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Results of low intensity extracorporeal shock wave therapy in patients with refractory angina

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Abbreviations
CCS: *Canadian Cardiovascular Society*
LVEF: Left ventricular ejection fraction

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ABSTRACT

Introduction: Low intensity extracorporeal shock wave therapy has proven useful in the treatment of patients with refractory angina pectoris.
Objective: To assess the results of this type of therapy in patients with refractory angina to drug treatment.
Method: A quasi-experimental study was carried out in 30 patients with refractory angina pectoris to treatment, selected in a non-probabilistic way, taking into account the following inclusion criteria. All patients were applied low intensity extracorporeal shock wave therapy in the Cardiocentro Ernesto Guevara of Santa Clara, in the period from January to December 2017. Epidemiological, clinical and echocardiographic variables were analyzed at the beginning of the treatment and six months after it was completed.
Results: The results obtained demonstrated an improvement of the functional class (FC) of the Canadian Cardiovascular Society (CCS). Previous to treatment, 76.7% of patients had a FC III and 23.3% a FC IV, and after six months of completed therapy, 73.3% improved to FC II and only 26.7 % remained in FC III. There was also an improvement with respect to echocardiographic parameters such as regional motility and left ventricular ejection fraction, which, in men, of an average at the start of therapy of 37.81% it reached 44.14% at six months of completed; and in women, of an average of 37.11% initially, it reached 47.22 % six months later.
Conclusions: The treatment with shock waves represents a therapeutic alternative for patients with refractory angina.
Keywords: Refractory angina pectoris, Extracorporeal shock wave therapy, Angiogenesis

Resultados de la terapia con ondas de choque extracorpórea de baja intensidad en pacientes con angina refractaria

RESUMEN

Introducción: La terapia con ondas de choque extracorpórea de baja intensidad ha demostrado ser útil en el tratamiento de los pacientes con angina de pecho refractaria.
Objetivo: Valorar los resultados de este tipo de terapia en pacientes con angina refractaria al tratamiento farmacológico.
Método: Se realizó un estudio cuasiexperimental en 30 pacientes con angina de

pecho refractaria a tratamiento, seleccionados de forma no probabilística a partir de los criterios de inclusión. A todos los pacientes se les aplicó terapia con ondas de choque extracorpórea de baja intensidad en el Cardiocentro Ernesto Guevara de Santa Clara, en el período comprendido de enero a diciembre de 2017. Se analizaron variables epidemiológicas, clínicas y ecocardiográficas al inicio del tratamiento y 6 meses después de concluido este.

Resultados: Los resultados obtenidos demostraron una mejoría de la clase funcional (CF) de la Canadian Cardiovascular Society (CCS). Previo al tratamiento el 76,7% de los pacientes tenían una CF III y un 23,3% una CF IV, y a los 6 meses de concluida la terapia el 73,3% mejoró a la CF II y solo un 26,7% quedó en CF III. También se evidenció mejoría con respecto a parámetros ecocardiográficos como la motilidad regional y la fracción de eyección del ventrículo izquierdo, la cual, en los hombres, de una media al inicio de la terapia de un 37,81% alcanzó 44,14% a los 6 meses de concluida; y en las mujeres, de una media de 37,11% inicial llegó a 47,22% a los 6 meses después.

Conclusiones: El tratamiento con ondas de choque constituye una alterativa terapéutica para los pacientes con angina refractaria.

Palabras clave: Angina de pecho refractaria, Ondas de choque extracorpórea, Angiogénesis

INTRODUCTION

Ischemic heart disease is one of the main health problems worldwide, both for its frequency of presentation and for its high mortality and social impact. The angina pectoris is a disease characterized by oppressive chest pain, caused by inadequate oxygen delivery to the myocardium, and it is caused, generally, by coronary artery disease[1-4].

The refractory angina pectoris is a chronic clinical syndrome (> 3 months) characterized by the presence of symptoms of ischemia despite optimal medical treatment in patients in whom traditional percutaneous coronary revascularization is not an option and they have suboptimal indication for coronary artery bypass grafting for several reasons that include: inadequate coronary anatomy, presence of comorbidities (severe left ventricular dysfunction, peripheral arterial disease, chronic renal or pulmonary obstructive disease), or elderly. Patients with previous failed revascularization are also included[3-4].

Some of the alternative treatments for these patients include stellate ganglion block, improved external counterpulsation, coronary artery bypass graft-ing with laser, nervous transcutaneous electrical stimulation, stem cell therapy and cardiac rehabilitation, among others.

Low intensity shock waves represent a therapeutic alternative for this type of patients[5]. They are longitudinal acoustic waves of continuous transmission with frequency between 16 and 20 MHz and a duration of less than 10 microseconds, which generate a pressure pulse and transport energy when propagated through a certain medium. The focus degree can be modulated non-invasively, resulting in a variable concentration of energy at the desired location[6]. When these waves are applied to an organ, they interact with the deep tissues and behave like transient mechanical micro forces that initiate several biological changes. These low intensity shock waves have angiogenic properties and they are used in the treatment of chronic wounds, peripheral neuropathy and ischemic heart tissue[5-7].

The objective of this research was to assess the results of extracorporeal low intensity shockwave therapy in patients with refractory angina.

METHOD

A development research was carried out through a quasi-experimental study, in patients treated with low intensity extracorporeal shock wave therapy at the Cardiocentro Ernesto Guevara of Santa Clara, in the period from January to December 2017.

Study population

The study population was made up of all the patients attended in the refractory angina office located in this hospital (58 patients) and the sample was made up of 30 patients selected in a non-probabilistic manner taking into account the following inclu-

sion criteria:

- Age over 18 years.
- Presence of refractory angina, according to the following criteria:
  a) Angina pectoris class III-IV, according to the Canadian Cardiovascular Society (CCS)[8], for three or more months.
  b) Optimal medical treatment with, at the least, two major antischemic drugs as beta-blockers, calcium antagonists and nitrates, at least six weeks.
  c) That percutaneous or surgical revascularization is not possible due to the severity of the lesions and the inadequate coronary anatomy or with previous failed revascularization.
  d) That the presence of myocardial viability has been documented by perfusion imaging techniques or stress echocardiogram.
- Absence of bio-psycho-social alterations that could interfere with the research.

Exclusion criteria

Patients presenting pericarditis, miocarditis or active endocarditis, severe valvulopathy, interventricular thrombus, advanced chronic obstructive pulmonary disease, and malignant disease in the treatment area; those who do not agree to participate in the research, or the ones having an improper echocardiographic acoustic window which could interfere with the application of shock waves.

Technique

All patients received 9 treatment sessions over a period of 9 weeks which represented 3 treatments per week, on alternate days, in weeks 1, 5 and 9. There were administered 100 shocks directed to each segment in each one of the sessions, with an energy intensity from 0.09 mJ/mm^2 to 14 kv. During the follow-up they were assessed periodically in external consultation until 6 months after the last treatment session.

Variables

Sociodemographic variables (age, sex, skin color, personal pathological history), the history of myocardial revascularization (percutaneous, surgical and both) and pharmacological treatment were evaluated. In addition, the functional class according to the CCS[8] and the New York Heart Association[9], and the echocardiographic variables were taken into account

The left ventricular ejection fraction (LVEF) was calculated by the method of Simpson modified, with differentiation of values according to sex[10], and the consumption of nitrates of intermediate action was grouped according to the recommendations of Tarkin and Kaski[11], in: no consumption, standard dose (15-60 mg/day) and maximum dose (>60 mg/día).

Análisis y procesamiento de la información

The information was stored in a file made in the statistical package SPSS version 20.0 for Windows, in which, in addition, the data was processed according to the proposed objectives. Absolute and relative frequency distributions, expressed in number and percentage for qualitative variables, were carried out; in the case of the quantitative ones, measures of central tendency and dispersion (mean and standard deviation) were used.

In order to analyze the results of the shock wave therapy, non-parametric tests were used for related samples according to the nature of the variables; in the dichotomized qualitative test it was used the McNemar test and in the polytomous, the marginal homogeneity test. For the treatment of quantitative variables, the Wilcoxon range test was used.

For all cases of hypothesis tests, an alpha significance level of 0.05 was prefixed to make the statistical decision. The information resulting from the primary data evaluation and the results of the tests used are shown in statistical tables for better interpretation.

RESULTS

In **table 1** is exposed the clinical characterization of patients. The mean age of the sample was 66.5 ± 9.05, with male predominance 21 (70.0%). A high prevalence of cardiovascular risk factors was observed, with an emphasis on high blood pressure (76.7%), diabetes mellitus (50.0%) and smoking (43.3%). Also it worth to notice that 60% of patients had suffered a previous myocardial infarction.

The presence of coronary artery disease evidenced by a conventional coronary angiography was present in all patients. There was observed that 76.7% suffered from disease of three main arteries and 20% had two-vessel disease (**Table 2**). The 53% was performed percutaneous coronary intervention and 23%, coronary artery bypass grafting. All patients (100%) were treated with nitrates and antiplatelets, and also there were used calcium channel

Table 1. Clinical characterization of the patients studied.

Variables	Nº	%
Age (average ±SD)	66.5 ± 9.05	
Sex		
Female	9	30.0
Male	21	70.0
Skin color		
White	18	60.0
Not white	12	40.0
Personal pathological history		
High blood pressure	23	76.7
Diabetes mellitus	15	50.0
Hyperlipidemia	11	36.7
Hyperuricemia	4	13.3
Previous AMI	18	60.0
Smoking habit	13	43.3
Enolic habit	2	6.7

AMI, acute myocardial infarction; SD, standard deviation.

Table 2. Angiographic data, history of previous revascularization and medical therapy.

Variables	Nº	%
Affected arteries	66.5 ± 9.05	
One-vessel disease	1	3.3
Two-vessel disease	6	20.0
Three-vessel disease	23	76.7
Previous revascularization		
Surgical	7	23.3
Percutaneous	16	53.3
Mixed	5	16.7
Pharmacotherapy		
Nitrates	30	100.0
Beta-blockers	28	93.3
CCB	29	96.9
Statins	21	70.0
ACE	24	80.0
Antiplatelet drugs	30	100.0

ACE, angiotensin-converting enzyme inhibitors; CCB, calcium channel blockers.

blockers (96.9 %), beta-blockers (93.3 %), among others.

In relation to the functional class of angina, according to the CCS, 76.7% were in class III and 23.3% in class IV before treatment, and after six months of completion, no patient had class IV, 73.3% improved to class II and only 26.7% remained in class III (**Table 3**).

The LVEF was one of the most important echocardiographic parameters valued in the evolution of patients and it showed significant improvement for both sexes at six months of completion of therapy (**Tabla 4**): 37.81±8.93 *vs.* 44.14±7.63 in women (p<0.0001) and 37.11±9.08 *vs.* 47.22±8.01 in men (p=0.008).

The left ventricle segmental wall motion was classified according to the values of normokinesia, hypokinesia, akinesia and dyskinesia and one of these values was given to each segment before and after the treatment. The segments anterior (p=0.004), api-

Table 3. Functional class of angina according to the CCS, before and after six months of treatment.

Functional class (CCS)	Pretreatment		Post-treatment	
	Nº	%	Nº	%
Class I	0	0.0	0	0.0
Class II	0	0.0	22	73.3
Class III	23	76.7	8	26.7
Class IV	7	23.3	0	0.0

p<0.0001
CCS, *Canadian Cardiovascular Society*

Table 4. Left ventricular ejection fraction according to sex before and after six months of treatment.

Sex	Pretreatment	Post-treatment	p
	Mean ± SD	Mean ± SD	
Female	37.81 ± 8.93	44.14 ± 7.63	<0.0001
Male	37.11 ± 9.08	47.22 ± 8.01	0.008

cal (p=0.00 8) and lateral (p=0.008) showed a significant improvement (**Table 5**); only the lower ones had no statistical significance (p=0.07).

Another parameter that was taken into account with these patients was the consumption of nitrates, which were used by all patients. In **tabla 6** can be observed that 80.0% of the cases used the maximum dosage of this drug group before initiating therapy, which was reduced to the 53.3% by the end of the research; in addition, patients with standard doses doubled and 6.7% stopped using them because they did not need to.

Table 5. Segmental wall motion at the beginning and after six months of treatment.

Segments	Pretreatment		Post-treatment		p
	Nº	%	Nº	%	
Anterior					
Normokinesia	12	40.0	16	53.3	
Hypokinesia	11	36.7	13	43.3	0.004
Akinesia	5	16.7	1	3.3	
Dyskinesia	2	6.7	0	0.0	
Inferior					
Normokinesia	8	26.7	9	30.0	
Hypokinesia	18	60.0	21	70.0	0.07
Akinesia	4	13.3	0	0.0	
Dyskinesia	0	0.0	0	0.0	
Apical					
Normokinesia	14	46,7	20	66,7	
Hypokinesia	14	46.7	9	30.0	0.008
Akinesia	1	3.3	0	0.0	
Dyskinesia	1	3.3	1	3.3	
Lateral					
Normokinesia	17	56.7	23	76.7	
Hypokinesia	12	40.0	7	23.3	0.008
Akinesia	1	3.3	0	0.0	
Dyskinesia	0	0.0	0	0.0	

DISCUSSION

The shock waves of low intensity are generated by three different methods: electrohydraulic, electromagnetic and piezoelectric. The oldest and most widely used mechanism in medical therapy is the electrohydraulic, where the shock wave is generated by a high voltage trigger in an electrode submerged on liquid. The generated wave is converted into mechanical energy by means of a semi-ellipsoid device with great precision, thus, allowing its therapeutic use[12,13].

The mechanism responsible for angiogenesis begins immediately after the tissue injury, with thrombosis in the vascular endings of the affected region. Next, there is a regeneration of capillaries from remaining functional vessels near the site of the injury. For initiating and regulating the angiogenic process, some mechanical factors are involved (blood pressure, wall tension, increased vascular flow, distended vessels of growing tissues, etc.) and metabolic or chemical (cytosine, monokine, vascular growth factors, among others). Cardiac myocytes respond to mechanical stimuli, activating several intracellular signaling pathways that involve the regulation and maintenance of the myocardial function. These stimuli are activated by mechanoreceptors, including the stretch-activated ion channels, G protein-coupled receptors and growth factor receptors and integrins[5,14].

The complex cascade promotes

Table 6. Long-acting nitrates consumption before and after treatment.

Nitrates	Pretratamiento		Postratamiento	
	Nº	%	Nº	%
Maximum dose	24	80.0	16	53.3
Standard dose	6	20.0	12	40.0
Non use	0	0.0	2	6.7

p=0.041

signaling activation of nuclear transcription factors and expression of mechanosensitive genes, followed by synthesis and release of autocrine and paracrine factors besides regulating the proliferation, migration, differentiation, hypertrophy and apoptosis mechanisms[14,15].

Despite that the precise mechanisms by which the shock wave therapy acts in relieving angina have not yet been fully described, the main effects can be related to vasodilatation, responsible for the immediate effects, and induction of neovascularization of treated tissue, which probably contributes to long-term effects[15]. In this way, the direct mechanical effects, accompanied by tissue injury, are capable of leading to increased tissue blood flow and to activate repairing mechanisms[16].

The distribution of patients with refractory angina in our research is similar to other studies[17,18], where males and patients over 65 years predominated, and a high percentage of diabetes mellitus and high blood pressure was found.

The pharmacotherapy and the coronary angiography are aspects of interest in the evaluation of patients with refractory angina. Our results agree with several authors like Silveira Duque[19], Prasad et *al*[20] and Kikuchi *et al*[21], who found that the three-vessel disease and pharmacotherapy with beta-blockers, nitrates and antiplatelets predominated in patients under study. These researchers[19-21], together with Vainer *et al*[22] and Faber *et al*[23], showed a significant improvement in the quality of life (Seattle Angina Questionnaire) in 83% of cases and of the angina rate of the CCS in approximately 74% of the patients to whom the shock wave therapy was applied. In addition, these patients improved their functional class according to the CCS, then, similar to the results of our research.

On the other hand, Wang *et al*[24], in a meta-analysis published in 2015, showed that the shock wave therapy is associated with an improvement of approximately 6.7% in the LVEF, and Zuozienė *et al*[18] assessed the response of the ventricular function by magnetic resonance imaging, and they identified an improvement of approximately 8% of the LVEF. These results match those found in our patients, but differ from Silveira Duque[19] who did not show an increased significance of the LVEF in patients at six months of treatment.

Wang *et al*[25], through evaluation by Doppler tissue, found an improvement in the ventricular dyssynchrony in 57.5% of patients receiving shock wave therapy (p=0.008), and Alunni *et al*[26] reduced, with the same therapy, the number of akinetic segments from 11.5 to 6.0% (p=0.03). These results agree with our research, but differ from those found in the study of Silveira Duque[19] where the segmental wall motion was analyzed through the echocardiographic method of myocardial deformity (longitudinal strain and speckle tracking) and they found no significant improvement (p=0.178). The possible explanation of whether or not there is an improvement in the LVEF and segmental wall motion in these patients could be related to the fact that many of these segments are in myocardial hibernation that, when improving the state of perfusion with the formation of microvessels, could leave that state partially or totally; although the wall motion may never be recovered in a certain ischemic area.

Moreover, Zuozienė *et al*[18], in a study conducted with 20 patients, reduced significantly the use of nitroglycerin and long-acting nitrates, as did Alunni *et al*[26] (p=0.001), who also reduced the number of hospitalizations of their patients. These results coincide with those found in our research. Probably, the symptomatic improvement and decreased consumption of nitrates are linked to the best myocardial perfusion resulting from the shock wave therapy.

CONCLUSIONS

Men in the seventh decade of life, the presence of high blood pressure and three-vessel coronary artery disease predominated. The improvement in the ventricular function and the segmental wall motion of left ventricle's walls was demonstrated. The angina symptoms and the consumption of long-acting nitrates were reduced. The treatment with low intensity extracorporeal shock waves represents a therapeutic alternative for patients with refractory angina.

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