Late Outcome of a Randomized Study on Oral Magnesium for Premature Complexes

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Abstract

Background: Ventricular and supraventricular premature complexes (PC) are frequent and usually symptomatic. According to a previous study, magnesium pidolate (MgP) administration to symptomatic patients can improve the PC density and symptoms.

Objective: To assess the late follow-up of that clinical intervention in patients treated with MgP or placebo.

Methods: In the first phase of the study, 90 symptomatic and consecutive patients with PC were randomized (double-blind) to receive either MgP or placebo for 30 days. Monthly follow-up visits were conducted for 15 months to assess symptoms and control electrolytes. 24-hour Holter was performed twice, regardless of symptoms, or whenever symptoms were present. In the second phase of the study, relapsing patients, who had received MgP or placebo (crossing-over) in the first phase, were treated with MgP according to the same protocol.

Results: Of the 45 patients initially treated with MgP, 17 (37.8%) relapsed during the 15-month follow-up, and the relapse time varied. Relapsing patients treated again had a statistically significant reduction in the PC density of 138.25/hour ($p < 0.001$). The crossing-over patients reduced it by 247/hour ($p < 0.001$). Patients who did not relapse, had a low PC frequency (3 PC/hour). Retreated patients had a 76.5% improvement in symptom, and crossing-over patients, 71.4%.

Conclusion: Some patients on MgP had relapse of symptoms and PC, indicating that MgP is neither a definitive nor a curative treatment for late follow-up. However, improvement in the PC frequency and symptoms was observed in the second phase of treatment, similar to the response in the first phase of treatment. (Arq Bras Cardiol. 2014; 103(6):468-475)

Keywords: Ventricular Premature Complexes; Arrhythmias, Cardiac; Magnesium.

Introduction

The incidence of premature ventricular complexe (PVC) and premature supraventricular complexe (PsVC) increases with age, their prevalence being estimated at as much as 50% of the general population[1-5]. The long-term prognosis is benign, but, when symptomatic, such premature complexe (PC) can be uncomfortable or even disabling. Several pharmacological and non-pharmacological measures for their clinical control have been suggested. However, under certain conditions, the results are limited or the risk-benefit relationship is arguable.

Magnesium (Mg) is an alkaline earth metal that participates in several metabolic processes, such as reactions in ATP generation. It is the second intracellular cation and the fourth cation of the human body[6-9]. That metal plays a significant role in maintaining proper cardiac rhythm, because of its action on the Na/K- ATPase pump[6,7] and its interaction with calcium[10]. Approximately half of the body Mg is within soft tissue cells, while the other half is within bone tissue[8,11]. Less than 1% of Mg is found in the blood, and approximately 0.3%, in the serum[12,13]. Thus, total body Mg has a weak correlation with its serum levels, which can be normal in the presence of low intracellular values[14,15].

The Mg intake has decreased in the past century[8], probably due to the increased consumption of processed foods[8,14,16], which can be a risk factor for Mg deficiency. That deficiency can be associated with cardiovascular disease, such as cardiac arrhythmias[8]. In selected patients, based on a simple treatment strategy, antiarrhythmics drugs, which can be harmful or poorly tolerated under certain circumstances, can be avoided. Recently, we have shown that Mg pidolate (MgP), after a 30-day continuous supplementation, can decrease ectopic beats and improve related symptoms[17]. Based on those initial findings, we assessed the outcome of this cohort of patients in the late follow-up.

This study was aimed at: 1) assessing the late clinical outcome of patients initially treated with placebo and/or MgP; 2) assessing whether patients with arrhythmia relapse in a 15-month follow-up, when treated for the second

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time, have the same response of the first treatment; and 3) assessing the response of patients to MgP after initially receiving placebo.

Methods

This study's methodology has been previously described when assessing the 30-day results[17]. In the first state of the treatment, ninety consecutive symptomatic patients were randomized (double-blind) to receive either 3.0 g/day of MgP, the equivalent of 260 mg of the Mg element, or placebo, for 30 days. All patients underwent transthoracic echocardiography, and had normal kidney function (Cockcroft-Gault formula) and structurally normal heart[18].

The serum levels of Mg, sodium, calcium and potassium were measured before and on the 15th and 30th day after randomization. The follow-up visits were monthly conducted to assess symptoms by using a specific questionnaire. As previously described[17], the questionnaire was elaborated with the following questions: 1- failures or "leaps", like a 'somersault' in the chest; 2- cough with palpitations; 3- dizziness; 4- dyspnea; 5- sweating and/or chest pain. According to the frequency of symptoms, points were attributed, which resulted in a score, and a two-point drop was considered a criterion of improvement. In addition, a categorical classification was conducted by asking the patients whether the symptoms improved, the answers being merely "yes" or "no" (Figure 1). In the long-term follow-up, all patients underwent 24-hour Holter monitoring twice, independently of symptoms, to assess the PC frequency. In addition, Holter monitoring (3 channels) was performed whenever symptoms appeared (before and 30 days of use of MgP).

In the second phase of the study, the patients with symptom relapse, of both the treatment and placebo groups ("crossing over"), received MgP for 30 more days, according to the same protocol.

Statistical analysis

The densities of PC in both phases of treatment (pre- and post-intervention) were measured by using mean, standard deviation, median, minimum and maximum values[19].

The PC densities were compared between times of treatment and between treatments by using repeated-measures two-way analysis of variance (ANOVA)[20]. A correlation matrix of symmetrical components was calculated between asssessments[20]. Multiple comparisons by using Bonferroni adjustment[21] were performed between the treatment times, and contrast was created to assess whether the improvement in the first treatment (pre-post 1st treatment) differed from that in the second treatment (pre-post 2nd treatment).

The improvement in symptoms was described at each treatment phase in both groups of patients, and McNemar tests[19] were performed to assess whether there was difference in the improvement percentages in each treatment. The results were illustrated by using graphs of mean profiles with the respective standard errors. The 5% significance level was adopted for all tests. The SPSS software, version 20.0, was used for statistical analysis.

Results

The 90 patients participating in the first phase of treatment were followed up for 15 months. Table 1 shows the outcome of the first intervention. Of the 45 patients initially randomized to receive MgP, 41 (91.1%) were asymptomatic after the first month assessment, and four relapsed. In subsequent months, more 13 patients relapsed, adding to a total of 17 relapses (37.8%). All patients were treated again. The relapse time varied during the 15-month follow-up, and no statistically significant relapse concentration in a certain time was observed.

Frequency of premature complexes

The relapsing patients (17 in the MgP group) who were retreated had a mean reduction in the PC density of 138.25/hour in both treatments ($p < 0.001$). No mean difference was observed in the PC density improvement between the successful initial treatment and that after relapse ($p = 0.159$), that is, patients using MgP repeated the response of the first treatment: significant improvement in symptoms and in PC (Table 2 and Figure 2).

The median value of PVC/day after the first treatment was 3, and was 1872 on Holter monitoring after relapse. After the new intervention, this frequency decreased to 280 ($p < 0.001$). Regarding PsVC, the median after the first treatment was 14 PsVC/day, 15 on Holter monitoring after relapse, increasing

Quiz	Symptom Points
Failures or "leaps" in the chest	
Couch with palpitation	
Dizziness	
Dyspnea	
Sudoresis and/or chest pain	
Total	

Points
A – Absent (never) - 0 point
B – Infrequent (once to 5 times/day) - 1 point
C – Frequent (6 to 20 times/day) - 2 points
D – Very Frequent (≥ 21 times/day) - 3 points
"Quality of Life" Score
Symptom Classification
I – Asymptomatic - 0 point
II – Mid Symptomatic - 01 a 05 points
III – Moderate Symptomatic - 06 a 11 points
IV – Severe Symptomatic - more than 12 points

Figure 1 – *This figure shows the score system to assess improvement of symptoms before and after the drugs in both groups (placebo and magnesium pidolate).*

Table 1 – Outcome of the first intervention with Magnesium pidolate (MgP) *versus* placebo (shown as median)

Variable	Group	1st treatment (N = 90)		Improvement (%)	p
		pre	post 30 days		
PVC/day					< 0.001
	Placebo (N = 45)	2634 (194 - 24534)	4211 (42 - 22526)	1 (-831.7 - 78.4)	
	MgP (N = 45)	1883 (2 - 38804)	165 (0 - 6677)	96 (-1250 - 100)	
PsVC/day					< 0.001
	Placebo (N = 45)	176 (0 - 15965)	785 (1 - 19861)	-5 (-2840 - 75)	
	MgP (N = 45)	84 (0 - 20019)	51 (0 - 15548)	62 (-3025 - 100)	
PC-Density/hour					< 0.001
	Placebo (N = 45)	158 (12.1 - 1022.3)	199 (24.8 - 938.6)	-3 (-794.7 - 19.1)	
	MgP (N = 45)	121 (21.1 - 1616)	12 (0 - 647.8)	87 (-7.7 - 100)	

Mann-Whitney test results, PC: premature complexe; PVC: premature ventricular complexes; PsVC: premature supraventricular complexes.

Table 2 – Results of the multiple comparisons of extrasystole density of the groups of treatment

Group	Comparison	Mean difference	Standard error	t value	gl	p
Crossing	Placebo pre vs post	-22.46	37.74	-0.59	20	> 0.999
	MgP pre vs post	224.55	37.74	5.95	20	< 0.001
	Placebo vs MgP pre	-0.01	37.74	0.00	20	> 0.999
	Placebo vs MgP post	246.99	37.74	6.54	20	< 0.001
	(pre-post) Placebo vs MgP	247.00	53.38	4.63	60	< 0.001
Relapse	Pre vs Post	138.25	24.11	5.73	16	< 0.001
	(pre-post) 1st Treat vs 2nd Treat	-66.86	46.72	-1.43	48	0.159

vs: versus; result of Bonferroni multiple comparisons.

to 38 after treatment ($p < 0.102$) (Table 3). The density of PC/hour after the first treatment was 10.3, increasing to 126.1 on relapse, and decreasing to 50.2 after the new treatment ($p < 0.001$) (Tables 3 and 4).

Only three patients relapsed twice, being retreated, and two of them responded similarly, with improvement in symptoms and in PC frequency. Only one patient relapsed three times, and had a good response after the retreatments. The patients who did not relapse had a low PC frequency on Holter monitoring, with a median of 3 PC/hour (Table 3).

Of the 45 patients treated with placebo in the first phase, 6 (13.3%) improved their symptoms and 39 (86.7%) remained symptomatic. Of those 39, 21 agreed to receive MgP and were selected for crossing-over. Patients who did not agree to receive MgP were excluded from the analysis. The crossing-over patients had a statistically significant mean reduction in the PC density when using MgP ($p < 0.001$), while, when on placebo, no change in density was observed ($p > 0.999$). The mean improvement in PC density was 247/hour, greater in the treatment with MgP than in the first treatment with placebo ($p < 0.001$) (Table 2 and Figure 3).

The median of PVC decreased from 2508/day to 689/day ($p < 0.001$), and that of PsVC, from 4/day to 1/day ($p < 0.015$) (Table 3). The density of PC/hour was 264.8 in the pre-treatment phase, dropping to 48 after the use of MgP (crossing-over) (Tables 3 and 4).

On Holter monitoring, PVC were more frequent, originating mainly (71%) from the outflow tract of the ventricles.

Symptoms

In relapsing patients, the improvement in symptoms of both treatments was statistically the same ($p = 0.125$) (Table 5). All 17 relapsing patients improved their symptoms in the first treatment, while 76.5% improved their symptoms in the relapse treatment. Similar response was obtained in the score of symptoms and in the categorical response of symptom improvement ('yes' or 'no').

The patients using placebo in the initial treatment and MgP in the second one (crossing-over) had a statistically greater improvement in symptoms with the second treatment (14.3% *versus* 71.4%, respectively; $p < 0.001$) (Table 5).

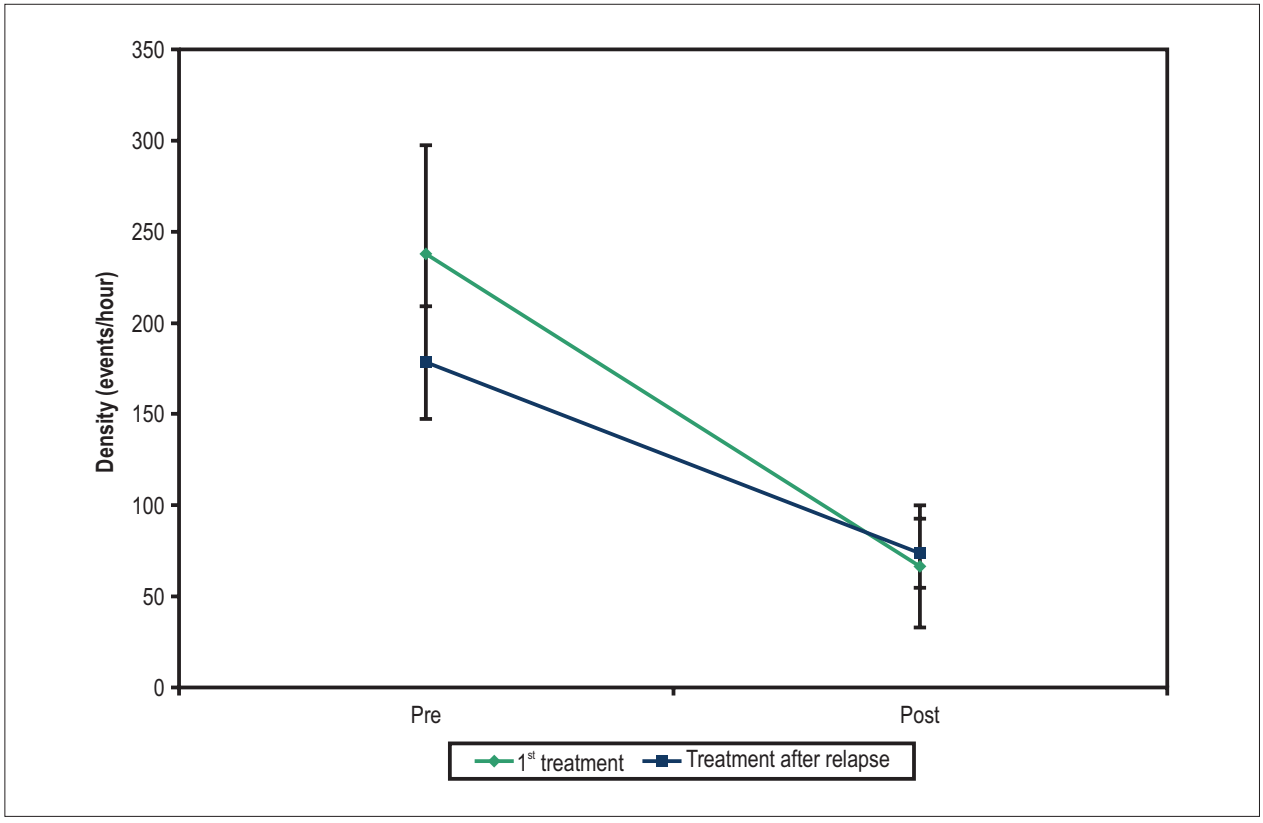

Figure 2 – *Mean profiles of extrasystole density in each treatment of relapsing patients.*

Table 3 – Description of ventricular and supraventricular extrasystoles in each group

	Variable	1st treatment		Follow-up	
		pre	post 30 days	pre (follow-up)	post (follow-up)
No relapse	PVC/day	2034 (0 - 38804)	264 (0 - 6677)	7.3 (0 - 710)	NA*
	PsVC/day	29.5 (0 - 19386)	18.5 (0 - 15548)	5.5 (0 - 973)	NA*
	PC/hour	119.9 (34.9 - 1616)	15.5 (0 - 647.8)	3 (0 - 40.5)	NA*
Relapse (N = 17)	PVC/day	1386 (0 - 6497)	3 (0 - 1616)	1872 (0 - 8040)	280 (0 - 3980)
	PsVC/day	78 (0 - 20019)	14 (0 - 13104)	15 (0 - 12020)	38 (0 - 7008)
	PC/hour	132 (21.1 – 839.7)	10.3 (0 - 546)	126.1 (33.4 - 511.3)	50.2 (1 - 292)
Crossing (N = 21)	PVC/day	3030 (0 - 22502)	3002 (0 - 21429)	2508 (0 - 22505)	689 (0 - 18812)
	PsVC/day	2 (0 - 15965)	3 (0 - 19861)	4 (0 - 15965)	1 (0 - 10900)
	PC/hour	264.8 (32.5-938.2)	299.3(34.6-899.6)	264.8 (32.5 - 938.3)	48 (0 - 784)

**Not applicable, PC: premature complexe; PVC: premature ventricular complexes; PsVC: premature supraventricular complexes.*

Table 4 – Description of densities of extrasystoles per hour in each group

Group/Treatment	Time	Mean	SD	Median	Minimum	Maximum	N
Placebo	Pre	339.82	263.67	264.75	32.50	938.20	21
	Post	362.28	275.71	299.25	34.58	899.60	21
MgP (crossing)	Pre	339.83	263.69	264.75	32.50	938.33	21
	Post	115.29	183.47	48.00	0.00	784.00	21
1st treatment	Pre	238.07	245.03	132	21.08	839.67	17
	Post	66.39	137.26	10.3	0.00	546.00	17
Treatment after relapse	Pre	178.28	126.75	126.08	33.42	511.25	17
	Post	73.46	78.15	50.21	1.00	292.00	17

SD: standard deviation; MgP: magnesium pidolate

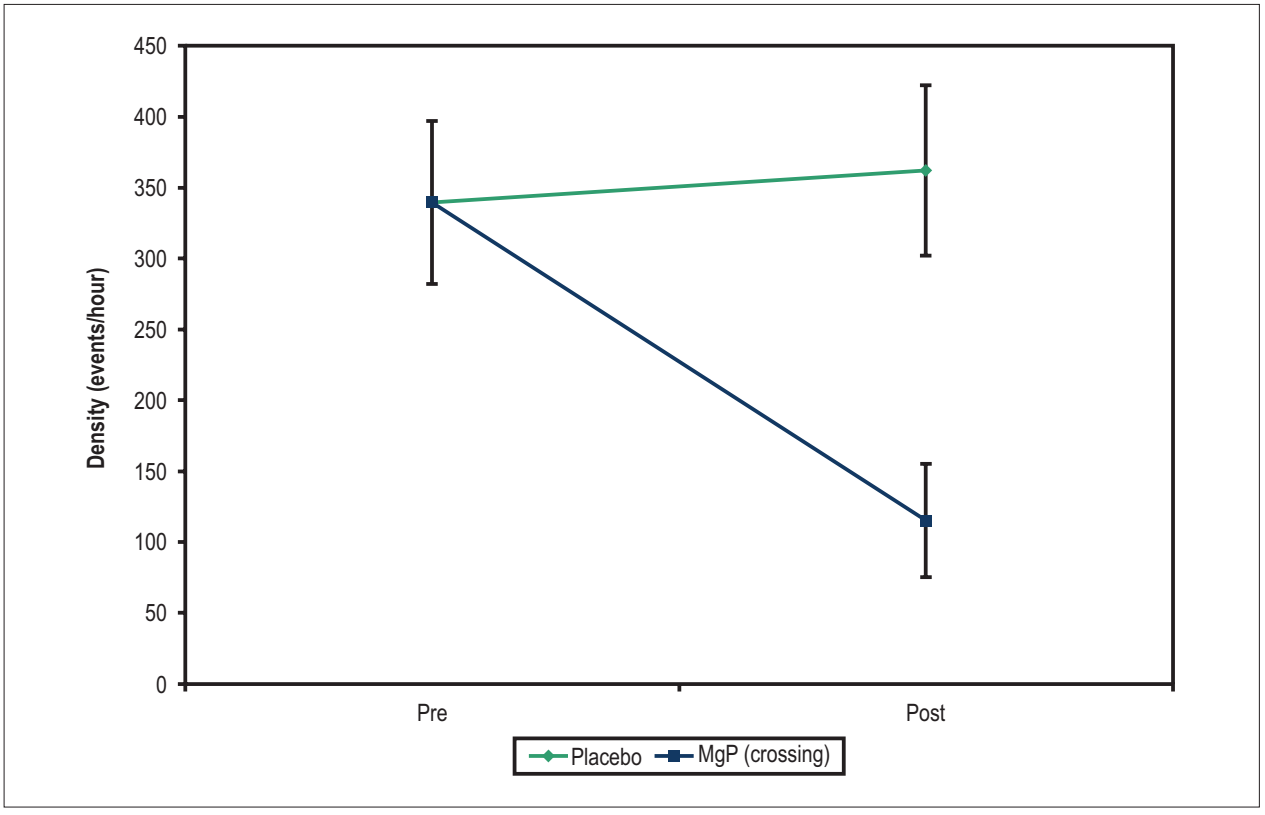

Figure 3 – *Mean profiles of density of extrasystoles in each treatment in patients of the placebo group undergoing crossing-over.*

No significant changes in the measurements of serum Mg, potassium and calcium were observed during the study. No side effects were observed in the long-term follow-up.

Discussion

The follow-up results show that the improvement in symptoms by using MgP was maintained (76.5%) in the relapsing group as compared with the initial treatment. The group using placebo initially (crossing-over) had a 71.4% improvement in symptoms with MgP *versus* a 14.3% improvement with placebo.

The use of MgP was effective in reducing PC. However, because that is mainly a symptomatic treatment and because the mechanism of PC is multifactorial, symptoms and PC relapsed in approximately 38% of the cases, indicating that MgP is neither a definitive nor a curative treatment in late follow-up. However, the patients who could use MgP again improved their frequency of PC and mainly their symptoms, the latter being this study's major

Table 5 – Improvement in symptoms of each group of patients for each treatment, and results of the marginal association test

Group	Improvement in symptoms	1st treatment		2nd treatment		p
		n	%	n	%	
Crossing	No	18	85.7	6	28.6	< 0.001
	Yes	3	14.3	15	71.4	
	Total	**21**	**100**	**21**	**100**	
Relapse	No	0	0	4	23.5	0.125
	Yes	17	100	13	76.5	
	Total	**17**	**100**	**17**	**100**	

McNemar test results

objective, because the group treated had a structurally normal heart.

It is worth noting that the patients initially treated with placebo also improved significantly their symptoms and frequency of PC after using MgP. This confirms that Mg administration is really better than placebo use.

The Mg reduces irregular heartbeats, and Mg deficiency should always be considered a potential factor for cardiac arrhythmias[22]. One hypothesis of the pathophysiological mechanisms relates to the fact that low Mg levels lead to an increase in intracellular calcium and sodium, and to a decrease in intracellular potassium[7,8]. Those changes in ionic loads cause membrane potential flotations, destabilizing atrial and ventricular myocardium, causing arrhythmias.

The Framingham study[23] has shown that low Mg levels are associated with the development of atrial fibrillation in individuals with no cardiovascular disease. Patients at intensive care units should undergo intravenous replacement of Mg for arrhythmias not responding to conventional drugs, such as *torsades de pointes*[15], and arrhythmias caused by digitalis intoxication[24]. Similarly to hypomagnesemia, digitalis inhibits the Na/K ATPase pump, increasing intracellular calcium and the contraction power of cardiomyocytes, PC being one of the most common arrhythmias in digitalis intoxication. The Mg deficiency caused by diuretic treatment in heart failure is associated with a higher incidence of arrhythmias, such as ventricular ectopy[6,8,25]. High concentrations of catecholamines can lead to the exit of intracellular Mg to the extracellular compartment, resulting in Mg reduction in the tissues, causing arrhythmias, especially in cardiac surgeries and in congestive heart failure patients[6].

According to Kleivay and Milne[26], the recommended daily Mg intake is 320 mg/day. Higher daily doses might be required by patients on diuretics, more prone to Mg level reduction, and, thus, with a higher potential and more susceptible to the development of ES[26]. Martynov and Akatova[27] have followed up, for 15 years, 31 patients with mitral valve prolapse, who, during that time, regularly used Mg preparations for three months, twice a year. A reduction in the following parameters were observed: mean and maximum heart rate; number of tachycardia episodes; QT interval duration; and incidence of paroxysmal supraventricular tachycardia and PC. In addition, improvements in quality of life and in sympathetic tone were observed.

More recently, Del Gobbo et al[28] have assessed obese adults with type 2 diabetes, and have shown that low serum Mg levels were associated with a high prevalence of PVC.

Our previous study, assessing 60 individuals with PVC and PsVC, has shown an improvement in the frequency of arrhythmia and mainly in symptoms[17]. Our current results indicate a significant improvement in PVC of the outflow tract. Right ventricular outflow tract is the most common origin of PVC in patients without structural heart disease[29]. That site might have remnant cells of the neural crest and of adrenergic modulation. The Mg reduction in those cells might be related to sympathetic modulation, more evident in the ventricles.

All those studies have shown that Mg intake can be a practical alternative to treat some arrhythmias. Considering its low cost, its efficacy and safety, the increase in daily Mg intake should be considered for symptomatic patients with PC and a structurally normal heart.

Limitations

Intracellular Mg was not measured, but the measurement of serum Mg levels has shown that supplementation to be safe and effective. The specific score for symptoms has not been validated, because it does not exist in the literature. However, a categorical assessment ('yes' or 'no') has also been performed, showing a good correlation between the reduction in PC frequency and improvement in symptoms. In addition, this study was not aimed at preventing life-threatening arrhythmias. These data should not be used to justify the treatment of patients for that purpose, especially those with heart diseases.

Conclusion

Some patients on MgP had relapse of symptoms and PC, indicating that MgP is neither a definitive nor a curative treatment in late follow-up. However, improvement in the PC frequency and symptoms was observed in the second phase of treatment, after relapse, being similar to the

response in the first phase of treatment. Treatment with MgP, even after the first phase with placebo, improved the symptoms and PC density of the population studied (structurally normal heart).

The increase in daily Mg intake should be considered for patients with PC and structurally normal heart.

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Author contributions

Conception and design of the research: De Falco CNML, Darrieux FCC, Scanavacca M; Acquisition of data: De Falco CNML, Darrieux FCC, Sacilotto L; Analysis and interpretation of the data: De Falco CNML, Darrieux FCC, Sacilotto L, Pisani C; Statistical analysis: De Falco CNML, Darrieux FCC, Pisani C; Obtaining financing: De Falco CNML; Writing of the manuscript: De Falco CNML, Darrieux FCC, Scanavacca M; Critical revision of the manuscript for intellectual content: De Falco CNML, Darrieux FCC, Sacilotto L, Lara S, Ramires JAF, Sosa E, Wu TC, Hachul D, Scanavacca M.

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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