# Original Article

# Factors associated with phlebitis in elderly patients with amiodarone intravenous infusion

## Fatores relacionados à flebite em idosos com infusão intravenosa de amiodarona

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## Abstract

**Objective:** To verify the incidence of phlebitis and identify factors associated with the development of phlebitis due to peripheral intravenous infusion of amiodarone in elderly patients.

**Methods:** Prospective and observational cohort study on risk factors for the development of phlebitis in patients aged over 60 years, who received peripheral intravenous infusion of amiodarone, hospitalized in 2012 in the coronary care (22 beds) and general semi-intensive units (43 beds) of a large private hospital in São Paulo, Brazil.

**Results:** Of the total 102 elderly people, 34 (33.3%) had phlebitis. It was more frequent in women (43.6%), in the dominant punctured member (36.2%), in the forearm basilica or cephalic veins (41.2%), in caliber 20G devices (40.0%), in IV Fix® sterile dressings (39.3%), in Intima® catheters (34.3%) and when there was device repositioning (33.3%). However, these variables were not statistically associated with phlebitis. Phlebitis absence in the exclusive bolus infusion was marginally significant (p = 0.051) compared to different types of infusion.

**Conclusion:** One-third of the studied elderly patients presented phlebitis. There was absence of phlebitis only in exclusive bolus infusions.

## Resumo

**Objetivo:** Identificar fatores associados à ocorrência de flebite decorrente da infusão intravenosa periférica de amiodarona em idosos.

**Métodos:** Coorte prospectiva, observacional sobre fatores de risco para ocorrência de flebite em pacientes com idade acima de 60 anos que receberam infusão intravenosa periférica de amiodarona, internados, no ano de 2012, nas unidades Coronarianas (22 leitos) e Semi Intensivas Gerais (43 leitos) de um hospital privado de grande porte, localizado na cidade de São Paulo, Brasil.

**Resultados:** Do total de 102 idosos, 34 (33,3%) apresentaram flebite. A flebite foi mais frequente em mulheres (43,6%), em membro dominante puncionado (36,2%), em veias basílica ou cefálica do antebraço (41,2%), nos dispositivos de calibre 20G (40,0%), em curativo estéril IV *Fix*® (39,3%), em cateter *Intima*® (34,3%) e quando houve reposicionamento do dispositivo (33,3%); mas essas variáveis não se associaram estatisticamente à flebite. Ausência de flebite na infusão rápida exclusiva foi marginalmente significante (p= 0,051) comparada aos diferentes tipos de infusão.

**Conclusão:** Um terço dos idosos estudados apresentou flebite, verificou-se ausência de flebite somente nas infusões rápidas exclusivas.

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# Introduction

The aging process causes changes that affect the cardiocirculatory system structure and may compromise the electrical stimulation conduction and generation, increasing cardiac arrhythmia prevalence in elderly people.[1] Atrial fibrillation (AF) is the most frequent condition in elderly patients admitted in emergency services. Amiodarone is the drug chosen for reversion of ventricular and atrial arrhythmias, and intravenous administration is necessary.[2]

This substance is a class III antiarrhythmic agent, with 3.8 - 4.0 pH, therefore, a vesicant medication whose most frequent local complication is phlebitis.[2,3] The development of phlebitis due to intravenous amiodarone administration varies from 23.2% to 73%, and it can be an important cause of prolonged length of hospital stay.[4]

In general, the literature provides factors that can be related to the development of phlebitis, such as the device caliber, patients' age, pharmacological properties (pH, solution osmolality), therapy duration, insertion technique of devices and care for maintenance of intravenous therapy.[3,5] Female patients, white skin, hypoalbuminemia and neutropenia are also pointed as favorable conditions for phlebitis.[2,3,5]

Phlebitis is an event with direct consequences for patients, especially elderly people, increasing the number of punctures, damage to peripheral venous network, aggression to the patients' defenses, pain and discomfort. As a result, it may increase the length of hospital stay and total treatment cost.[6,7] Analysis of intravenous infusion of amiodarone in elderly patients may indicate factors especially related to phlebitis, and offer resources to prevention, aiming to reduce its occurrence and consequences for the elderly. Therefore, the objective of the present study was to verify the incidence of phlebitis and identify factors associated with it due to peripheral intravenous infusion of amiodarone in elderly patients.

# Methods

A prospective and observational cohort study was conducted on risk factors for the development of phlebitis in patients aged over 60 years, who received peripheral intravenous infusion of amiodarone, hospitalized in 2012 in the coronary care (22 beds) and step down units (43 beds) of a large private hospital, located in the city of São Paulo, Brazil.

Patients who received intravenous amiodarone through central catheters or any other device different from the peripheral were not included in the sample. Moreover, those who received other medications simultaneously with amiodarone in the same peripheral device were not considered either. After confirming the medication use and the inclusion criteria, patients were contacted and the objectives of the study were explained. Once the patient agreed to participate in the study, the written informed consent was presented. The study sample was thus made, and the individuals included were monitored daily by the researcher to evaluate the puncture site with amiodarone infusion and to check information in the patient medical record.

Phlebitis was identified and classified according to the scale recommended by the Infusion Nurses Society (INS) that defines grade 0 as no symptoms, grade 1 as erythema at access site with or without pain, grade 2 with pain at access site with erythema and/or edema, grade 3 when there is pain at access site with erythema and/or edema; streak formation; palpable venous cord and grade 4 with the presence of pain at access site with erythema and/or edema; palpable venous cord greater than 2.5 cm in length; purulent drainage.[5] Phlebitis was defined as a dependent variable and the other variables were constituted as independent variables.

Patients aged ≥60 years were considered elderly. Age and sex variables were obtained from the patients' records.

Puncture site was categorized according to vessel punctured in: basilic vein of the forearm, basilic vein in the arm, cephalic vein of the forearm, cephalic vein of the arm and dorsal metatarsal vein. The punctured member was classified as dominant or not dominant.

The type of peripheral intravenous puncture catheter was defined according to the standard of the study institution: Íntima® or Insyte®, both designed with polyurethane. The caliber of intravenous puncture was categorized in 18 Gauges (G), 20G, 22G and 24G.

Fixation type of the catheter was categorized according to the used material: transparent film (Tegaderme IV®), sterile fixator (IV-FIX®) and micropore.

The intravenous catheter repositioning was related to the condition in which, during puncture, when the device was already inserted into skin and subcutaneous tissue, there was the need of repositioning or manipulating it to reach the venous blood. The variable was categorized as yes, no and no record.

The forms of amiodarone infusion were classified in exclusive bolus infusion, bolus infusion followed by continuous infusion and exclusive continuous infusion. The type of administration considered bolus was related to any type of volume and diluent, in which the administration occurred in 30 minutes at the most. The continuous type was defined as amiodarone solution administered in more than 30 minutes.

The categorical variables were analyzed considering absolute and relative frequencies. To assess the association of the categorical variables with the development or not of phlebitis, the Chi-square test was used, and likelihood ratio test or Fisher's exact test, when necessary.

Significance was set at $p \leq 0.05$ and the data were processed by means of the SPSS (SPSS Inc. SPSS Statistics 2008 for Windows, version 17.0, Chicago, USA).

The study was registered in the Plataforma Brasil under Certificate of Presentation for Ethical Appreciation (CAAE, as per its acronym in Portuguese) number 25588914.0.0000.5505.

# Results

The sampled was made up of 102 elderly patients, with a mean age of 70.6 years (SD 4.3), of whom 34 (33.3%) had phlebitis, and 24 (70.5%) were classified as grade 1. Seventy-two hours after the end of amiodarone infusion, no phlebitis was observed in patients that completed the treatment without the presence of such adverse event during therapy. Results will be shown according to variables related to the patient, to the intravenous puncture procedure and to the amiodarone infusion.

Data in table 1 show that the development of phlebitis was more frequent in women (43.6%), in the dominant punctured member (36.2%) and in punctures in the basilic or cephalic veins of the forearm (41.2%). However, the differences observed were not statistically significant.

According to table 2, calibers 20G and 22G were the most used in punctures (79.4%). Regarding the other variables, phlebitis was more frequent with the use of IV Fix® sterile dressings (39.3%), Intima® catheters (34.3%) and the occurrence of device repositioning (33.3%). Differences observed in the groups, however, were not statistically significant.

Data in table 3 show greater frequency of administration of bolus infusions followed by the continuous type (56.9%). There was absence of phlebitis in exclusive bolus infusions, and a marginally significant difference as for the development of phlebitis (p=0.051) comparing different infusion types.

**Table 1.** Development of phlebitis in elderly patients with intravenous infusion of amiodarone

| Variables | Phlebitis | | | p-value |
| | Yes n(%) | No n(%) | Total n(%) | |
| --- | --- | --- | --- | --- |
| Sex | | | | |
| Male | 17(27.0) | 46(73.0) | 63(100.0) | 0.083* |
| Female | 17(43.6) | 22(56.4) | 39(100.0) | |
| Dominant member | | | | |
| Yes | 17(36.2) | 30(63.8) | 47(100.0) | 0.574* |
| No | 17(30.9) | 38(69.1) | 55(100.0) | |
| Puncture site | | | | |
| Basilic and cephalic: forearm | 21(41.2) | 30(58.8) | 51(100.0) | |
| Basilic and cephalic: arm | 2(22.2) | 7(77.8) | 9(100.0) | 0.224* |
| Intermediate | 6(37.5) | 10(62.5) | 16(100.0) | |
| Dorsal metacarpal | 5(19.2) | 21(80.8) | 26(100.0) | |

*Chi-square test

**Table 2.** Development of phlebitis in elderly patients related to intravenous peripheral puncture

| Variables | Phlebitis | | | p-value |
|---|---|---|---|---|
| | Yes n(%) | No (%) | Total n(%) | |
| Caliber | | | | |
| 16 | -(-) | 1(100.0) | 1(100.0) | |
| 18 | -(-) | 4(100.0) | 4(100.0) | |
| 20 | 10(40.0) | 15(60.0) | 25(100.0) | - |
| 22 | 22(39.3) | 34(60.7) | 56(100.0) | |
| 24 | 2(12.5) | 14(87.5) | 6(100.0) | |
| Dressing | | | | |
| IV Fix | 11(39.3) | 17(60.7) | 28(100.0) | 0.432* |
| Film | 23(31.1) | 51(68.9) | 74(100.0) | |
| Catheter type | | | | |
| Intima | 23(34.3) | 44(65.7) | 67(100.0) | 0.768* |
| Insyte | 11(31.4) | 24(68.6) | 35(100.0) | |
| Repositioning* | | | | |
| Yes | 6(33.3) | 12(66.7) | 14(100,0) | 0.738** |
| No | 12(25.0) | 36(75.0) | 34(100,0) | |

*Chi-square test; **Fisher's exact test

**Table 3.** Development of phlebitis in elderly patients according to infusion type

| Variables | Phlebitis | | | p-value |
|---|---|---|---|---|
| | Yes n(%) | No n(%) | Total n(%) | |
| Infusion type | | | | |
| Exclusive bolus infusion | -(-) | 7(100.0) | 7(100.0) | 0.051* |
| Exclusive continuous infusion | 13(35.1) | 24(64.9) | 37(100.0) | |
| Bolus followed by continuous infusion | 21(36.2) | 37(63.8) | 58(100.0) | |

*Likelihood Ratio

# Discussion

Amiodarone is a medication widely used in injectable presentation, managed in both peripheral and central routes. In daily practice, because of the ease, speed and lower cost and complication risk related to insertion and maintenance, peripheral intravenous devices are widely used to administrate this medication. Among adverse local events caused by this treatment, phlebitis is highlighted. It interrupts the treatment continuity and prevents a new peripheral device insertion in the vessel or even in the affected limb.[8,9]

As of 1982, there are studies in literature showing the relationship of phlebitis to amiodarone administration in peripheral intravenous devices. In 1983, a study showed a 73% development rate of phlebitis related to intravenous amiodarone administration;[10] in 1999, another investigation revealed lower phlebitis frequency (25%).[11] Other studies highlighted phlebitis rates lower than those published until that moment.[6,8,12] The present study reveals a 33.3% phlebitis rate in elderly patients and this result is consistent with those found in literature.

Studies on intravenous treatment show higher phlebitis rates in groups of patients aged over 60 years.[7] Elderly people present greater capillary frailty and their vessel inner tunic is more prone to suffer inflammatory procedures. In addition, elderly people have more comorbidities, which may aggravate their health status and, as a consequence, generate weakness in peripheral vasculature and lead to a higher incidence of phlebitis.[13]

Studies on risk factors related to the development of phlebitis showed that the frequency of this event in women is higher.[7,14] Among the aspects shown in literature to explain higher phlebitis frequency in women are higher hormone circulation, which predisposes the inner tunic to inflammatory events, and the peripheral vessel anatomy of women, whose vessels are smaller and have more difficult visibility.[7]

The development of phlebitis in elderly people with infusion of peripheral intravenous amiodarone was also assessed observing puncture in the dominant member, considering its use in mobilization performed by the patient. Some studies show traumatic phlebitis as an important occurrence related to catheters inserted in flexion areas or areas of large member mobility, culminating in accidental removal of the device.[5,15] In the present study, however, the development of phlebitis was not different between groups of elderly people with punctures in dominant members or not.

As for the puncture area, the study shows higher development of phlebitis related to puncture in vessels of the forearm.[5] Results obtained in the present investigation are similar to those found in others that also verified higher development of phlebitis in vessels of the forearm, however, without significant statistical difference when compared to other puncture sites.[16]

In catheters composed by polyurethane, low occurrence of phlebitis was evidenced.[5] In this study, no statistically significant difference was observed

in both studied devices, composed by polyurethane, they differ only regarding the format. Intima® has a security device, flexible wings and a two-way extensor tube in the extremity, which makes it more anatomical compared to Isyte®.

Studies show that catheters with larger caliber (14 to 18G) result in higher phlebitis rates, because they make more attrition against the vessel wall.[5,16] Some studies, however, do not verify statistically significant differences regarding the development of phlebitis and the device diameter.[4,9] In this study, the statistical analysis for phlebitis between different catheter calibers was impaired because of the low frequency of 16G catheter use. Phlebitis, however, was more frequent in individuals who used 20 and 22G caliber devices. Regarding the dressing used to the catheter fixation, although INS does not establish a restriction for the applied material type, they strongly recommend materials designed especially for this reason. In this study, no statistically significant difference was observed regarding phlebitis in both fixation types.

For amiodarone bolus infusions, it is still possible to use polyvinyl chloride containers (PVC). Because of the leaching process, there is instability and consequent loss of 82% of the drug within two hours. In infusions lasting more than two hours, use of glass or low density polyethylene (LDPE) is recommended. LDPE is compatible with a wide range of intravenous solutions, because it does not allow adhesion of fluid molecules to the container wall. This type of bottle maintains stability of amiodarone solutions for 24 hours.[14]

Phlebitis incidence may reach 55% when amiodarone is administered in peripheral vessels in a concentration higher than 3 mg/ml for a period greater than one hour. Dilution of the drug in 5% GS is also recommended, in order to obtain a solution with 1.5 mg/ml when in bolus administration or 1.8 mg/ml for continuous infusion.[6,7]

In addition to following these recommendations, efforts to reduce the frequency of phlebitis can also be associated with both technological development and the deepening of scientific knowledge related to infusion therapy. Technology con-

tributes significantly to reduce this adverse event with more anatomical devices whose material promotes greater biocompatibility and with its own dressing for coverage and fixation of the peripheral intravenous device.[5]

Institution of intravenous therapy protocols based on scientific evidence, control of service quality and availability of professionals specializing in intravenous therapy are also examples of actions that generate safety and care quality related to infusion therapy. Use of infusion pumps for the administration of vasoactive drugs and antiarrhythmic drugs is an established practice in order to promote increased control of infusion rate and time.[5]

In daily practice, there are variations on how to prescribe amiodarone, different from those recommended by the companies, and these directly affect aspects involving its administration, such as: bolus (attack) and continuous (maintenance) administration. It is understandable, therefore, that the analysis of factors related to the development of phlebitis by amiodarone in peripheral venous catheters is elucidated considering types or forms of administration to which the puncture is exposed. In this study, similar phlebitis rates were found in both bolus infusion administrations followed by continuous infusion (36.2%) and exclusive continuous infusion (35.1%). Exclusive bolus infusions, however, did not present phlebitis. A marginally significant difference was observed (p=0.051) regarding infusion types. Therefore, there was a tendency of elderly patients not developing phlebitis when they received exclusively bolus infusions of amiodarone.

Exclusive bolus infusion of amiodarone is characterized by high drug dosage, administered in a short period of time. In addition to the high dosage, the infusion rate (mg/h) was also high in all cases, resulting in short vein exposure time to amiodarone. High solution concentrations, therefore associated with high infusion speed, may justify the result obtained in this study. This result corroborated a study published in 2012 that included 105 patients with a mean age of 66 years. It found that the bolus or rapid infusion of amiodarone (with dose equal or

superior to 150mg) was associated with the development of phlebitis.[4]

In peripheral intravenous punctures receiving bolus infusion of amiodarone followed by continuous infusion, drug administration was made with amiodarone doses in periods of time that also varied, and drug exposure to the vein was higher than that of exclusive bolus infusions group. Longer exposure time of the vessel to amiodarone may have favored the progression of an inflammatory process, leading to phlebitis. In peripheral intravenous injections with continuous infusion, doses and concentrations of amiodarone were unique in at least two hours of exposure of the vein, which means longer exposure time of the vessel. Literature shows a higher frequency of phlebitis occurring in the first 24 hours of treatment.[4]

Risk of phlebitis by exposure of the vessel to amiodarone solutions is directly related to the pH of the drug. PH extremes are among the causes that can lead to the development of chemical phlebitis, as they result in an inflammatory response by the inner layer of the vein, causing infiltration, edema, thrombosis, and cell death. Values of pH lower than 5.5 and higher than 8.0 represent risks of complications during intravenous therapy.[17] Amiodarone has pH between 3.8 and 4.0, so it is a drug with potential risk to the impairment of the vessel. Forms of amiodarone administration, which relate to the respective variations in the vein exposure time, should be taken into consideration and may justify the non-occurrence of phlebitis in puncture groups that received exclusive bolus infusion and the occurrence of the event in the other groups analyzed.

Phlebitis related to intravenous amiodarone in the elderly is a major impact event for both patients and health services. In daily clinical practice, nurses must work actively to prevent or reduce patients' exposure to factors that may be related to the development of mechanical phlebitis.[9] The best performance of the technique as well as the member to be punctured, puncture site, catheter type and type of attachment must be chosen taking into account the patients' characteristics and type of intravenous therapy to be administrated.

More intensive and accurate monitoring is recommended during intravenous therapy using amiodarone, especially in elderly patients and women who receive bolus followed by continuous infusions. Moreover, it is important to note that values above 3.0mg/ml are directly related to the development of phlebitis, requiring constant attention of nurses for early identification.

The continuing efforts to identify factors related to phlebitis due to amiodarone infusion through peripheral venous catheter considering the forms of administration may reveal other aspects that allow individualizing even more the care provided to patients, seeking safety and quality care.

This study on risk factors for the development of phlebitis related to peripheral intravenous administration of amiodarone in elderly patients had the limitation of sample size, given that the calculation for the sample did not consider phlebitis rates in the elderly in general and the different forms of administration: bolus exclusive, exclusive continuous and bolus then continuous.

## Conclusion

The results of this study showed that the incidence of phlebitis in an elderly sample was 33.3%. Among the different types of infusion, there was no phlebitis in exclusive bolus infusions. The variables analyzed in this study did not confirm an association with phlebitis, it is important to observe these aspects for peripheral intravenous infusion of amiodarone in the elderly and further research in search of evidence for this matter are suggested.

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### Collaborations

Buzatto LL and Massa GP collaborated with the project design, analysis and interpretation of data, article writing and final approval of the version to be

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## References

1. Camm AJ, Savelieva I, Potpara T, Hindriks G, Pison L, Blömstrom-Lundqvist C. The changing circumstance of atrial fibrillation - progress towards precision medicine. J Intern Med. 2016; 279 (4):1-16.

2. January CT, Wann LS, Alpert JS, Calkins H, Cigarroa JE, Cleveland JC Jr, Conti JB, Ellinor PT, Ezekowitz MD, Field ME, Murray KT, Sacco RL, Stevenson WG, Tchou PJ, Tracy CM, Yancy CW; American College of Cardiology/American Heart Association Task Force on Practice Guidelines. 2014 AHA/ACC/HRS guideline for the management of patients with atrial fibrillation: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines and the Heart Rhythm Society. J Am Coll Cardiol. 2014 Dec 2; 64(21):e1-76. doi: 10.1016/j.jacc.2014.03.022. Epub 2014 Mar 28. Review. Erratum in: J Am Coll Cardiol. 2014 Dec 2; 64(21):2305-7. PubMed PMID: 24685669.

3. Boyce BB, Yee BH. Incidence and severity of phlebitis in patients receiving peripherally infused amiodarone. Crit Care Nurse. 2012; 32:27-34.

4. Norton L, Ottoboni LK, Varady A, Yang-Lu C, Becker N, Cotter T, et al. Phlebitis in amiodarone administration: incidence, contributing factors, and clinical implications. Am J Crit Care. 2013; 22(6):498-505.

5. Gorski L, Hadaway L, Hagle ME, McGoldrick M, Orr M, Doellman D. Infusion therapy standards of practice. J Infus Nurs. 2016; 39 (1S):S11-S159.

6. Mowry JL, Hartman LS. Intravascular thrombophlebitis related to the peripheral infusion of amiodarone and vancomycin. Western J Nurs Research. 2011; 33(3): 457-71.

7. Halonen J, Loponen P, Järvinen O, Karjalainen J, Parviainen I, Halonen P, et al. Metoprolol versus amiodarone in the prevention of atrial fibrillation after cardiac surgery: a randomized trial. Ann Intern Med. 2010; 153(11):703-9.

8. Oliveira FT, Paes GO, Mesquita MG, Souza VM, Carlos ES, Martins CS. Assistance algorithm of nursing for amiodarone intravenous infusion . Rev RENE. 2014; 15(5):878-887.

9. Spiering M. Peripheral amiodarone-related phlebitis: an institutional nursing guideline to reduce patient harm. J Infus Nurs. 2014; 37(6):453-60.

10. Antonelli D, Barzilay J. Acute thrombophlebitis following IV amiodarone administration [letter]. Chest.1983; 84(1):120b-120.

11. Kreiss Y, Sidi Y, Gur H. Efficacy and safety of intravenous amiodarone in recent-onsetatrial fibrillation: experience in patients admitted to a general internal medicine department. Postgrad Med J. 1999; 75:(883) 278-81.

12. do Rego Furtado LC. Maintenance of peripheral venous access and its impact on the development of phlebitis: a survey of 186 catheters in a general surgery department in Portugal. Infus Nurs. 2011; (6):382-90.

13. Dragana M, Dragana S, Davor Z. Risk factor for phlebitis: a questionnaire study of nurses' perception Rev Lat Am Enfermagem. 2015; 23(4):677-84.

14. Nassaji-Zavareh M, Ghorbani R. Peripheral intravenous catheter-related phlebitis and related risk factors. Singapore Med J.2007; 48(8):733-6.

15. Wallis MC, McGrail M, Webster J, Marsh N, Gowardman J, Playford EG, et al. Risk factors for peripheral intravenous catheter failure: a multivariate analysis of data from a randomized controlled trial. Infect Control Hosp Epidemiol. 2014; 35(1): 63-8.

16. Dychter SS, Gold D, Carson D, Haller M. Intravenous therapy: a review of complications and economic considerations of peripheral access. J Infus Nurs. 2012; 35(2):84-91.

17. Gorski, LA., Hagle ME; Bierman S. Intermittently delivered IV medication and pH: reevaluating the vidence. J Infus Nurs. 2015; 38( 1): 27-46.