri Değiştirilerek Uygulanan Amiodaron Uygulamasında Flebit ile İlişkili Faktörler

ABSTRACT

Objective: This study aimed to determine the incidence of phlebitis in patients undergoing amiodarone treatment by changing the infusion site and affecting factors in the coronary intensive care unit.

Methods: A total of 30 patients who received similar doses of amiodarone treatment for 12 months in the coronary intensive care unit were examined. The catheter, duration, catheter diameter (20-22 G) of amiodarone therapy, etc., factors, and factors related to phlebitis formation were examined. Descriptive statistics were used to analyze the data.

Results: In the study, 60 catheters undergoing amiodarone therapy applied to 30 patients were examined. It was observed that phlebitis developed in 9 (30%) out of 30 patients and 10 (16.6%) out of 60 catheters. More occurrences of phlebitis were detected in cases using a 22-G catheter ($P < .05$). Phlebitis occurred more commonly in women (37.5%) and catheters were attached to the intra-elbow area (50%). However, the development of phlebitis with these variables was not statistically different ($P > .05$).

Conclusion: In the present study, phlebitis developed in 30% of the patients. Therefore, it is recommended to change the infusion site after 12 hours of amiodarone infusion, and if possible, to apply with a central venous catheter.

Keywords: Amiodarone, critical care, peripheral venous catheter, phlebitis

ÖZ

Amaç: Bu çalışma koroner yoğun bakım ünitesinde infüzyon yeri değiştirilerek uygulanan amiodarone tedavisi kaynaklı flebit insindansını ve etkileyen faktörleri belirlemek amacıyla planlandı.

Yöntemler: Koroner yoğun bakım ünitesinde 12 ay boyunca benzer dozlarda amiodarone tedavisini infüzyon yeri değiştirilerek alan 30 hasta incelendi. Amiodarone tedavisinin yolu, süresi, kateter çapı (20-22 G) vb. faktörler ile flebit oluşumu ile ilgili faktörler incelendi. Verilerin analizi için tanımlayıcı istatistikler ve regresyon analizleri kullanıldı.

Bulgular: Çalışmada 30 hastaya takılan 60 kateter incelendi. Otuz hastanın 9 tanesinde (%30), 60 kateterin 10 tanesinde (%16,.6) flebit geliştiği gözlendi. 22 G çaplı kateter kullanılan olgularda daha fazla flebit saptandı ($P < ,01$). Kadınlarda (%37,5) ve dirsek içi bölgesine takılan kateterde (%50) flebit daha sıktı. Ancak bu değişkenler ile flebit gelişimi arasında istatistiksel olarak anlamlı fark bulunmadı ($P > ,05$).

Sonuç: Bu çalışmada hastaların%30'unda flebit gelişmiştir. Bu nedenle amiodaron infüzyonunda infüzyon yerinin 12 saatten daha sık değiştirilmesi ve mümkünse santral venöz kateter ile uygulanması önerilmektedir.

Anahtar Sözcükler: Amiodarone, flebit, periferal venöz kateter, yoğun bakım

ORIGINAL ARTICLE

Introduction

Intravenous amiodarone therapy is commonly used for treating arrhythmias including ventricular arrhythmia, paroxysmal supraventricular tachycardia, atrial fibrillation, and atrial flutter, or postcardiac prophylaxis in adults.[1] A meta-analysis study in which randomized controlled trials were included revealed that prophylactic amiodarone therapy reduced arrhythmia deaths in high-risk patients, and this effect led to a

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13% overall reduction in overall mortality. However, side effects such as phlebitis, bradycardia, atrioventricular (AV) block, hypertension, heart failure, torsade de pointes, and death have been reported in amiodarone treatment,[2] but the most common side effect of peripheral amiodarone therapy is phlebitis. However, peripheral catheters are feasible in emergency situations or short-term infusions. Therefore, administration via a central venous catheter was recommended. However, central venous catheters carry the risk of life-threatening complications such as hematoma, arrhythmias, pneumothorax, and infection.[3,4]

The development of phlebitis in the infusion site of amiodarone reduces the comfort of the patient, increases hospital costs, and delays discharge from the hospital. It causes stress to the patient and their families and more workload for nursing staff. Also, bacterial phlebitis can cause sepsis and lead to death if it progresses.[1]

Amiodarone-induced phlebitis is thought to be caused by the chemical and mechanical effects of amiodarone due to its particulate nature. Amiodarone may break down into particles during the storage process because of poor quality control, poor assembly processes, or amiodarone's physical instability. Amiodarone crystallization may occur if the drug approaches its solubility limits during dilution and administration, and this may facilitate phlebitis formation.[5] In addition, amiodarone can dissolve the plastic in the intravenous (IV) cannula as a polyvinyl chloride structure and directly irritate the vessel wall. This dissolution process increases during amiodarone infusion administered from the same IV cannula at high concentration and low speed and for a long time.[6,7] Therefore, the objective of the present study was to determine the incidence of phlebitis in patients undergoing amiodarone treatment by changing the infusion site and affecting factors in the coronary intensive care unit.

Methods

Study Design

This single-center, descriptive, cross-sectional study was conducted using total sampling method with 30 patients who were treated in the coronary intensive care unit.

The inclusion criteria for patients were as follows: (1) staying in intensive care unit, (2) being older than 18 years, and (3) not having their blood pressure measured on the treated arm (applying pressure to the vein is a risk factor for phlebitis). The exclusion criteria for patients were as follows: (1) receiving chemotherapy, (2) receiving immunosuppressive therapy, and (3) receiving intravenous amiodarone therapy with a central venous catheter and (4) with peripheral catheters that have been used previously and inserted into the vein with developed phlebitis/thrombophlebitis.

Instruments

The data were collected by the researchers using the Patient Information Form, Peripheral Venous Catheter Evaluation Form, and Visual Infusion Phlebitis Diagnostic Scale. *The Patient Information Form* prepared by the researchers consisted of 3 sections: personal and disease-related features, treatment-related features, and skin-related features, based on risk factors that increase the risk of developing infusion phlebitis associated with peripheral amiodarone therapy.[8,9] The personal characteristics section included questions about the patient's gender, age, education, marital status, and employment status. In the features related to the disease process, questions about medical diagnosis and chronic diseases were included. There were questions about the treatment, including antibiotic and anticoagulant use that were applied concurrently in the treatment features section. The patient's sensitivity history was questioned in the section on the properties of the skin structure. *The Peripheral Venous Catheter Evaluation Form* was prepared by the researchers according to the literature[2,3,8-10] included questions about catheter size, anatomic region of catheterization, frequency of catheterization in the region, duration of catheterization in the vein, medical department where the catheter was applied, phlebitis development status, and grade of phlebitis (determined according to the Visual Infusion Phlebitis Diagnostic Scale). *The Visual Phlebitis Diagnostic Scale*, developed by Alyce Schultze and Paulette Gallant, is a widely used scale that remains valid.[11] This scale grades phlebitis into 5 grades (grade I: absence of symptoms of phlebitis such as pain, redness, and edema; grade II: redness less than 2.5 cm around the catheter and the presence of pain that appears with palpation; grade III: redness greater than 2.5 cm but less than 5 cm around the catheter and presence of pain on palpation around the IV area; grade IV: redness of 5 cm or more around the catheter and pain on palpation or stiffness around the IV area; and grade V: presence of grade IV phlebitis findings and purulent drainage findings). Validity and reliability of the Turkish version were made by Paşalıoğlu and Kaya. The internal consistency of Cronbach's alpha was 0.97.[12]

Data Collection

Data were collected in a coronary intensive care unit. The unit had 10 beds and 12 nurses working in total. The working hours were 8:00 AM-4:00 PM and 4:00 PM-8 AM. During the daytime (8:00 AM-4 PM), there were 3 nurses and 1 head nurse. During the night, 2 nurses worked in the unit. Teflon (polytetrafluoroethylene)-type peripheral intravenous catheter (PIVC) was used in the unit. During IV catheterization, the area was cleaned with 70% alcohol, and the catheter was secured by white fixation dressings. In all patients receiving amiodarone therapy, the infusion site was changed every 12 hours. However, if there were phlebitis symptoms in the patients such as pain and tenderness in the catheter area, catheters were changed immediately. New vascular access was opened for the patient, and the infusion site of the patient was changed before the infusion time was 12 hours.

Data were collected between November 2015 and October 2016 in the coronary intensive care unit of the Istanbul University Institute of Cardiology. The clinic nurse maintained hand hygiene before the procedure, and she used disposable gloves during the intervention. The PIVC was placed by moving through the vein and fixed with plaster. The date, time, and person who performed the intervention were noted. The amiodarone infusion for patients was applied through the first PIVC when no signs or symptoms of phlebitis were seen

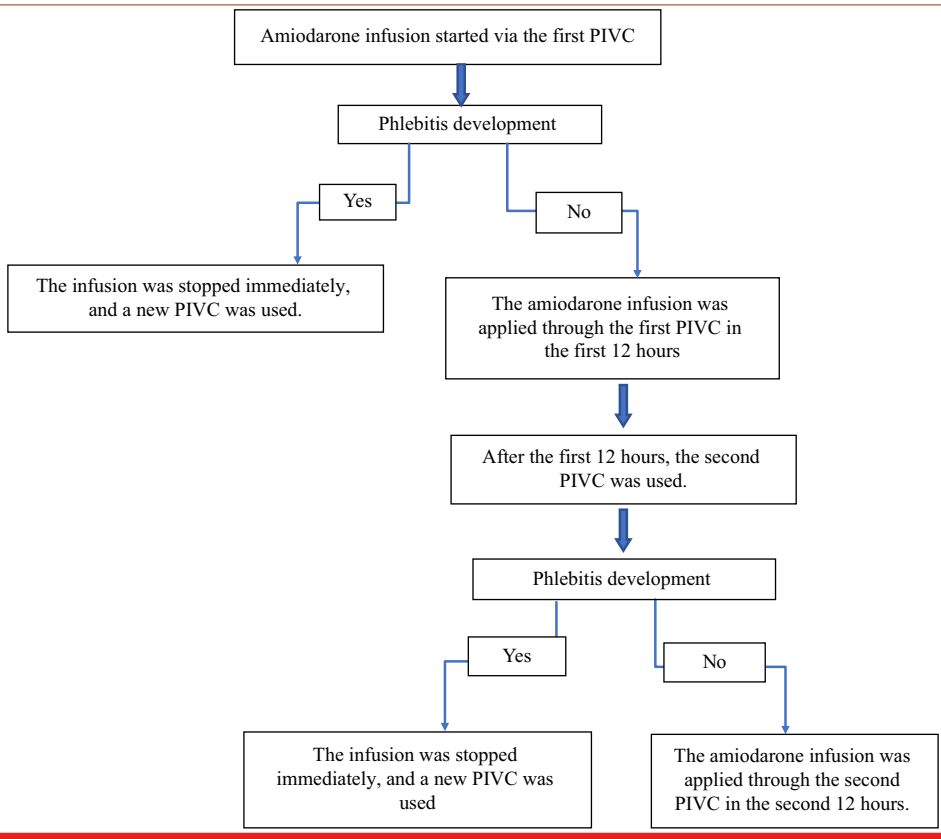

Figure 1. Research methodology flow chart. PIVC, peripheral venous catheter.

in the first 12 hours. Then, a new site was used. When any signs or symptoms of phlebitis developed in the patient, the infusion was stopped immediately, and a new PIVC was used (Figure 1). The researcher observed the patient during the infusion (24 hours on average) and collected data using data collection forms.

Ethical Approval

All procedures in the study complied with institutional ethical standards, the 1964 Helsinki Declaration, and subsequent amendments or similar ethical standards. The ethical and institutional approval was obtained from Istanbul University Ethics Committee (B.08.06.YÖK.2.İ.Ü.E.50.0.05.00/11) and institutional approval was obtained from the Istanbul University Institute of Cardiology. Written approval was obtained to use the Visual Infusion Phlebitis Diagnosis Scale from the study by Paulette Gallant, who created the scale, and by Kadriye Burcu Paşalıoğlu, who translated the scale into Turkish and confirmed the validity and reliability. Additionally, the participants were informed about the study, and their oral and written consents were taken.

Data Analysis

Statistical Package for the Social Sciences version 20.0. (IBM SPSS Corp.; Armonk, NY, USA) was used for descriptive and statistical analyses. Besides descriptive statistical methods, the Mann–Whitney *U* test was used for the pairwise comparison of the quantitative data of non-normally distributed groups. Fisher's exact test was used to compare qualitative data. The grade of significance was evaluated as $P < .05$.

Results

Description of the Sample

The study sample consisted of 30 patients, including 8 women (26.7%) and 22 men (73.3%), who were under amiodarone treatment with a PIVC. The mean age was 64.73 years, and most of the patients were married (66.7%) and had degrees lower than high school (83.3%). Almost half of them were retired (43.3%). The patients were categorized as those with ventricular tachycardia (63.3%), atrial fibrillation (30%), and supraventricular tachycardia (6.7%). Chronic disease was present in most (93.3%) of the cases. The most common chronic disease was hypertension (46.7%), followed by diabetes (30%), heart failure (26.7%) and chronic obstructive pulmonary disease (COPD), and asthma (13.3%). Some of the cases were under anticoagulant (46.7%) and antibiotic (23.3%) treatments (Table 1).

Incidence and Indications of Phlebitis

The results were analyzed into 2 groups the PIVC inserted into the first site (first PIVC) and the PIVC inserted into the second site (second PIVC). In the first site, phlebitis developed in 20% (n=6) of the cases and was in stages as different grades; grade I (80%), grade II (16.7%), and grade III (3.3%) in stages. In the second site, phlebitis developed in 13.3% (n=4) of the cases [grade I (83.3%), grade II (13.3%), and grade III (3.3%)]. In total, phlebitis developed in 6 cases (20%) in the first PIVC group and 4 cases (13.3%) in the second PIVC group; both PIVCs developed in 1 patient. Phlebitis was detected in 9 cases (30%). The time that passed before phlebitis development was found to be 7 hours in the first PIVC and 9 hours in the second PIVC.

Table 1. Sociodemographic and Disease-Related Features of the Patients

	Age (Mean ± SD)	64.73 ± 14.60, n(%)
Gender	Female	8 (26.7)
	Male	22 (73.3)
Education	Lower degrees than high school	25 (83.3)
	High school	3 (10.0)
	University	2 (6.7)
Marital status	Married	20 (66.7)
	Single	2 (6.7)
	Divorced	8 (26.7)
Employment status	Worker	7 (23.3)
	Housewife	8 (26.7)
	Student	1 (3.3)
	Retired	13 (43.3)
	Unemployed	1 (3.3)
Medical diagnosis	Atrial fibrillation	9 (30.0)
	Ventricular tachycardia	19 (63.3)
	Supraventricular tachycardia	2(6.7)
Chronic diseases	Diabetes	9 (30.0)
	Hypertension	14 (46.7)
	COPD/asthma	4 (13.3)
	Heart failure	8 (26.7)
Anticoagulant use		14 (46.7)
Antibiotic use		7 (23.3)

COPD, chronic obstructive pulmonary disease; SD, standard deviation.

Table 2. Development of Phlebitis in Patients with Intravenous Infusion of Amiodarone

		Phlebitis Development		
Features		**Yes (n=9)**	**No (n=21)**	***P***
Age	Mean ± SD	65.44 ± 11.57	64.43 ± 15.97	*.946*[a]
	Min-Max (Median)	50-82 (69)	30-88 (69)	
		n (%)	n (%)	
Gender	Female	3 (37.5)	5 (62.5)	*.666*[b]
	Male	6 (27.3)	16 (72.7)	
Boby side	Right	3 (50.0)	8 (33.3)	*.641*[b]
	Left	3 (50.0)	16 (66.7)	
PIVC size 1	20 G	1 (4.8)	20 (95.2)	*.005*[b,**]
	22 G	5 (55.6)	4 (44.4)	
PIVC size 2	20 G	1 (5.6)	17 (94.4)	*.274*[b]
	22 G	3 (25.0)	9 (75.0)	
Anatomic region	Hand	1 (16.7)	11 (45.8)	*.303*[c]
	Forearm	2 (33.3)	7 (29.2)	
	Elbow	3 (50.0)	4 (16.7)	
	Upper arm	0 (0)	2 (8.3)	
The intervention frequency	First time in use	6 (100)	21 (87.5)	[b]*1.000*
	Repeatedly used	0 (0)	3 (12.5)	
Length of stay in the vein	0-24 hours	6 (100)	21 (87.5)	[b]*1.000*
	24-48 hours	0 (0)	3 (12.5)	
Place of insertion	Emergency	0 (0)	2 (8.3)	[c]*1.000*
	Cardiology service	0 (0)	3 (12.5)	
	Coronary intensive care	6 (100)	19 (79.2)	

[a]Mann–Whitney *U* test; [b]Fisher's exact test; [c]Fisher–Freeman–Halton test; SD, standard deviation.

***P < .01*

Min-Max, minimum-maximum; PIVC, peripheral venous catheter; PIVC size 1, amiodarone treatment was applied for the first 12 hours; PIVC size 2, amiodarone treatment was applied for the second 12 hours.

Factors Contributing to Phlebitis

No statistically significant difference was found between the age distributions and genders of the cases according to the phlebitis development. Also, no statistically significant differences were observed in the body parts, anatomical regions, frequencies of intervention in the site used, duration of stay in the vein and intervention sites, and phlebitis development. ($P > .05$). The rate of phlebitis development was significantly higher in the cases that used 22-G PIVC than in the cases that used 20-G PIVC ($P < .01$) (Table 2).

Additionally, no statistically significant difference was observed in patients who had chronic disease (diabetes, hypertension, COPD, asthma, and heart failure), used antib iotic/anticoagulant, and had past skin sensitivity and phlebitis development ($P > .05$) (Table 3).

Discussion

Among the side effects of IV amiodarone treatment, infusion phlebitis was reported as the most common complication of this process. None of the studies so far reported 8%-85% change in the rate of phlebitis development with amiodarone treatment because each study was designed differently with different doses, routes, and rates of infusion.[2,5]

As far as we know,[5] the present study is the first study on the incidence of phlebitis development in amiodarone infusion administered with different catheters at intervals of 12 hours. Studies have shown that amiodarone infusion, administered by the same IV route for a long time, has an effect on the development of phlebitis.[2] A control group could not be taken because the coronary intensive care unit where the study was conducted is against the amiodarone application protocols of other units. The findings were compared with the literature.

Table 3. Findings Related to the Comparison of the Phlebitis Development Chronic Diseases, Antibiotic-Anticoagulant Use, and Past Skin Sensitivity

		Phlebitis Development		
		Yes (n=9)	No (n=21)	
Features		n (%)	n (%)	*P*
Chronic disease	Yes	9 (32.1)	19 (67.9)	*1.000*[b]
	No	0 (0.0)	2 (100.0)	
Diabetes	Yes	2 (22.2)	7 (77.8)	*.681*[b]
	No	7 (33.3)	14 (66.7)	
Hypertension	Yes	5 (35.7)	9 (64.3)	*.694*[b]
	No	4 (25.0)	12 (75.0)	
COPD asthma	Yes	1 (25.0)	3 (75.0)	*1.000*[b]
	No	8 (30.8)	18 (69.2)	
Heart failure	Yes	2 (25.0)	6 (75.0)	*1.000*[b]
	No	7 (31.8)	15 (68.2)	
Antibiotic use	Yes	2 (28.6)	5 (71.4)	*1.000*[b]
	No	7 (30.4)	16 (69.6)	
Anticoagulant use	Yes	2 (14.3)	12 (85.7)	*.118*[b]
	No	7 (43.8)	9 (56.3)	
Past skin sensitivity	Yes	0 (0.0)	2 (100.0)	*1.000*[b]
	No	9 (32.1)	19 (67.9)	

[b]Fisher's exact test.

COPD, chronic obstructive pulmonary disease.

In the present study results, if the amiodarone infusion was applied to patients with different catheters at 12-hour intervals, the incidence of phlebitis was found to be 30%. It has been reported that 14%-85% of phlebitis developed in patients with amiodarone treatment at a similar concentration (1.8 mg/mL) and a similar infusion rate (0.62 mg/min) as in this study.[2] In the present study, it was determined that phlebitis developed in the first PIVC at an average rate of 20% after 7 hours and in the second PIVC, at an average rate of 13.3% after 9 hours. This can be interpreted as the first PIVC treatment of amiodarone in the first 10 minutes of loading dose, and maintenance dose is administered from a high dose, resulting in phlebitis in a shorter period of time. In accordance with these results, in a retrospective study conducted by Jole'L and Hartman[1], a total of 339 patients were examined in 3 periods. In these 3 different periods examined, 900 mg, 600 mg, and 69 mg of amiodarone were administered to 97, 173, and 900 patients, respectively. In each period, phlebitis developed at the rates of 10.3%, 5.8%, and 23.2%, respectively. Although amiodarone was administered in all 3 periods, the rates of infusion of phlebitis in the first and third periods with high-dose amiodarone were determined to be approximately 2 and 4 times higher than that of the second period, respectively. Buzatto et al's[12] study on older individuals also found significant phlebitis in patients undergoing bolus infusion.

Mechanical phlebitis is caused by friction of the cannula in the vein and irritation occurring in the tunica intima layer of the vein.[13] The use of small-size PIVCs can significantly reduce the incidence of phlebitis because larger PIVCs lead to more mechanical irritation and bacterial colonization with a greater risk of extravasation than small-sized PIVCs.[10,13-16] When Boyce and Yee (2012)[17] did not find a significant correlation between the first PIVC size and phlebitis development, they emphasized avoiding the use of small-size PIVCs in large veins. On the contrary, in the present study, phlebitis development was significantly higher in 22-G PIVCs than in 20-G PIVCs ($P < .05$).

In addition, the region where the cannula was inserted, the frequency of intervention, and the duration of venous stay of the catheter have been reported to play a role in the development of mechanical phlebitis.[7,15,16] For catheter application, regions away from areas where the vein is divided into 2 bone protrusions and joint areas such as the wrist should be preferred.[13] Uslusoy (2008)[18] detected phlebitis in the PIVC inserted into the elbow area. The present study found that phlebitis developed mostly in the elbow (50%) with no statistically significant difference since this site moved a lot due to being a joint area and the PIVC material might traumatize the vessel wall. In another study, Mermel[19] explained the high phlebitis rate in the site that was used repetitively. There is a high phlebitis risk in this vein since the repetitive PIVC insertion caused mechanical and chemical trauma. In the present study, no statistically significant difference was found between phlebitis development and the intervention frequency in the PIVC applications (PIVC might be inserted in a region for the first time or the place of previous insertion might be reused).

The risk of phlebitis and thrombophlebitis increases if a catheter stays longer in a vein.[13] Lundgren et al[20] found that the rate of phlebitis development increased after the first 24 hours, while Maki and Ringer[21] found that the rate of phlebitis progression increased gradually after the second day.[2] In the present study, there was also no significant difference between the length of stay of PIVCs in the vein and phlebitis development, since the duration of stay of PIVCs in most of the patients was 0-24 hours owing to acute atrial fibrillation and ventricular tachycardia.

Thrombosis and fibrin accumulation on a PIVC may be a focus for microbial colonization of intravascular PIVCs. Therefore, anticoagulants are widely used to prevent thrombosis in PIVCs.[22,23] In the present study, phlebitis predominantly developed in patients who did not use anticoagulants (77%) ($P > .05$).

A study conducted by Paşalıoğlu and Kaya (2014)[12] reported that antibiotic-treated PIVCs developed 2.4 times more phlebitis compared with those who had no antibiotic treatment. Lanbeck et al[22] (2002) reported that antibiotics such as dicloxacillin and erythromycin increased the risk of phlebitis development. However, Jole'L and Hartman (2011)[1] found that antibiotics had protective effects against phlebitis development. In the present study, no difference was observed between the use of antibiotics and phlebitis development due to the low frequency of administration of drugs in the antibiotic group ($P > .05$).

Study Limitations

Since only 20-G and 22-G PIVCs were present in the clinic, catheters of other sizes were not examined in the study. A control group could not be taken because the infusion of the drug

from a single cannula for 24 hours or longer was contrary to clinical application protocols.

Conclusion

The results of this study showed that the incidence of phlebitis was 30%. The highest grade of phlebitis (grade I) was observed, followed by grade II phlebitis. Grade III phlebitis was observed in only 1 case. Approximately 7 hours after the infusion started, phlebitis developed in the first PIVC, and 9 hours later, phlebitis developed in the second PIVC. The phlebitis development rate was higher in the cases using 22-G PIVC compared with that in the cases using 20-G PIVC.

According to the results of this study, since phlebitis was mostly detected in the elbow region, this region should be the last choice when inserting a catheter. Since the second-degree phlebitis finding is pain, pain in the catheter site should be used in the evaluation of the vein in terms of phlebitis. Since the rate of formation of phlebitis in patients with a 22-G catheter is significantly higher than that in patients with a 20-G catheter, choosing an appropriate-sized catheter according to the intended use and the planned vein is recommended, especially following a catheter where a bolus dose of a drug was previously applied. In terms of phlebitis development, the following suggestions should be considered: diagnosis at certain intervals to prevent phlebitis development caused by catheter applications, using measurement tools such as Visual Infusion Phlebitis Diagnostic Scale for diagnosis, timely recording of results, and taking into account the instructions on the scale. Finally, researchers should conduct future comparative, large-sample, and evidence-based research to reduce the incidence of phlebitis associated with the administration of amiodarone in patients.

Ethics Committee Approval: Ethical committee approval was received from the Ethics Committee of Istanbul University Institute of Cardiology (Date: October 7, 2015, Decision No: B.08.06.YÖK.2.İ.Ü.E.50.0.05.00/11).

Informed Consent: Written informed consent was obtained from all participants who participated in this study.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept – Y.K.U., N.E.; Design – Y.K.U., N.E.; Data Collection and/or Processing – Y.K.U.; Analysis and/or Interpretation – Y.K.U.; Literature Search – Y.K.U., Other – Y.K.U., N.E.

Declaration of Interests: The authors have no conflicts of interest to declare.

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