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ANALYSIS OF THE INTERACTION BETWEEN WARFARIN AND SOME ANTIBIOTICS IN OLDER PATIENTS AT A TERTIARY HOSPITAL OF DHAHRAN: A RETROSPECTIVE COHORT STUDY

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Abstract:

Warfarin is an oral anticoagulant that is indicated for the prevention and treatment of various cardiovascular disorders. Potential drug interactions of warfarin are observed to be one of the most frequently appearing challenge that may alter the pharmacokinetics and pharmacodynamics of the drug thus alter the overall therapeutic response. The aim of this study was to determine the effect of antibiotics on INR values over time in patients > 50 years receiving stable warfarin therapy. Data for this retrospective cohort study were collected through a medical record review of patients in an ambulatory anticoagulation clinic. A total of 121 patients from 185 prescriptions qualified the inclusion criteria and were included in the study. The results revealed that there was a significant increase in INR values because of antibiotic and warfarin interactions. The results indicated that the pattern of INR change for the 5 antibiotics was significantly different across the time. The mean INR increase was significant for amoxicillin (0.191, $p < 0.05$), ciprofloxacin (0.13, $p < 0.05$), azithromycin (0.32, $p < 0.05$), levofloxacin (0.32, $p < 0.05$), and cefuroxime (0.24, $p < 0.05$). *It has been concluded that the use of antibiotics in older patients receiving a stable warfarin therapy, may lead to an increase in the INR. However, this increase in INR may not be too significant as long as the INR is routinely monitored.*

Keyword: *International Normalized Ratio, Warfarin, Antibiotics, Drug interaction.*

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INTRODUCTION:

Warfarin is an oral anticoagulant that is indicated for the prevention and treatment of various cardiovascular disorders. Its use is the highest in older adults due to the increased prevalence of conditions such as atrial fibrillation and other thromboembolic disorders with advancing age [1]. Potential drug interactions of warfarin are observed to be one of the most frequently appearing challenge that may alter the pharmacokinetics and pharmacodynamics of the drug thus alter the overall therapeutic response. Warfarin therapy may be complicated by several factors, and maintaining therapeutic levels of warfarin is challenging because it is a drug with a narrow therapeutic index, and it exhibits considerable variability in dose response [2]. The most important and frequent complications that may occur with the use of warfarin are hemorrhages, which may be related to the value of the International Normalized Ratio (INR). Other adverse reactions include hypersensitivity reactions, cholestatic jaundice, hepatitis, vasculitis, nausea and vomiting, diarrhea, alopecia, etc. The risk of an interaction may be higher in older adults due to age-related physiologic changes which may result in an altered pharmacodynamic response for warfarin [3]. Warfarin therapy is monitored by measuring the International Normalized Ratio (INR). The INR needs to be monitored more frequently following any dose change, use of other medication, or when a patient's medical condition changes [4].

A systematic review of warfarin–drug interactions recommends exercising caution when prescribing antibiotics to patients taking warfarin because antibiotics may cause a change in the patient's hematological response to warfarin [5]**.** The American Society of Consultant Pharmacists (ASCP) [6, 7] has stated that some dangerous warfarin-antibiotic interactions may occur in older patients. The risk of an interaction may be higher in older adults due to age related factors which may result in an altered pharmacodynamic response to warfarin [8] and altered pharmacokinetics of antibiotics [9]. Some studies have been reported related to the analysis of warfarin and antibiotic interaction [10-20]. However, we believe that no such study has been carried out at any tertiary hospital of Dhahran. Therefore, it was decided to analyze the interaction between warfarin and some antibiotics in older patients at a tertiary hospital of Dhahran.

MATERIALS AND METHODS:

Study Design and Setting

This single-centered, retrospective, cohort analysis was conducted at an ambulatory anticoagulation clinic (ACC) at the Department of Cardiology, Johns Hopkins Aramco Healthcare (JAHA), Dhahran, Kingdom of Saudi Arabia, using the data from the medical records over the period from January 2015 to December 2016. The study protocol was approved by Johns Hopkins Aramco Health Care (JHAH) Institutional Review Board (IRB).

Study Population

Patients receiving long-term warfarin therapy between January 2015 to December 2016 were studied. The study included all adults (age $\geq$ 50 years) which were on stable warfarin therapy. The stable warfarin therapy is defined as preantibiotic INR values within ± 0.2 of recommended therapeutic INR range during the 4-week period before the antibiotic start date, preantibiotic INR $\geq$ 2. Patients must also have had at least 1 INR value recorded during their antibiotic therapy or during the 14-day period after discontinuation of the antibiotic (i.e., postantibiotic INR) to be included. In addition, patients must have had a prescription for the antibiotic for 3 or more days to be included. Patients will be excluded if they did not have an anticoagulation clinic note before and after the period of starting the antibiotic. Without a clinical note, it will not be possible to ascertain whether patients were on stable warfarin therapy and were compliant with therapy or to gather information on other concomitant interacting medications that the patient may have been prescribed. Patients who are not compliant with warfarin therapy were excluded because noncompliance may lead to fluctuating INR values. Patients undergoing a dental procedure were not included because antibiotics are usually given prophylactically to these patients. Patients receiving another anticoagulant e.g. enoxaparin (LMWH) concomitantly with warfarin were excluded because this may further complicate anticoagulant activity. Patients newly started on amiodarone therapy were not included because a warfarin dose reduction of 20% to 50% is generally done for these patients. However, long-term users of amiodarone were not excluded. Finally, patients were excluded if they received a prescription, both a refilled and new prescription, for other potentially interacting medications. The potentially interacting medications that patients were screened for included metronidazole, trimethoprim-sulfamethoxazole, carbamazepine, phenytoin, fluconazole, ketoconazole, rifampin, isoniazid, prednisone, and phenobarbital because they are known to have a well-documented interaction with warfarin. Collected patient characteristics included date of visit, INR value, dose and duration, diagnosis, other medications and disease, e.g. diabetes mellitus, gender, age, BMI (body mass index) and city.

RESULTS:

A total of 185 patients received antibiotic prescription concomitantly with the warfarin therapy. However, the data of only 121 patients were analyzed because they fulfilled the following inclusion criteria. Patients ≥ 50 years of age who received a prescription of warfarin and at least one antibiotic (amoxicillin, azithromycin, ciprofloxacin, levofloxacin, or cefuroxime). Patients were on stable warfarin therapy, defined as pre-antibiotic INR values within ±0.2 of recommended therapeutic INR range during the 4-week period before the antibiotic start date. This would eliminate patients with fluctuating INR values. In the presence of ≥ 2 pre-antibiotic INR values, all INR values were recorded. Patients had at least 1 INR value recorded during their antibiotic therapy or during the 14-day period after discontinuation of the antibiotic (i.e. post-antibiotic INR). Patients had a prescription for the antibiotic for 3 or more days. Patients were excluded if there was a change in their warfarin dose from the date of recording the pre-antibiotic INR to the date of starting the antibiotic prescription, or if there was a change in the patient's warfarin dose after the antibiotic start date and before the post-antibiotic INR value was recorded. Patients were excluded if they did not have an anticoagulation clinic note before and after the period of starting the antibiotic. Without a clinical note, it would not be possible to ascertain whether patients were on stable warfarin therapy and were compliant with therapy or to gather information on other concomitant interacting medications that the patient may have been prescribed. Patients who were not compliant with warfarin therapy were excluded because noncompliance may lead to fluctuating INR values. Patients undergoing a dental procedure were not included because antibiotics are usually given prophylactically to these patients and may be prescribed as a 1-time course of the 1 day. These patients may also not be the same as the other study patients with an active infection. Patients receiving enoxaparin (low molecular weight heparin) concomitantly with warfarin were excluded because this may further complicate anticoagulant activity. Patients newly started on amiodarone therapy were not included because a warfarin dose reduction of 20% to 50% is generally done for these patients. However, long-term users of amiodarone were not excluded. Finally, patients were excluded if they received a prescription, both a refilled and new prescription, for other potentially interacting medications. The potentially interacting medications that patients were screened for included metronidazole, trimethoprim-sulfamethoxazole, carbamazepine, phenytoin, fluconazole, ketoconazole, rifampin, isoniazid, prednisone, and phenobarbital because they are known to have a well-documented interaction with warfarin [21].

The baseline demographic, clinical characteristics of study patients, international normalized ratio changes and secondary outcomes of over anticoagulation data are provided in Table 1. The main findings of the results are; Among the 121 patients, there were 56 prescriptions for Amoxicillin, 30 for Ciprofloxacin, 14 for Azithromycin, 14 for Levofloxacin, and 7 for Cefuroxime during the time frame of the study. The mean (SD) age of the patients was 70.70 (10.94), and the median age was 73 (IQR = 55-92). The mean (SD) of pre-antibiotic for patients range from 2.05 to 2.68 (0.39-0.75) across the 5 antibiotics. The post-antibiotic INR values were recorded at 11.04 days on average after the start of the antibiotic prescription.

The most common indication for warfarin use were Atrial fibrillation (AF), Aortic valve replacement (AVR), and Mitral valve replacement (MVR). The main indications for which antibiotics were used, include lower respiratory infection, upper respiratory infection, urinary tract infection, and skin and soft tissue infection. The results indicate that the pattern of INR changes for the 5 antibiotics was significantly different across the time. The mean INR increase was significant for Amoxicillin (0.191 [1], $p < 0.05$), Ciprofloxacin (0.13 [0.95], $p < 0.05$), Azithromycin (0.32 [0.66], $p < 0.05$), Levofloxacin (0.32 [0.67], $p < 0.05$), and Cefuroxime (0.24 [0.55], $p < 0.05$). For an increase in the INR above the therapeutic range, the percentages of patients were significantly higher ($p < 0.05$) for all the antibiotics. Contrary to the reported data, this study also revealed a decrease in INR values during this study. There were no reports of major or minor bleeding events, hospitalization, or even emergency department visit during concomitant warfarin use and antibiotic therapy.

Table 1: Baseline demographic, clinical characteristics of study patients, international normalized ratio changes

Characteristic	Amoxicillin (N = 56)	Ciprofloxacin (N = 30)	Azithromycin (N = 14)	Levofloxacin (N= 14)	Cefuroxime (N = 7)
Age, y, mean (SD)	70.66 (10.75)	70.13 (11.60)	70.5 (11.47)	73.86 (9.94)	68.43 (11.76)
Age, y, median (IQR)	73 (55-92)	69.5 (55-89)	72 (55-87)	75 (55-92)	72 (55-82)
Preantibiotic INR 1, mean (SD)	2.39 (0.75)	2.24 (0.70)	2.05 (0.63)	2.35 (0.57)	2.3 (0.46)
Preantibiotic INR 2, mean (SD)	2.58 (0.72)	2.37 (0.75)	2.37 (0.39)	2.68 (0.67)	2.54 (0.45)
INR change (from preantibiotic INR 2 to postantibiotic INR 1), mean (SE)	0.191 (1.0)*	0.13 (0.95)*	0.32 (0.66)*	0.32 (0.67)*	0.24 (0.55)*
Mean (SD) duration of antibiotic use, d	9.91 (2.38)	14.47 (2.05)	6.57 (1.55)	12.21 (2.08)	12.0 (1.53)
Mean (SD) of medications	4.98 (2.03)	4.73 (1.96)	4.93 (2.20)	4.57 (1.50)	6.43 (2.51)
Mean (SD) of disease conditions	3.23 (1.11)	3.30 (1.12)	3.79 (1.12)	2.86 (1.23)	3.14 (1.46)
Males, no. (%)	28 (50)	15 (50)	4 (28.57)	10 (71.42)	5 (71.42)
Female, no. (%)	28 (50)	15 (50)	10 (71.42)	4 (28.57)	2 (28.57)
Indication for warfarin use, no. (%)					
Atrial fibrillation	28 (50)	13 (43.33)	9 (64.28)	7 (50)	3 (42.85)
AVR / MVR	17 (30.35)	8 (26.66)	3 (21.42)	4 (28.57)	2 (28.57)
left ventricular thrombosis	1 (1.78)	-	-	-	-
PE	7 (12.5)	2 (6.66)	2 (14.28)	1 (7.14)	-
right artery desection	1 (1.78)	-	-	-	-
sinus thrombosis	1 (1.78)	-	-	-	-
Stroke	1 (1.78)	6 (20)	-	1 (7.14)	-
DVT	-	1 (3.33)	-	1 (7.14)	-
Others	-	-	-	-	2 (28.57)
Indication for antibiotic use, no. (%)					
Lower respiratory infections	11 (19.64)	3 (10)	8 (57.14)	1 (7.14)	1 (14.28)
Upper respiratory infections	11 (19.64)	2 (6.66)	4 (28.57)	2 (14.28)	-
Urinary tract infections	8 (14.28)	16 (53.33)	-	9 (64.28)	3 (42.85)
Skin and soft-tissue infections	20 (35.71)	4 (13.33)	1 (7.14)	1 (7.14)	3 (42.85)
Other	6 (10.71)	5 (16.66)	1 (7.14)	1 (7.14)	-
Secondary outcomes of over anticoagulation, no (%)					
INR (no change)	5 (8.92)*	1 (3.33) *	1 (7.14) *	-	-
INR increased ≤ 1	21 (37.5) *	11 (36.66) *	7 (50) *	7 (50) *	4 (57.14)*
INR ≤ 2	6 (10.71) *	3 (10) *	2 (14.28) *	2 (14.28)*	-
INR ≤ 3	3 (5.35) *	-	-	-	-
INR decreased	21 (37.5) *	15 (50) *	4 (28.57) *	5 (35.71)*	3 (42.85)*

DVT = deep venous thrombosis; IQR = interquartile range; PE = pulmonary embolism; AVR = Aortic valve replacement; MVR = Mitral valve replacement; *p < 0.05.

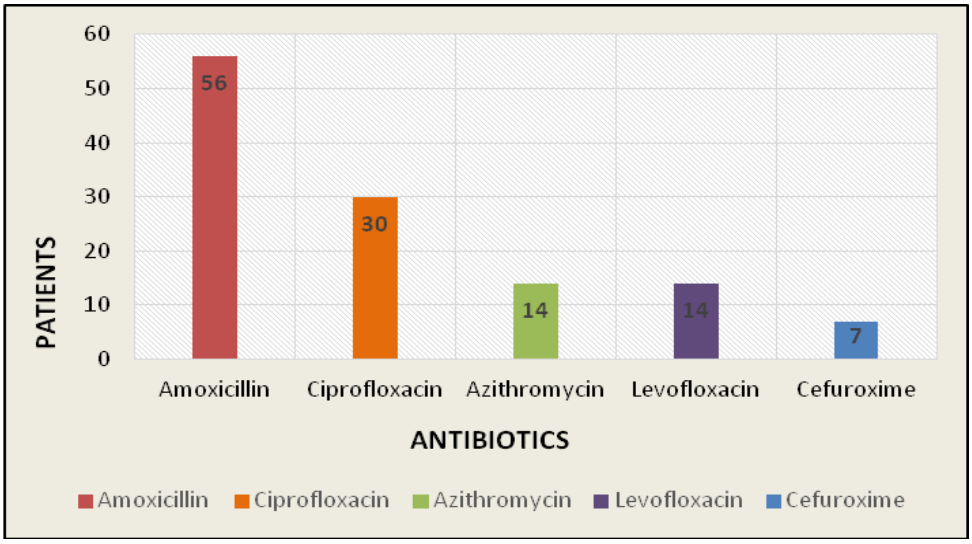

Fig. 1: Name of the antibiotics vs number of patients

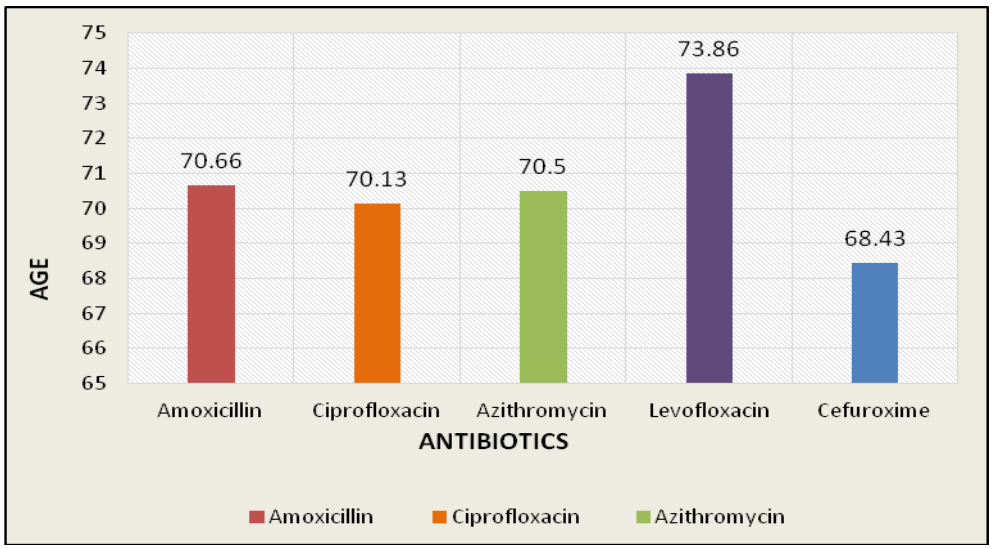

Fig. 2: Name of the antibiotics vs mean age of the patients

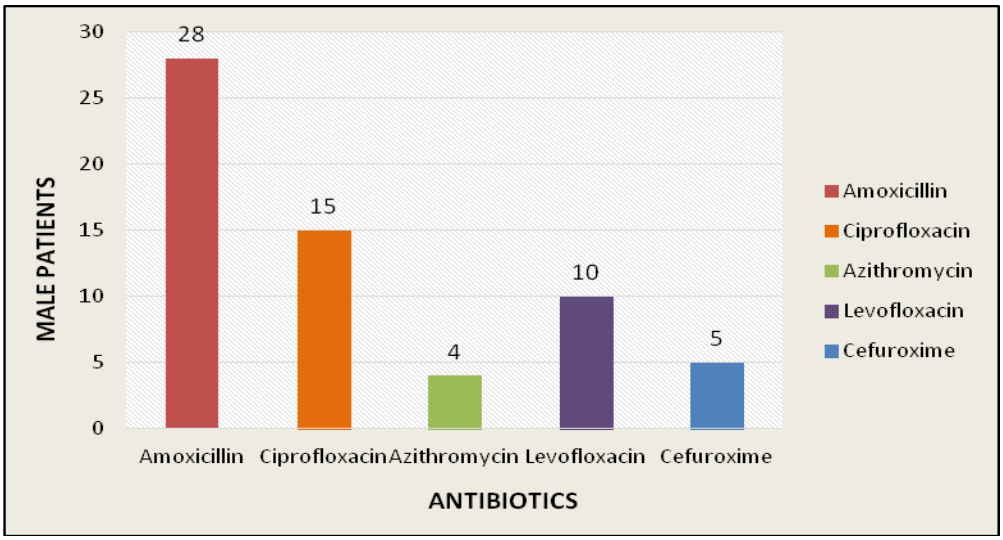

Fig. 3: Name of the antibiotics vs number of male patients

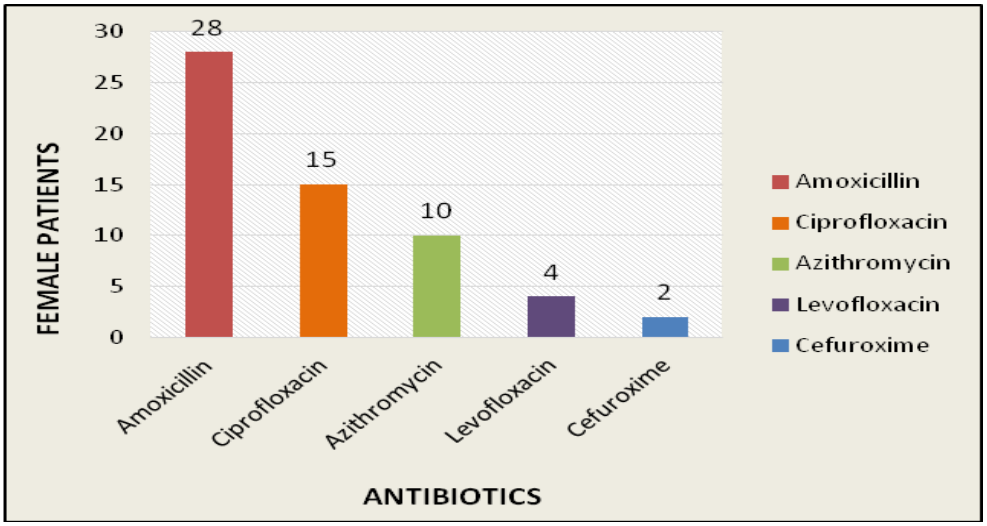

Fig. 4: Name of the antibiotics vs number of female patients

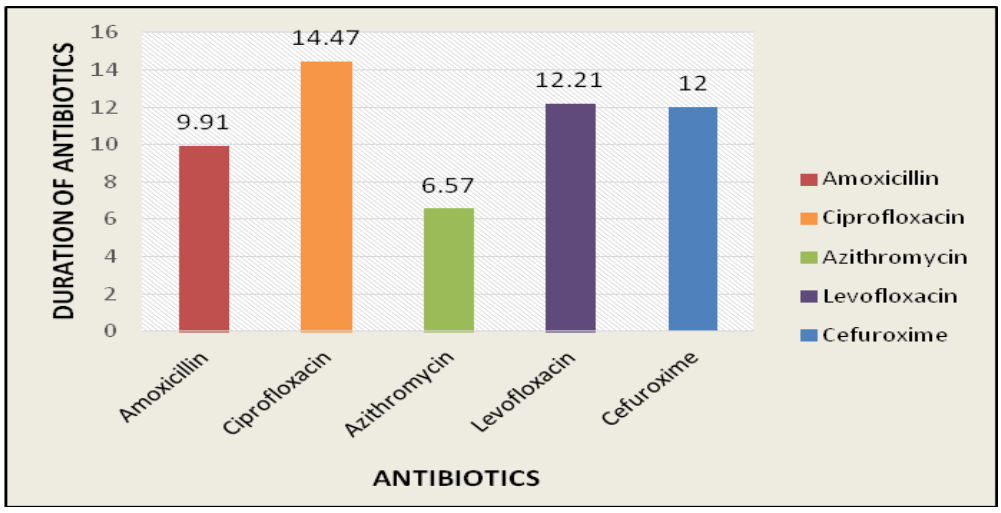

Fig. 5: Name of the antibiotics vs mean of the duration of antibiotic treatment

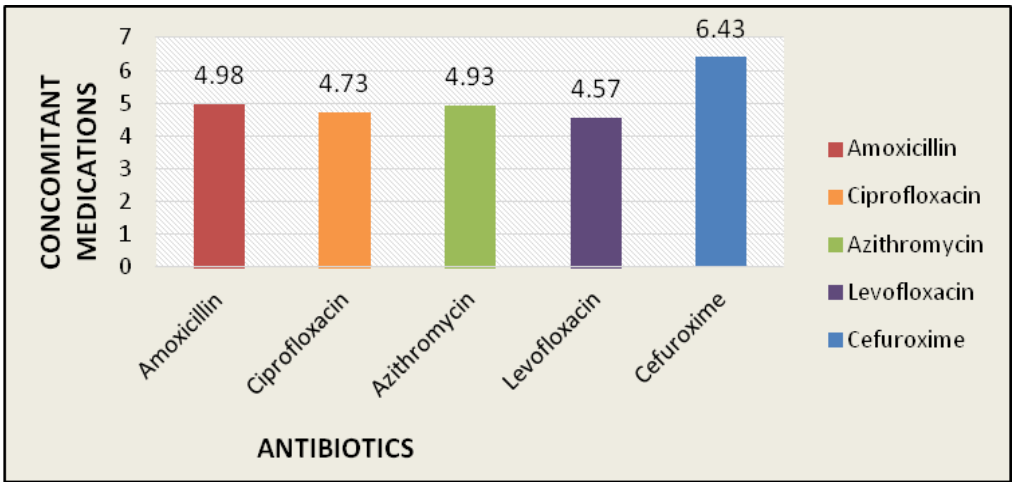

Fig. 6: Name of the antibiotics vs mean of the number of concomitant medications during treatment

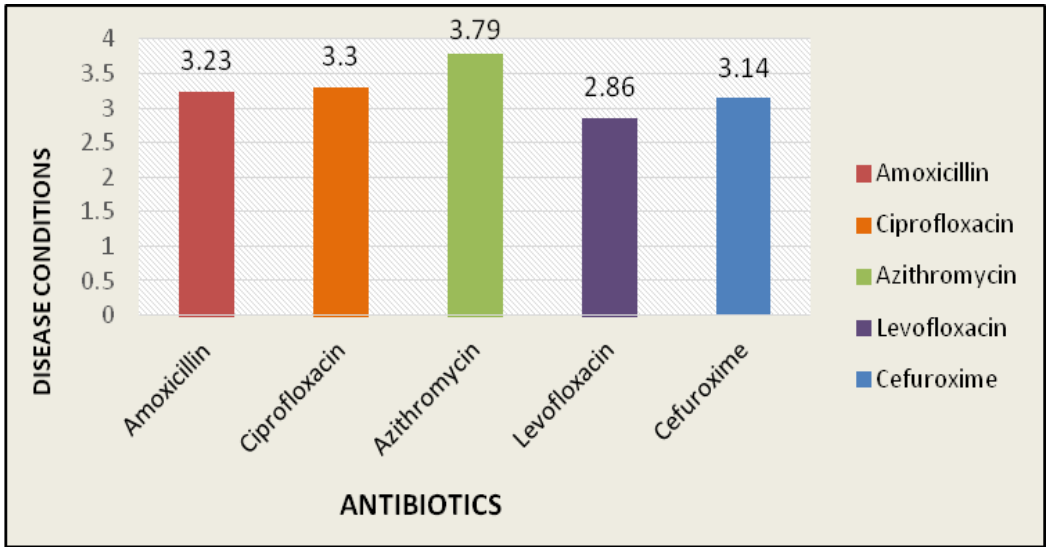

Fig. 7: Name of the antibiotics vs mean of the number of disease conditions

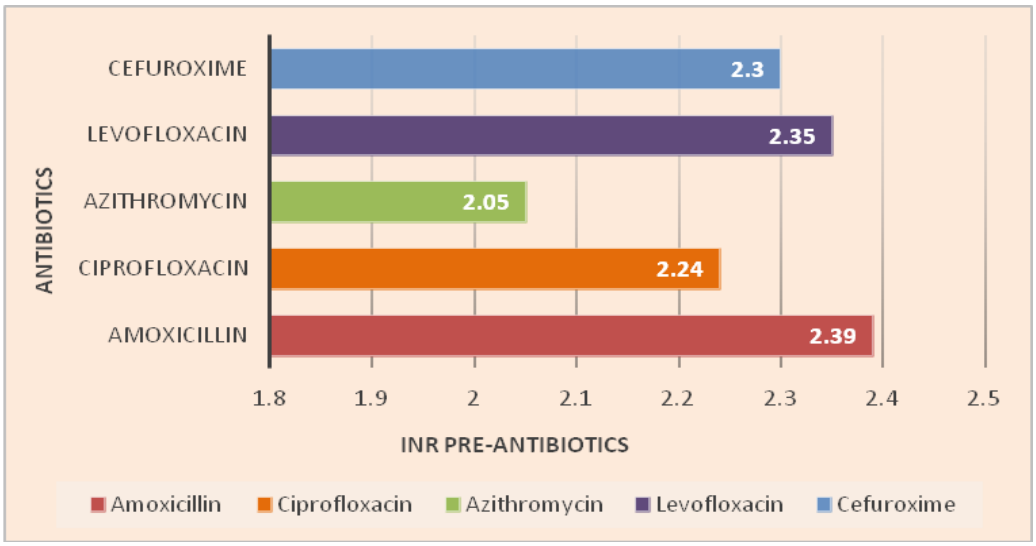

Fig. 8: Name of the antibiotics vs mean of the Pre-antibiotic INR (1)

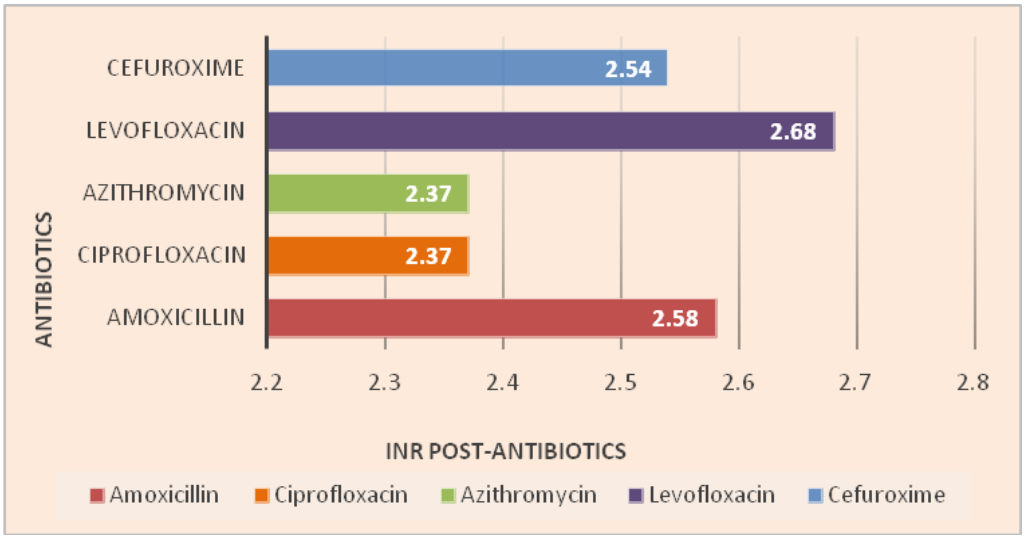

Fig. 9: Name of the antibiotics vs mean of Post-antibiotic INR (2)

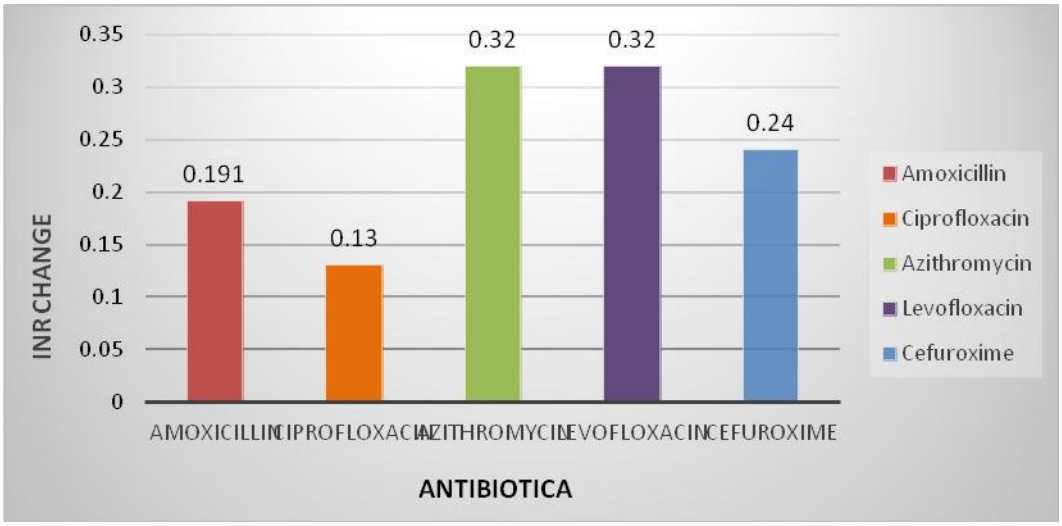

Fig. 10: Name of the antibiotics vs mean of the INR change (from post- antibiotic INR 2 to pre-antibiotic INR 1)

Statistical Analysis

The data were analyzed by using GraphPad Prism version 5.00 for Windows (GraphPad Software, San Diego California USA). The results were considered significantly different at $p < 0.05$.

DISCUSSION:

The results of this study showed that all antibiotics lead to a significant increase in INR values post-antibiotic use in older patients when taken concomitantly with warfarin. However, this increase in post-antibiotic INR did not lead to clinically significant outcomes of bleeding or hospitalization. In this study, patients also showed a decrease in INR values. The reason for this result is not clear. It is expected that this decrease in INR may be related to intake of particular foods, herbal medicine, OTC drugs, or the type of infection .i.e. lower / upper respiratory infection and UTI, during the concomitant therapy of antibiotic and warfarin [21]. However, our data is silent about these factors. The strength of this study include the mean age of patients who were included in this study was about 70 years. This is important because the older population is at higher risk of drug interaction due to increased sensitivity in pharmacodynamic response to warfarin. The internal validity of the study was enhanced by including only those patients who were on stable warfarin therapy before starting the antibiotic. Thus, any increase in INR value after starting the antibiotic may become apparent in such patients.

There were some limitations of this study given the retrospective nature of data collection. The effect of the particular food, herbal medicine, OTC drugs, or the type of infection .i.e. lower / upper respiratory infection and UTI, during the concomitant therapy of antibiotic and warfarin has not been studied. The results of this study are only generalizable to patients receiving routine monitoring in an anticoagulation clinic compared with other models of anticoagulant care. The results are not generalizable to those patients who may have fluctuating INR values or warfarin dosage adjustments being made before starting antibiotic therapy, as may be routinely seen in clinical practice. Thus, the effect of a warfarin–antibiotic interaction was evaluated in a restricted sample of patients on stable warfarin therapy. Although a restricted sample may increase the internal validity, it may reduce the generalizability by not entirely representing the true clinical picture. Another possible limitation of the study is that several patients had only 1 pre- and the postantibiotic INR value recorded. The presence of ≥ 2 pre- and the post-antibiotic INR values for all patients would have further enhanced the internal validity of the study. The time points at which pre- and post-antibiotic INR values were recorded were not the same for all patients. The aim of the study was to characterize warfarin–antibiotic interactions in older patients, thus, the results may not be entirely applicable to other patient populations.

CONCLUSION:

The results of this study provide evidence of an increase in a patient's INR after antibiotic use that may lead to a warfarin dose adjustment in several patients; however, there was no evidence of clinical outcomes of bleeding or hospitalization as a result of this increase in INR. Based on the results of this study, a change in clinical practice such as an empirical reduction of warfarin dose when antibiotics are prescribed concomitantly with warfarin may not be required. Thus, antibiotics

may be prescribed to older adults receiving warfarin therapy as long as their INR is closely monitored. In this study, patients also showed a decrease in INR values. The reason for this result is not clear. Therefore, it is recommended to study the effect of intake of particular food, herbal medicine, OTC drugs, or the type of infection. i.e. lower / upper respiratory infection and UTI, during the concomitant therapy of antibiotic and warfarin.

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