Incidence of Ventricular Arrhythmias after Stem Cell Therapy in Patients with Chagas Cardiomyopathy

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Abstract

Background: **Treatment with stem cells in several cardiomyopathies may be related to the increase in arrhythmias.**

Objectives: **To determine whether intracoronary injection of stem cells in patients with Chagas cardiomyopathy is associated with increased incidence of ventricular arrhythmias, compared to the Control Group.**

Methods: **A retrospective cohort study that evaluated the medical records of 60 patients who participated in a previous cross-sectional study. The following data were collected: age, gender, drugs used and Holter variables that demonstrated the presence of arrhythmias. Holter was performed in four stages: randomization, 2, 6 and 12 months segments. The Control Group received medical treatment and intracoronary injection of placebo and the Study Group had drug treatment and autologous stem cell implant.**

Results: **There was no difference between Control Group and Study Group when analyzing the arrhythmia criteria. In the intra-group analysis, significant difference was found between the Holter tests of the Study Group for the variable total ventricular premature beats when compared with baseline, with p = 0.014 between Holter at randomization and Holter at 2 months, p = 0.004 between Holter at randomization and Holter at 6 months, and p = 0.014 between Holter at randomization and Holter at 12 months. The variable non-sustained ventricular tachycardia between Holter at randomization and Holter at 6 months showed p = 0.036.**

Conclusion: **The intracoronary injection of stem cells did not increase the incidence of ventricular arrhythmias in patients with Chagas cardiomyopathy compared to the Control Group. (Arq Bras Cardiol. 2014; 102(5):489-494)**

Keywords: **Arrhythmias, Cardiac; Stem Cell Transplantation; Chagas Cardiomyopathy.**

Introduction

In the past decades, heart failure (HF) has emerged as a public health problem. Kannel, based on epidemiological studies obtained in the Framingham Heart Study, estimated that in the United States, there are 5 million HF patients, with approximately 400,000 new cases per year. The problem is presumed to be of the same magnitude in Brazil[1].

According to data from the World Health Organization (WHO), although vectorial transmission has been interrupted in countries such as Brazil, Chile and Uruguay, the prevalence of patients with chronic chagasic cardiopathy was estimated between 18 and 20 million people in Latin America, with 300,000 new cases each year, and 50,000 annual deaths associated with the disease[2].

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Despite the widely positive impact with new drugs for the treatment of HF, the disease progresses and patient prognosis remains reserved, with reduced quality of life and survival. Thus, there is an enormous interest and need to seek new therapies that may offer beneficial effects in the evolution of these patients[3].

Of the new therapeutic procedures, the most promising seems to be stem cell therapy.

In Brazil, preliminary studies including a limited number of patients have shown that the use of stem cells from bone marrow is safe and potentially effective in patients with HF[4,5].

Stem cells have an intrinsic potential for arrhythmia, mainly related to their common lack of electromechanical integration in the recipient myocardium; it is also important to recognize that patients eligible for cell replacement therapy are likely to develop arrhythmias due to underlying heart disease[6].

The study by Satsuki Fukushima provided experimental evidence that direct intramyocardial injection of stem cells from bone marrow can induce severe ventricular arrhythmias in the first 14 days after the injection in chronic HF models[7].

The aim of this study was to compare the frequency of ventricular arrhythmia in a group of patients who received intracoronary injection of stem cells with a control group.

Methods

This study was approved by the Ethics and Research Committee of Hospital das Clinicas of Universidade Federal de Goiás, protocol number 179/2011.

This is a retrospective analysis of a cohort of patients enrolled in a prospective, double-blind, randomized clinical trial, included in the Multicenter Randomized Study of Cell Therapy in Cardiopathies (EMRTCC) - chagasic cardiopathy arm, carried out at the Heart Failure Service of Hospital das Clinicas of Universidade Federal de Goiás.

The sample consisted of 60 patients included in the abovementioned protocol from April 2006 to November 2009, followed for at least 1 year after randomization. This was a convenience sample. Inclusion criteria were: having been included in the study and undergone Holter monitoring during the follow-up period. Patients were divided into two groups in a double-blind fashion: the control group (CG) received appropriate medical treatment and optimized for HF and intracoronary injection of placebo; the Study Group (SG) received, in addition to adequate drug treatment, autologous stem cell transplant obtained from bone marrow aspirate.

A total of 34 patients were randomly assigned to the SG and 26 to the CG. Data collection was performed from January to July 2012 from medical records. This randomization was carried out by the EMRTCC national study, which explains the fact that the groups ended up with different samples at the Heart Failure Service, Hospital das Clinicas, Universidade Federal de Goiás.

Data regarding age (in years), gender (male or female); death (yes or no), medications used (renin-angiotensin system blocker, digitalis, angiotensin-converting enzyme inhibitors, spironolactone, diuretics, amiodarone, beta-blockers), and the number and viability of stem cells used for transplant were collected.

The presence of arrhythmia was assessed from Holter results. Holter monitoring was performed at randomization (baseline - Holter 1) and after 2 (Holter 2), 6 (Holter 3) and 12 (Holter 4) months of follow-up.

The criteria assessed by Holter were total number of beats, ventricular premature beats, supraventricular premature beats, total episodes of Nonsustained Ventricular Tachycardia (NSVT), and Sustained Ventricular Tachycardia (SVT). The presence of three or more consecutive ventricular premature beats in a 30-second interval with heart rate above one hundred beats per minute was considered NSVT, while SVT was considered in the presence of ventricular premature beats for a period greater than 30 seconds or causing hemodynamic instability at any time interval with heart rate above one hundred beats per minute. For this study, ventricular arrhythmia was considered as an increase in the total incidence of NSVT and SVT episodes.

Statistical Analysis

Data were entered in Excel for Windows software spreadsheets and analyzed using the Statistical Package for Social Sciences (SPSS), releases 17.0 and 19.0.

Age was shown as mean and standard deviation and gender as absolute and relative frequency.

Fisher's test was used to compare the frequency of medication use between the SG and the CG.

After applying the Kolmogorov-Smirnov test for quantitative variables obtained at Holter, Student's *t* test was performed for normally distributed variables and the Mann Whitney's test for those with non-normal distribution. These tests were used to compare the groups.

To compare the Holter variables at different intragroup moments, the Student's *t* test or Wilcoxon test was used for choosing data distribution. Wilcoxon's test was used to compare the percentages of the findings in relation to the total number of beats of the variables: salvos of NSVT and total SVT episodes, in relation to Holter at different intragroup moments, to verify whether there was a significant difference between the Holter results.

A 95% level of confidence was established for all analyses, i.e., $p < 0.05$ was considered significant.

Results

Patients included in the study had a mean age of 50.7 ± 9.6 years; 70% (42) were males and 30% (18) females. There were ten deaths in the SG and nine in the CG during the 12-month follow-up.

Stem cell viability was 98% in both groups. The amount of cells in the CG was on average 2.75×10^8 and in the SG, 2.62×10^8. There was no significant difference between the groups.

Holter data are shown in Table 1, with no difference between groups regarding the variables that demonstrated the presence of arrhythmia on Holter examinations at any time (randomization, 2 months, 6 months and 12 months of follow-up).

When comparing Holter 1 (randomization) to the others, in the SG, there was a significant difference between total ventricular premature beats in all comparisons, differences in total number of beats and NSVT between Holter monitoring tests 1 and 3 (Table 2). The same analysis was performed in the CG (Table 3), which showed no statistical significance.

A statistical evaluation of the SG was carried out with the variables NSVT and SVT, percentage-wise, in relation to the total number of beats at Holter monitoring, which showed no significance in the intragroup analysis (Table 4). This evaluation was performed due to the observation that the total number of beats, as well as the NSVT, increased at Holter monitoring in the follow-up.

There was no statistical difference in terms of medications for the treatment of HF used by the patients in both groups, at the time of randomization (Table 5).

Discussion

The present study found no increase in numbers of isolated ventricular premature beats compared with the CG, in agreement with studies by Vilas Boas et al[4,8]. The studies by Vilas Boas et al[4,8] had a patient profile similar to ours. We studied 28 chagasic patients in functional class III and IV

Table 1 – Variables obtained by Holter performed at randomization (Holter 1), 2 months (Holter 2), 6 months (Holter 3) and 12 months (Holter 4) of study follow-up, n = 60, Goiânia, Goiás, 2010

Variable	Study Group	Control Group	p value
Holter 1	(n = 34)	(n = 26)	
Total number of beats	81,209.33 ± 17,417.57	86,343.54 ± 17,474.21	0.189
Total ventricular premature beats	2,685.18 ± 3,052.48	2,640.06 ± 3,412.12	0.435
Total supraventricular premature beats	926.77 ± 3,659.93	2.330.33 ± 9,875.09	0.514
NSVT	5.15 ± 12.02	3.79 ± 5.68	0.744
Total SVT episodes	0.00 ± 0.0	0.0 ± 0.0	-
Holter 2	(n = 32)	(n = 26)	
Total number of beats	89,474.62 ± 10,906.01	88,457.09 ± 20,175.04	0.994
Total ventricular premature beats	3,764.00 ± 5,313.65	3,611.22 ± 4,549.22	0.478
Total supraventricular premature beats	1.363.07 ± 4,609.85	457.41 ± 1,703.04	0.994
NSVT	29.92 ± 135.33	14.77 ± 33.31	0.456
Total SVT episodes	0.0 ± 0.0	0.0 ± 0.0	-
Holter 3	(n = 28)	(n = 21)	
Total number of beats	92,394.25 ± 11,519.21	94,715.06 ± 19,856.30	0.836
Total ventricular premature beats	4,817.48 ± 6,152.71	5,072.41 ± 7,508.33	0.379
Total supraventricular premature beats	1,893.07 ± 5,341.60	2,580.45 ± 9,623.00	0.809
NSVT	30.11 ± 135.37	24.12 ± 56.53	0.956
Total SVT episodes	2.11 ± 10.96	0.0 ± 0.0	0.277
Holter 4	(n = 26)	(n = 16)	
Total number of beats	96,965.00 ± 10,386.72	91,487.25 ± 16,403.77	0.255
Total ventricular premature beats	9,713.17 ± 1,8607.40	4,234.29 ± 4,010.05	0.459
Total supraventricular premature beats	1,480.58 ± 2,957.37	2,477.79 ± 8,422.73	0.862
NSVT	19.17 ± 36.47	2.25 ± 4.59	0.117
Total SVT episodes	0.12 ± 0.61	0.0 ± 0.0	0.400

Mann-Whitney test; p < 0.05. NSVT: nonsustained ventricular tachycardia; SVT: sustained ventricular tachycardia.

Table 2 – Comparison between Holter tests performed in the Study Group during the 12-month follow-up, n = 60, Goiânia, Goiás, 2010

Variable	Total number of beats*	Total number of ventricular premature beats**	Salvos of NSVT**	Total episodes of SVT**
Holter 1 vs. Holter 2	0.524	0.014***	0.070	1.000
Holter 1 vs. Holter 3	0.024***	0.004***	0.036***	0.317
Holter 1 vs. Holter 4	0.083	0.014***	0.375	0.102

** Student test was used; ** in total heartbeats and Wilcoxon test; p < 0.05. ***: in total ventricular extrasystoles NSVT and SVT episodes and was found significance p < 0,05 for both items. Holter 1: performed at randomization; Holter 2: performed at 2 months of follow-up; Holter 3: performed at 6 months of follow-up; Holter 4: performed at 12 months of follow-up. NSVT: nonsustained ventricular tachycardia; SVT: sustained ventricular tachycardia.*

Table 3 – Comparison between Holter tests performed in the Control Group during the 12-month follow-up, n = 60, Goiânia, Goiás, 2010

Variable	Total number of beats*	Total number of ventricular premature beats**	Salvos of NSVT**	Total episodes of SVT**
Holter 1 vs. Holter 2	0.026***	0.239	0.984	1.000
Holter 1 vs. Holter 3	0.014***	0.161	0.975	0.317
Holter 1 vs. Holter 4	0.015***	0.128	0.061	1.000

** Student test was used; ** in total heartbeats and Wilcoxon test; p < 0.05. ***: in total ventricular extrasystoles NSVT and SVT episodes and was found significance p < 0,05 for both items. Holter 1: performed at randomization; Holter 2: performed at 2 months of follow-up; Holter 3: performed at 6 months of follow-up; Holter 4: performed at 12 months of follow-up. NSVT: nonsustained ventricular tachycardia; SVT: sustained ventricular tachycardia.*

Table 4 – Comparison test of the variables: nonsustained ventricular tachycardia (NSVT) and sustained ventricular tachycardia (SVT) as percentages in Holter examinations at 2 months, 6 months and 12 months of follow-up, n = 60, Goiânia, Goiás, 2010

Comparison	Control group		Study group	
	Salvos of NSVT (p)	Total episodes of SVT (p)	Salvos of NSVT (p)	Total episodes of SVT (p)
Holter 1 vs. Holter 2	0.904	1.000	0.286	1.000
Holter 1 vs. Holter 3	0.796	0.317	0.198	1.000
Holter 1 vs. Holter 4	0.753	1.000	0.381	0.317

Wilcoxon Test; p < 0.05. Holter 1: performed at randomization; Holter 2: performed at 2 months of follow-up; Holter 3: performed at 6 months of follow-up; Holter 4: performed at 12 months of follow-up. NSVT: nonsustained ventricular tachycardia; SVT: sustained ventricular tachycardia.

Table 5 – Analysis of medications taken by patients at the time of randomization, n = 60, Goiânia, Goiás, 2010

Variable	Study Group (n = 34) n (%)	Control Group (n = 26) n (%)	p value
ARB	7 (25.9)	10 (30.3)	0.212
Digitalis	14 (51.9)	14 (42.4)	0.158
ACEI	8 (29.6)	10 (30.3)	0.222
Spironolactone	19 (70.4)	21 (63.6)	0.188
Diuretics	19 (70.4)	25 (75.8)	0.206
Amiodarone	10 (37.0)	11 (33.3)	0.204
Beta-blockers	2 (7.4)	12 (36.4)	0.171

Source: patients' files. Fisher's test. ARB: angiotensin-II receptor blocker; ACEI: angiotensin-converting enzyme inhibitor.

of the New York Heart Association (NYHA). Vilas Boas et al[4,8], similarly to this study, evaluated patients with advanced-stage cardiomyopathy and demonstrated the safety regarding the genesis of arrhythmias in this group of patients.

In the SG, which received the stem cell therapy, it is possible to observe an increase in the density of ventricular premature beats, when comparing the baseline Holter monitoring with those subsequently performed after 2, 6 and 12 months of follow-up, with a statistically significant difference. Thus, it is possible to consider that there was an increase in the incidence of ventricular premature beats when compared with the group baseline assessment. In disagreement with the HEBE study[9] carried out in Holland, which evaluated 200 ischemic patients who received cell therapy and stem cell infusion within 12 hours of the ischemic event, with excellent safety profile, the present study showed no severe arrhythmia events.

When we analyzing the presence of NSVT, compared with baseline of the SG itself, a difference was observed between Holter 1 and Holter 3, with statistical significance. This fact is in disagreement with the randomized multicenter STAR-HEART study[10], which analyzed 191 patients with ischemic cardiomyopathy, of which follow-up showed improvement of arrhythmia in those treated with stem cells.

At the analysis of NSVT and SVT data, percentage-wise when compared to the total number of beats, it became clear that this increase was proportional and without statistical significance, exactly as in the multicenter studies BOOST[11] and TOPCARE-AMI[12], which evaluated patients with ischemic cardiomyopathy and found no increase in the number of ventricular arrhythmia events.

Stem cell therapy has been used in several different diseases, showing a good safety profile[13].

Conclusion

Chronic heart failure is a progressive disease, in spite of intensive pharmacological treatment, and remains a severe health problem worldwide. Therefore, in addition to conventional therapy, treatment regimens are needed that can improve quality of life and increase ventricular performance and survival.

Treatment with bone marrow cells does not cure Chagas disease, but attempts to repair the damage that results from years or even decades of aggression to the myocardium.

Our data suggest that patients with heart failure due to Chagas disease and class III and IV heart failure submitted to transplantation of stem cells from bone marrow to the myocardium, showed no increase in the incidence of sustained ventricular tachycardia, but showed increase in nonsustained ventricular tachycardia between Holter at randomization and Holter at 6 months in the Study Group, as well as increased VPB density in the Study group. At the percentage analysis, there was no significant increase of nonsustained ventricular tachycardia, or sustained ventricular tachycardia.

Author contributions

Acquisition of data:Costa SA, Freitas EMM, Carvalho G; Analysis and interpretation of the data: Souza ASB, Sá LAB; Statistical analysis: Souza ASB; Writing of the manuscript: Souza ASB; Critical revision of the manuscript for intellectual content: Souza WKSB, Souza ASB, Rassi S.

Potential Conflict of Interest

No potential conflict of interest relevant to this article was reported.

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Study Association

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References

1. Kannel WB. Incidence and epidemiology of heart failure. Heart Fail Rev. 2000;5(2):167-73.
2. Engels D, Savioli L. Reconsidering the underestimated burden caused by neglected tropical diseases. Trends Parasitol. 2006;22(8):363-6.
3. Almeida DR. Avanços no tratamento clínico da insuficiência cardíaca. In: Barreto AC, Bocchi EA. Insuficiência cardíaca, Local: Segmento, 2003. p. 251-67.
4. Vilas-Boas F, Feitosa GS, Soares MB, Pinho-Filho JA, Mota AC, Almeida AJ, et al. Bone marrow cell transplantation in chagas' disease heart failure: report of the first human experience. Arq Bras Cardiol. 2011; 96(4):325-31.
5. Bocchi EA, Bacal F, Guimarães G, Mendroni A, Mocelin A, Filho AE, et al. Granulocyte-colony stimulating factor or granulocyte-colony stimulating factor associated to stem cell intracoronary infusion effects in non ischemic refractory heart failure. Int J Cardiol. 2010;138(1):94-7.
6. Menasché P. Stem cell therapy for heart failure: are arrhythmias a real safety concern? Circulation. 2009;119(20):2735-2740.
7. Fukushima S, Varela-Carver A, Coppen SR, Yamahara K, Felkin LE, Lee J, et al. Direct intramyocardial but not intracoronary injection of bone marrow cells induces ventricular arrhythmias in a rat chronic ischemic heart failure model. Circulation. 2007;115(17):2254-61.
8. Vilas-Boas F, Feitosa GS, Soares MB, Mota A, Pinho-Filho JA, Almeida AJ, et al. Early results of bone marrow cell transplantation to the myocardium of patients with heart failure due to Chagas disease. Arq Bras Cardiol. 2006;87(2):159-66.
9. Hirsch A, Nijveldt R, van der Vleuten PA, Tijssen JG, van der Giessen WJ, Tio RA, et al; HEBE Investigators. Intracoronary infusion of mononuclear cells from bone marrow or peripheral blood compared with standard therapy in patients after acute myocardial infarction treated by primary percutaneous coronary intervention: results of the randomized controlled HEBE Trial. Eur Heart J. 2011;32(14):1736-47.
10. Strauer BE, Yousef M, Schannwell CM. The acute and long-term effects of intracoronary Stem cell Transplantation in 191 patients with chronic heARt failure: the STAR-HEART study. Eur J Heart Fail. 2010;12(7):721-9.
11. Meyer GP, Wollert KC, Lotz J, Pirr J, Rager U, Lippolt P, et al. Intracoronary bone marrow cell transfer after myocardial infarction: 5-year follow-up from the randomized-controlled BOOST Trial. Eur Heart J. 2009;30(24):2978-984.
12. Britten MB, Abolmaali ND, Assmus B, Lehmann R, Honold J, Schmitt J, et al. Infarct remodeling after intracoronary progenitor cell treatment in patients with acute myocardial infarction (TOPCARE-AMI): mechanistic insights from serial contrast-enhanced magnetic resonance imaging. Circulation. 2003;108(18):2212-8.
13. Martin-Rendon E, Brunskill SJ, Hyde CJ, Stanworth SJ, Mathur A, Watt SM. Autologous bone marrow stem cells to treat acute myocardial infarction: a systematic review. Eur Heart J. 2008;29(15):1807-18.