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Original Research Article

Use of rivaroxaban and acetylsalicylic acid as a combined treatment for peripheral arterial disease in Central Military Hospital

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ABSTRACT

Background: The objective of this research was to evaluate the behavior of 3 risk indicators for peripheral arterial disease in patients under oral treatment with rivaroxaban 2.5 mg every 12 hours plus, acetylsalicylic acid 100 mg every 24 hours. It was hypothesized that the oral combination of rivaroxaban and acetylsalicylic acid presents a therapeutic advantage over other treatments.
Methods: A prospective longitudinal and non-randomized study of a single center was performed. 59 patients with peripheral arterial disease were included and treated with acetylsalicylic acid + rivaroxaban. Peak systolic velocity, ankle-brachial index and C reactive protein index were evaluated.
Results: Significant changes were found at month 1 and 3 of follow-up in maximum systolic velocity, ankle-arm index and C-reactive protein index. The baseline peak systolic velocity (PSV) in the anterior tibial artery had significant differences after one month of treatment (p=0.001) and after 3 months (p=0.001). The baseline PSV in the posterior tibial artery had significant differences compared to the values found at the month of treatment (p=0.001) and 3 months (p=0.001). In the ankle-brachial index a baseline median of 0.790 was found, one month after the treatment of 0.795 (p=0.147) and 3 months after 0.800 (p=0.019). The mean baseline C-reactive protein obtained was 73.142 mg/l, at one month 87.233 mg/l (p=0.001) and at 3 months at 79.009 mg/l (p=0.294) with a standard deviation of 67.18, 74.78 and 69.69 respectively.
Conclusions: The combined use of acetylsalicylic acid and rivaroxaban allows a clinical improvement in patients with peripheral arterial disease.

Keywords: Peripheral arterial disease, Rivaroxaban, Aspirin, Intermittent claudication, Critical ischemia, Amputation, Extremity salvaging

INTRODUCTION

Peripheral arterial disease (PAD) is a clinical manifestation of atherosclerosis. It occurs after the stenosis and obstruction of the arterial lumen due to atheroma plaques causing hemodynamic changes and diminishing the perfusion pressure leading to ischemia in distal tissues. Associated risk factors include smoking, diabetes, hypertension and elevated homocysteine blood levels.[1-5]

There are 2 main groups in PAD: intermittent claudication and those with critical limb threatening ischemia. The ankle-brachial index (ABI) is a non-invasive diagnostic tool and aids with monitoring the diseases progression. Pharmacological modulation of the coagulation and platelet activation processes is of crucial clinical importance. Several clinical trials have repeatedly proven the efficacy of anticoagulation and platelet activation in different thrombotic disorders. Most recent data suggest that antithrombotic strategies require a delicate balance between anticoagulation and platelet activation.[6] Such strategy was recently confirmed as beneficial for the secondary prevention in 27, 395 patients with coronary events and PAD with stable atherosclerosis in the COMPASS study.[7,8]

ABI

The ABI is a non-invasive useful tool for both diagnostic and monitoring of the PAD as well as an important marker in generalized atherosclerosis and cardiovascular risk (CR). An ABI≤0.90 is associated with an increase of 2-3 times of death risk for all causes including cardiovascular ones. An ABI>1.40 indicates arterial rigidity (medial arterial layer calcification) and is also associated with higher risk of cardiovascular events and death. ABI has the advantage of being an independent risk evaluation method when taking into account traditional risk factors of each ethnic group. Compared to coronary calcium and intima-media carotid thickness, the ABI is a low cost, available and quick test.

Peak systolic velocity and duplex ultrasound

The duplex ultrasound allows to study the blood flow of the different vessels. The sonographic impulse emitted by the transducer is reflected in the red blood cells of the vessel, it goes back to the transducer with a beam deviation directly proportional to the speed of the red blood cells (flow). It is a non-invasive and fast method that can be practiced as many times as necessary without any risk to the patient. The basic examination of the arterial system is based on the assessment of the presence of pulses, which in the lower limb will include the femoral, popliteal, dorsalis pedis and posterior tibial arteries. PSV determines between stenosis and the proximal arterial region are more accurate than absolute PSV measurements for classifying peripheral arterial stenosis. Stenosis is defined as; mild (0-19%), moderate (20-49%) and severe (≥50%) according to the percentage decrease in the luminal diameter with pulsed wave duplex ultrasonography scan.[10] A concentric reduction of 50% of arterial diameter lumen will produce a reduction of 75% in the transversal section producing significant changes in blood flow. The main criteria for classification lower limb grade stenosis is the measurement of the peak systolic velocity ratio. The peak systolic velocity ratio (PVR) is calculated by dividing the peak systolic velocity recorded through stenosis by the peak systolic velocity recorded in a normal area of the artery proximal to the stenosis.

C-reactive protein and atherothrombosis

Atherothrombosis is a complex inflammatory pathological process initiated by the deposition of lipids in the arterial wall with subsequent recruitment of circulating leukocytes. The growing atheromatous plaque may become unstable and rupture, causing thrombus formation due to accumulation of platelets and coagulation proteins, which may eventually induce an ischemic event.[11]

C-reactive protein (CRP) actively participates by activating the complement system and inducing apoptosis, vascular cell activation, leukocyte recruitment, lipid accumulation, platelet aggregation and finally thrombosis.[12] Monomeric CRP (mCRP) is detectable in the vessel wall during the early stages of atherogenesis but not in healthy vessels, and increases as atherosclerosis develops, while pentameric CRP (pCRP) is not detectable in healthy or atherosclerotic vessels.[13]

Current treatment of peripheral arterial disease

The current optimal medical treatment includes the control of cardiovascular risk factors with appropriate pharmacological treatment and the establishment of non-pharmacological measures such as tobacco cessation, a healthy diet, weight loss and regular physical exercise. Pharmacological treatment should include antihypertensive, lipid-lowering and antithrombotic drugs, in diabetic patients, optimal glycemic control should be performed. Aspirin, statins and angiotensin modulators are effective in patients with peripheral arterial disease. Recent evidence showed that an oral treatment strategy with rivaroxaban added to the basic antiplatelet therapy reduced the risk of ischemia in patients with recent acute coronary syndromes, as well as in patients with stable atherosclerotic vascular disease selectively and competitively inhibits free FXa and prothrombinase/clot-associated FXa through reversible interactions, thereby inhibiting thrombin generation and decreasing fibrin clot formation.[14-17]

Objectives

The objectives of the study were to evaluate the behavior of 3 risk indicators for peripheral arterial disease in patients under oral treatment with rivaroxaban (2.5 mg every 12 hours) plus acetylsalicylic acid (100 mg every 24 hours).

Hypothesis

The oral combination of rivaroxaban and acetylsalicylic acid presents a therapeutic advantage over other treatments indicated or reported in previous studies in peripheral arterial disease and this can be evaluated by measuring ankle-brachial index, C-reactive protein levels and the peak systolic velocity (Figure 1).

$H_i = PSV_B \neq PSV_1 \neq PSV_3$ $H_0 = PSV_B = PSV_1 = PSV_3$	$H_1 = CRP_B \neq CRP_1 \neq CRP_3$ $H_0 = CRP_B = CRP_1 = CRP_3$	$H_0 = ABI_B \neq ABI_1 \neq ABI_3$ $H_1 = ABI_B \neq ABI_1 \neq ABI_3$

Figure 1: Null and alternating hypothesis of the PSV, CRP and ABI.

METHODS

During the period from March 2019 to September of 2019 in the angiology and peripheral vascular surgery service of the Central Military Hospital, 59 patients who met the inclusion criteria were treated (Table 1).

Type of study

The type of the study was analytical, prospective, and longitudinal.

Statistical analysis

For the statistical analysis, the data obtained were tabulated in the statistical package for the social sciences (SPSS) database and presented in tables and graphics for analysis. Descriptive statistics were performed for each of the demographic variables. Age, CRP, the ABI as well as the peak systolic velocity as quantitative variables were expressed in measures of central tendency (mean and median), as well as distribution with the standard deviation. The frequency of qualitative variables was expressed as a percentage. For the analysis performed with inferential statistics for the CRP and ABI, the Wilcoxon range test was used and for the PSV analysis the Pearson chi-square test was used.

Table 1: Inclusion, exclusion and elimination criteria.

Inclusion criteria	Exclusion criteria	Elimination criteria
Age ≥50 years with risk factors for PAD (DM, HTA and/or smoking)	Patients with asymptomatic PAD or mild claudication without functional limitation. Acute limb ischemia within 2 weeks prior to the start of the study	Those patients who present major bleeding events that require hospitalization and / or blood transfusion, which in turn will be incorporated into a follow-up group with the treatment adjusted to their clinical situation for reporting within the present study
Moderate to severe symptomatic atherosclerotic PAD of lower limb	Significant loss of tissue in any of the lower extremities. Any contraindication for the use of acetylsalicylic acid and/or rivaroxaban	
Hemorrhagic tendency tests, as well as renal function tests within normal parameters	Clinical requirement of acetylsalicylic acid dose> 100mg per day. Patients with chronic liver disease. Planned use of any additional antiplatelet agent other than acetylsalicylic acid. Serum creatinine greater than 1.5mg / dL in the last follow-up study less than 6 months. Acute infectious process or in treatment during the last 2 weeks that require emergency surgery	
Authorization to enter the study by signing the consent validly informed in writing	Requirement of double planned antiplatelet therapy with clopidogrel by a peripheral and/or coronary revascularization procedure. Requirement for dialysis therapy or renal replacement, or renal insufficiency evaluated by a glomerular filtration rate <15 ml/min/1.73m^2	If the patient presents during their follow-up any medical condition included in the exclusion criteria
The patient understands, is willing and able to comply with the instructions of the study and the follow-up	Patients with acute coronary event in the last 6 months. Patients with a history of trauma or major surgery in the last 6 months. Patients diagnosed with autoimmune disease. Patients with chronic inflammatory disorders with or without treatment. Diagnosis of active malignancy and/or under study. Intracranial and/or extracranial cerebrovascular disease diagnosed and under treatment	Need for urgent revascularization before or during medical follow-up, same patients who in turn will be incorporated into a follow-up group for their report within the present study
	Any medically documented history of intracranial hemorrhage, stroke or transient ischemic attack. Poorly controlled diabetes or severe uncontrolled hypertension	The patient's refusal to participate or withdraw their participation at any time during the follow-up

Informed consent, research and ethics committees

This work was evaluated and approved by the research and ethics committees of the Central Military Hospital. All patients were given duly informed consent explaining risks, benefits, confidentiality, voluntary participation and withdrawal of the research protocol, as well as telephone numbers of the responsible investigator and the ethics committee of the Central Military Hospital (C. INV.-062). Consent was written, all procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation of the Central Military Hospital and with the Helsinki declaration of 1975, as revised in 2008.

RESULTS

For the anatomical description of the main sites of location of arterial lesions, a diagram was drawn up in which the frequency data are included as described in Figure 2. During the study period, 59 patients who met the inclusion criteria were admitted.

The average age of the patients was 66.39+11.22 years. A higher proportion of male patients were recorded with 61%. 96.6% of the patients were diabetic, of which 98.31% had an insulin treatment. In this study there were no patients with chronic kidney disease, and 57.63% with hypertension.

The main comorbidities found in this study population were coronary artery disease (20.34%) and smoking (15.25%). The distribution of treatment schemes included cilostazol, rivaroxaban 20 mg, rivaroxaban 2.5 mg, acetylsalicylic acid, statins, and antibiotics (Table 2). All patients received according to their scheme; combination of statin, cilostazol, antiplatelet and anticoagulant.

Table 2: Treatment schemes in patients who entered the study (n=59).

Treatment	Category	N	%
Treatment with cilostazol	Yes	47	79.66
	No	12	20.34
Treatment with rivaroxaban 20 mg	Yes	3	5.08
	No	56	94.92
Treatment with rivaroxaban 2.5 mg e/12h	Yes	56	94.92
	No	3	5.08
Treatment with antiaggregating (acetylsalicylic acid 100 mg/24 hours)	Yes	59	100.00
	No	0	0.00
Treatment with statins (atorvastatin, pravastatin, simvastatin)	Yes	59	100.00
	No	0	0.00
Antibiotic treatment scheme	1: monotherapy	3	5.08
	2: double scheme	23	38.98
	3: triple scheme	1	1.69
	4: none	32	54.24

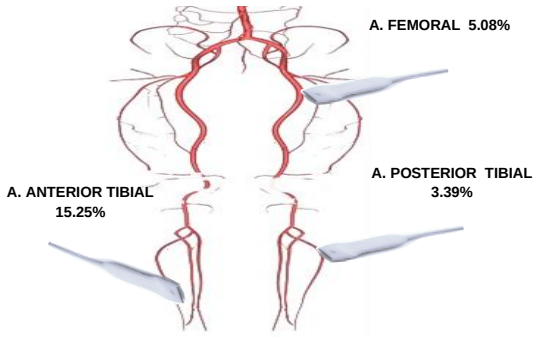


Figure 2: Distribution of arterial lesion localization sites.

Peak systolic velocity

The pooled values of the peak systolic velocity are presented for analysis by arterial sector including each sector's frequency, as detailed in Figure 3. The baseline PSV in the anterior tibial artery had significant differences after one month of treatment (p=0.001) and after 3 months (p=0.001). The baseline PSV in the posterior tibial artery had significant differences compared to the values found at the month of treatment (p=0.001) and 3 months (p=0.001).

Table 3: Distribution of site locations of arterial injuries.

Anatomical location	Freq	%
1: Femoral	3	5.08
2: Anterior tibial	9	15.25
3: Posterior tibial	2	3.39
4: Femoral and anterior tibial	6	10.17
5: Femoral and posterior tibial	7	11.86
6: Anterior and posterior tibial	12	20.34
7: All of them	18	30.51

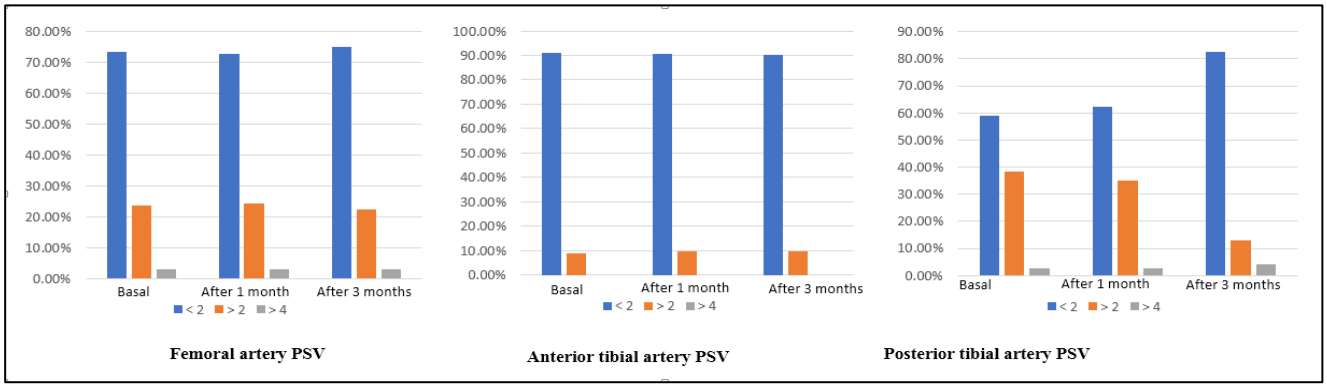
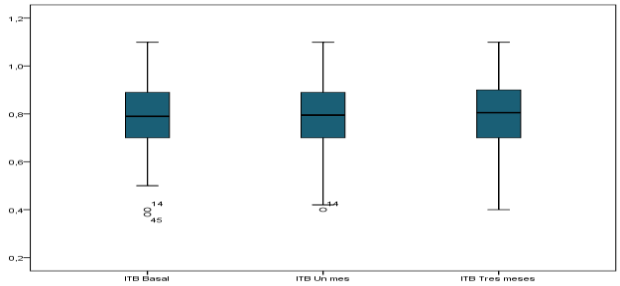


Figure 3: Distribution of the PSV in the femoral artery, anterior tibial and posterior basal artery, after 1-month and 3 months of treatment.

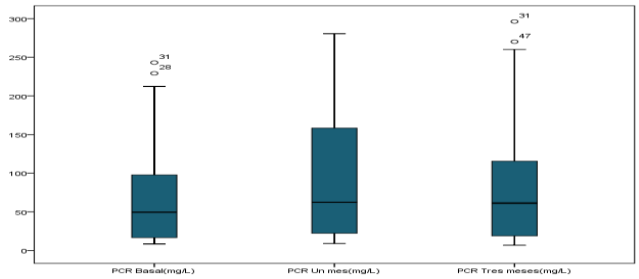
ABI

A baseline median of 0.790 was found, one month after the treatment of 0.795 (p=0.147) and 3 months after 0.800 (p=0.019), with a standard deviation of 0.2201, 0.2269 and 0.2027 respectively. Figure 4 shows the measures of central tendency as well as the maximum and minimum values with 3-month follow-up.



ABI Basal ABI after 1 month ABI after 3 months

Figure 4: Comparison of ABI behavior before and after treatment.



CPR Basal CPR after 1 month CPR after 3 months

Figure 5: Comparison of pre and post-treatment CPR behavior.

C-reactive protein

The mean baseline CRP obtained was 73.142 mg/l, at one month 87.233 mg/l (p=0.001) and at 3 months at 79.009 mg/l (p=0.294) with a standard deviation of 67.18, 74.78 and 69.69 respectively. The maximum and minimum baseline values obtained were 243.1 mg/l/, 8.4 mg/l, 280.5 mg/l/, and 8.9 mg/l at one month and 296.2 mg/l, and 6.8 mg/l at 3 months (Figure 5).

DISCUSSION

Peripheral arterial disease (PAD) secondary to the development of atherosclerosis in the vessels that supply the limbs affects more than 200 million people worldwide.[4] Although manifested primarily in the lower limbs, the underlying disease is systemic arteriosclerosis and, therefore, systemic vascular prevention strategies are essential. Current guidelines recommend antiplatelet therapy, either aspirin alone or with clopidogrel for the reduction of cardiovascular risk in PAD.[18-21] These recommendations in stable disease are derived from subgroup analyzes of large cardiovascular trials, small trials focusing on PAD as well as expert opinion. Despite preventive antiplatelet therapy, patients with PAD maintain an increased risk of both systemic and limb atherosclerotic complications, thus, it has been reported that one in ten of these patients will have a systemic or limb vascular event each year.[22, 23]

The persistently high rate of ischemic events in this risk population emphasizes the need for more effective secondary prevention strategies. The general objective of the present study was to determine in a Mexican sample of patients with PAD from the reference hospital, if the oral combination of 2.5 mg of rivaroxaban every 12 hours plus 100 mg of acetylsalicylic acid every 24 hours presents a therapeutic advantage over other treatments indicated or reported in previous studies.[24] Based on the findings found in this investigation, it is accepted that there is a difference when using the combined oral treatment of rivaroxaban plus acetylsalicylic acid and can be noted in the behavior of risk markers of PAD and evaluated by measuring the ABI and CRP levels; however, when evaluating the PSV, no significant difference was found during the follow-up. These results may correspond to the hypothesis that supports the ATLAS ACS-TIMI 51 and COMPASS studies in relation to the net clinical benefit obtained by

combining an anti-platelet agent plus a specific anticoagulant with a short half-life and a constant pharmacokinetics, at a low dose in population with PAD. Although this study evaluated the levels of the ABI, CRP and PSV, it can be clinically associated with an improvement in claudication as well as a decrease in the progression of PAD to medium and long term with the subsequent prevention of complications such as amputation. In future research, mCRP measurement could be used as a selective marker of endothelial damage with the use of statins+cilostazol.

CONCLUSION

In this population studied, with the treatment of acetylsalicylic acid (100 mg/24 hours) and rivaroxaban (2.5 mg/12 hours) there are significant changes at one month and 3 months of follow-up in the PSV. There are significant changes in the ABI and CRP index at one month and 3 months of follow-up, showing clinical improvement of peripheral arterial disease in the included patients. Due to the nature of this study with a smaller sample size, no inference of clinical behavior can be made in the short, medium and/or long term, so a multicenter, comparative and double-blind study should be performed in patients with arterial disease peripheral which will help reduce the presence of complications such as amputation.

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Conflict of interest: None declared
Ethical approval: The study was approved by the institutional ethics committee

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