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Effect of the Magnesium Infusion on the Late Potentials in Patients After Acute Myocardial Infarction

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AKUT MİYOKARD İNFARKTÜSÜ GEÇİREN HASTALARDA İNTRAVENÖZ MAGMEZYUM TEDAVİSİNİN GEÇ POTANSİYALLER ÜZERİNE ETKİSİ

ÖZET

Akut miyokard infarktüsü (MI) geçiren hastalarda geç potansiyaller (LP) malign ventriküler aritmi riski olan hastaların tanınmasında yaygın olarak kullanılmaktadır. Bu çalışma MI geçiren hastalarda magnezyum tedavisinin LP üzerine etkisini incelemek için planlandı. ***Metod:*** *Akut MI geçiren hastalarda ilk 5 gün 1 gr/gün $MgSO_4$ infüzyonu alan 26 hasta çalışma grubu olarak (ÇG) ve almayan 15 hasta kontrol grubu (KG) olarak incelendi. Bütün hastaların 1.(birinci) ve 6.(ikinci) günlerde sinyal-ortalamalı EKG ve ritm analizi kayıtları alındı.* ***Bulgular:*** *Birinci ve ikinci kayıtlarda, ÇG için sırasıyla 10 (%38) ve 5 (%19) olguda (azalma oranı %50), KG için sırasıyla 5(%33) ve 4 (%27) olguda (azalma oranı %18) LP pozitif bulundu (sırasıyla p=0.13 ve p=0.69). Birinci ve ikinci kayıtlarda QRS süresi, "Root Mean Square" voltajı (RMS40) ve "düşük amplitüd sinyali" süresi (LAS40) ÇG'da sırasıyla 107.4±13.9 ve 99.3±14.2 msn; p=0.043, 32.9±19.4 ve 44.7±20.1 μV; p=0.035, 36.8±17.9 ve 27.6±12.8 msn; p=0.037, ve KG'da sırasıyla 110.4±12.0 ve 105.4±13.2 msn, 31.8±17.9 ve 39.1±18.7 μV, 39.2±14.8 ve 33.7±12.1 msn bulundu (hepsi için p>0.05). Birinci ve ikinci kayıtlar karşılaştırıldığında, ÇG'da QRS süresindeki azalma (%7.6±3.2 ve 4.6±4.4, p=0.03), RMS40'daki artış (%52.9±37.8 ve 30.4±22.0, p=0.002) ve LAS40'daki azalma (%24.2±11.3 ve 12.6±11.7, p=0.004) oranlarının KG'na göre daha fazla olduğu görüldü. Birinci ve ikinci kayıtlar ≥grade II ventriküler aritmi bakımından karşılaştırıldığında, ÇG'da anlamlı azalma olurken (sırasıyla 20 olgu %77 ve 4 olgu %15, p<0.001), KG'da anlamlı değişme olmadı (sırasıyla 11 olgu %73 ve 9 olgu %60, p>0.05). Sonuç: Miyokard infarktüsü geçiren hastalarda $MgSO_4$ infüzyonu LP parametrelerinde anlamlı iyileşme ve ventriküler aritmi sıklığında önemli azalma sağlamaktadır.*

Anahtar kelimeler: *Geç potansiyel, Magnezyum, akut miyokard infarktüsü*

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It is well known that late potential (LP) is closely related with ventricular arrhythmias and acute myocardial infarction [1]. The presence of LP on a signal-averaged electrocardiogram predicts fatal and nonfatal ventricular arrhythmias in patients with coronary artery disease [2-4].

Magnesium (Mg) is known to lower systemic vascular resistance, dilate coronary arteries, decrease platelet aggregation, improve myocardial metabolism, protect against cathecolamine-induced myocardial necrosis, and stabilize cell membranes [5-9]. Magnesium treatment is also useful on ventricular arrhythmias in patients with acute myocardial infarction [9]. The definite mechanism of the beneficial effect of Mg is still not well known. Beneficial effects of Mg in patients with acute myocardial infarction are not limited to the antiarrhythmic effect, as mentioned above. We planned this study to investigate the effect of Mg on LP, which is related malignant ventricular arrhythmias in patients with acute myocardial infarction.

METHODS

Forty-one patients who were admitted to the coronary care unit with acute myocardial infarction were prospectively randomized to two groups. The study group (SG) consisted of 26 patients who received Mg infusion therapy and control group (CG) consisted for 15 patients who received placebo without Mg infusion. The patients with complete bundle- brunch block and not in sinus rhythm were not included in the study.

Laboratory parameters of the two groups are demonstrated in table-1.

Protocol

All cases were admitted to coronary care unit as acute myocardial infarction, and standard thrombolytic regimen was applied to the patients whose clinical conditions were suitable for the thrombolysis. Tissue plasminogen activator, 100 mg in 90 minutes, was applied as the thrombolytic

Table 1. Laboratory parameters of the patients

	Study Group	Control Group	p
*SVT (n)	2	1	NS
#EF < 40% (n)	7 (27%)	5 (33%)	NS
†Na (mmol/L)	135.2±4.3	136.9±4.9	NS
†K (mmol/L)	3.9±0.6	4.2±0.6	NS
β blocker usage (n)	20	9	NS
Amiodarone usage (n)	3	3	NS
Lidocaine usage (n)	6	3	NS

**First day suraventricular tachycardia (SVT),*
#Sixth day ejection fraction (EF),
†First laboratory values of sodium (Na) and potassium (K).

regimen. The patients in SG received 1 g /day MgSO4 infusion in 100 ml 0.9 % NaCl solution (25 ml/hr) for the first five days, and first dose was infused just after the sixth hour of the treatment. Control group received only 100 ml 0.9 % NaCl solution (25 ml/hr) at the same time intervals.

Magnesium level was measured before the treatment and daily for the first five days. In addition to Mg measurement, potassium, sodium, chlorine and calcium concentrations were measured daily. Oxygen saturation was obtained by pulse oxymeter monitoring system and maintained at 90 % or greater.

Late potentials and arrhythmia

The signal-averaged electrocardiogram was performed on the Del Mar Avionics (Model 563 Holter Analysis System) Signal-Averaged Electrocardiographic System. An orthogonal X+Y+Z lead system was used and signals from these leads were combined into a vector magnitude = $(X^2+Y^2+Z^2)$. The square root of this magnitude $(X^2+Y^2+Z^2)^{1/2}$ provided the total energy found in the sum of the averaged X, Y, and Z leads. After acquiring QRS complexes, averaging of QRS complexes was obtained. Using a time-domain mode with 25-250 Hz bi-directional filtering and a computer algorithm, root-mean-square voltage of the terminal 40 ms of the filtered QRS, and the terminal signal duration < 40 μV or low amplitude signals, were determined by an automated technique. At least 250 QRS complexes were obtained to achieve a noise level of < 1.0 μV. The filtered QRS complexes were analyzed for total QRS time, Root Mean Square voltage during last 40 ms of QRS (RMS40), and the duration of terminal portion of QRS with vector magnitude < 40 μV (LAS40). Late potentials were defined as present if the signal-averaged electrocardiogram met 2 to 3 of the following criteria: filtered QRS duration > 114 ms, RMS40 < 20 μV, or LAS40 >38 ms.

After the completion of the thrombolytic treatment at first day, first continuous monitoring of cardiac rhythm was performed for four hours using Del Mar Digicorder recording device. Second rhythm analysis was performed at sixth day of the treatment for four hours using the same recorder. All the recorded rhythms were assessed using Del Mar Avionics Model 563 Holter Analysis System system.

Assessment of ventricular arrhythmias was based on the Lown-Wolf classification [10]: frequency of the ventricular ectopic impulses is lower than 10 beats per hour in Grade I, more than 10 beats per hour in Grade II, multiform in Grade III, couplet salvos in Grade IV, and at least triplet salvos in Grade V.

Statistical analysis

Patients and in-hospital characteristics were reported as mean ± standard deviation. Demographic and clinical variables, and ventricular arrhythmia incidence were analyzed using χ^2 test or Fisher's exact test for categorical variables and paired and unpaired t test for continuous variables. Statistical analysis was performed using SPSS statistical software 10.0 version (SPSS Inc, Chicago, IL). Variables were considered significant at p values less than 0.05.

RESULTS

Three patients were admitted to emergency room with ventricular fibrillation and two with ventricular tachycardia, and after resuscitation and restoration of sinus rhythm, acute myocardial infarction pattern was detected on their electrocardiograms. In the SG, twenty cases with acute Q-wave myocardial infarction received thrombolytic treatment, and four cases with nonQ-wave myocardial infarction and two cases who were not an appropriate candidate for thrombolysis did not receive thrombolytic agent. In the CG, eleven cases with acute Q-wave myocardial infarction received thrombolytic treatment, and four cases with nonQ-wave myocardial infarction did not receive this agent.

There was no significant difference between the SG and CG with respect to age (55.4±11.0 vs 58.4±8.2 years, respectively), sex (7 female and 19 male vs 5 female and 10 male, respectively), hypertension (n= 8 vs 7, respectively), diabetes mellitus (n= 6 vs 3, respectively), and previous myocardial infarction (n= 9 vs 4, respectively).

The ratio of thrombolytic agent usage in SG and CG (n= 20 vs 11, respectively) was not different between the two groups.

Table 2 illustrates clinical and laboratory parameters in SG and CG at baseline and on the sixth day.

In the first and the second records, LP was found to be positive in 10 (38%) and 5 (19%) cases (p=0.13), respectively in SG with a relative reduction ratio of 50%, and 5 (33%) and 4 (27%) cases (p=0.69) res-

Table 2. Clinical and signal-averaged parameters of the groups at 1st and 6th day

	1st day			6th day		
	Study Group	Control Group	p	Study Group	Control Group	p
Heart rate (/min)	76±15	69±14	NS	73±11	69±11	NS
≥ Grade II VA (n)	20 (77%)	11 (73%)	NS	4 (15%)	9 (60%)	=0.003
Mg (mmol/L)	1.97±0.12	2.01±0.13	NS	2.18±0.19	1.95±0.13	<0.001
QRS time (ms)	†107.4±13.9	*110.4±12.0	NS	99.3±14.2	105.4±13.2	=0.04
RMS40 (μV)	†32.9±19.4	*31.8±17.9	NS	44.7±20.1	39.1±18.7	NS
LAS40 (ms)	†36.8±17.9	*39.2±14.8	NS	27.6±12.8	33.7±12.1	NS
Noise (μV)	0.7±0.2	0.6±0.2	NS	0.7±0.1	0.7±0.1	NS
Late potentials + (n)	**10 (38%)	*5 (33%)	-	5 (19%)	4 (27%)	-

*†p<0.005 when compared sixth day value in study group, *p= NS when compared sixth day value in control group **p= NS when compared sixth day value in study group. VA; Ventricular arrhythmia, Mg; Magnesium.*

pectively in CG with a relative reduction ratio of 18 %.

In the first records, QRS interval, RMS40 and LAS40 were found similar in the two groups. In comparison of the first and the second records, QRS interval, RMS40 and LAS40 were found significantly different in SG, however, these parameters were found similar in CG (Table 2). In comparing of the SG and CG, shortening ratio in QRS interval (7.6±3.2 vs 4.6±4.4% respectively, p=0.03), increasing ratio in RMS40 (52.9±37.8 vs 30.4±22.0% respectively, p=0.002) and reduction ratio in LAS40 (24.2±11.3 vs 12.6±11.7 % respectively, p=0.004) were significantly higher in SG (Figure 1, Figure 2).

In comparison of the first and the second records, the incidence of ≥ grade II ventricular arrhythmia was significantly reduced (20 cases 77% vs 4 cases 15% respectively, p<0.001) in SG, but it did not change in CG (11 cases 73% vs 9 cases 60%, p>0.05).

All electrolyte values were within normal limits, and potassium was administered as required to maintain the concentration of potassium at 4 mmol/L or greater.

DISCUSSION

The objective of this study was to investigate relationship between Mg infusion therapy and LP in patients with acute myocardial infarction. The most striking finding of this study was to show a 50% decrease on LP by using Mg infusion. Presence of LP is closely related with an increased risk of ventricular arrhythmia.

Intravenous administration of Mg was associated with a significant reduction in the incidence of ventricular arrhythmias [11,12]. The mechanisms for this reduction in arrhythmias are not exactly known although there are several physiological effects that may produce this result. Magnesium is a cofactor for Na,K-ATPase and Ca-ATPase, both of which are important in maintaining membrane stability [13,14]. Myocardial excitability is reduced and may account for the lower incidence of arrhythmias. When the extracellular Mg concentration is increased, membrane depolarizes before the generation of action potential, thus the velocity of conduction is increased [15]. In our study, serum Mg level was increased in SG, and at the end of the sixth day serum Mg level was found significantly higher in SG. However, it is not clear whether serum Mg level is closely related with ventricular arrhythmia. Since, our study could not show a good correlation between them. So, serum Mg ions rapidly transport to the intracellular compartment where is highly concentrated with Mg. In addition, the high intracellular sodium concentration of Mg deficiency increases the Na/Ca countertransport mechanism, which leads to a higher intracellular concentration of calcium and a tendency to transient depolarization and arrhythmias [16]. The reverse would be expected with Mg infusi-

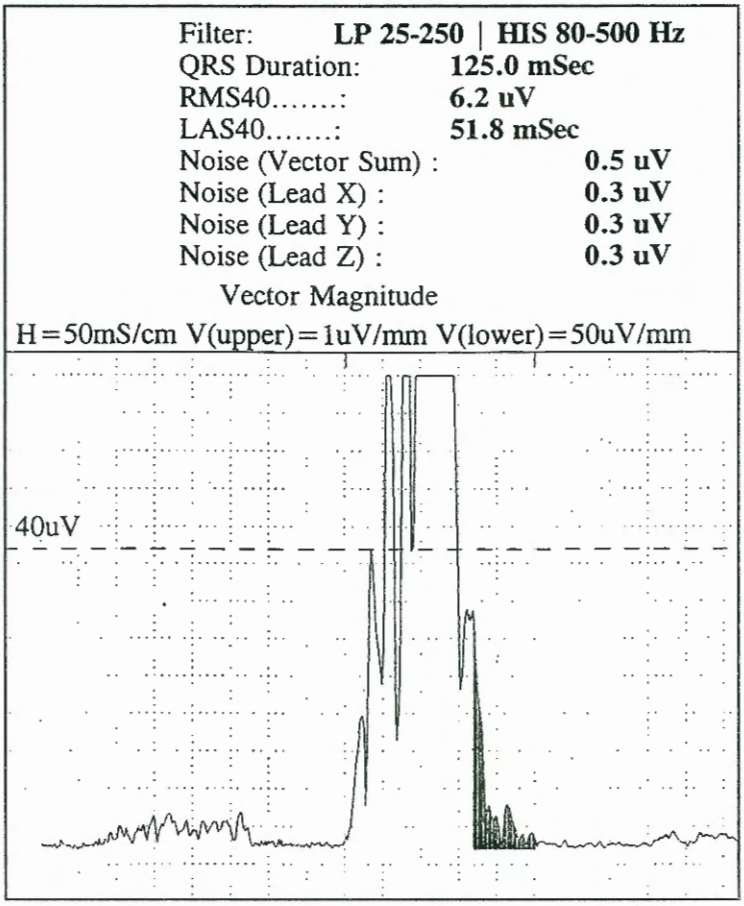

Figure 1. Illustration of the signal-averaged electrocardiogram in a patient at 1st day before magnesium treatment

on. In our study, serum calcium level of the patients were within normal limits, thus excluding the Na/Ca countertransport mechanism. Magnesium infusion also increases the absolute refractory period and decreases the relative refractory period, leading to a decrease in the vulnerable period [15]. Serum potassium level is increased by the raised levels of Mg which reduces renal potassium excretion [17], and the reduced serum Mg level may be possible cause of an arrhythmia precipitated by hypokalemia. In present study serum potassium level obtained at 4 mmol/L or greater, but within normal limits to avoid the arrhythmia precipitated by hypokalemia. Conversely, Mg has been found to antagonise the effects of a high extracellular potassium concentration; this may be important in the genesis of arrhythmias related to ischemia [18]. Thus, it is possible that ectopic impulse formation is suppressed, the vulnerable period decreased, and synchronous conduction improved, theoretically reducing the likelihood of a reentrant arrhythmia arising. However, there is no an adequate explanation for how magnesium infusion reduces myocardial irritability and ventricular arrhythmia. It still remains unclear whether Mg exerts its antiarrhythmic effect by stimulating the Na,K-ATPase, by directly inhibiting the efflux of potassium from the cell, by altering cellular calcium metabolism, or whether it works through some other mechanism.

The American Heart Association (AHA) currently recommends intravenous Mg infusion of only for correction of documented Mg deficiency and for the treatment of torsades de pointes type ventricular tachycardia in patients with acute myocardial infarction [19]. The AHA also suggests that Mg may be considered in high-risk patients and/or for those in whom reperfusion therapy is not suitable. In a recent study multivariate analyses suggested that intravenous Mg therapy may be useful in patients who receive thrombolytic therapy, those with congestive heart failure on admission, or sustain ventricular tachycardia and/or ventricular fibrillation [20]. In LIMIT-2 study an intravenous regimen of magnesium sulfate in patients with suspected acute myocardial infarction. LIMIT-2 has been shown to decrease the mortality rate from ischaemic heart disease by 21% (p=0.01) and all-cause mortality rate by 16% (p=0.03) [21]. These findings confirms the results of our study.

The electrophysiological basis of LP is a slow, delayed, and fragmented activation in the vicinity of the myocardial infarction scar [22,23]. These infarcted area may constitute a substrate for reentry circuits [24], the electrophysiological basis of the prolonged filtered QRS duration and its possible arrhythmogenic mechanism in patients with acute myocardial infarction remains to be determined. The fact that the duration of high-level activity during the QRS complex (QRS-LAS, excluding late potentials) had the same discrimination power for all arrhythmic events as the QRS duration (including late potentials) suggest the involvement of a large mass of myocardium [25]. It is believed that the main cause of

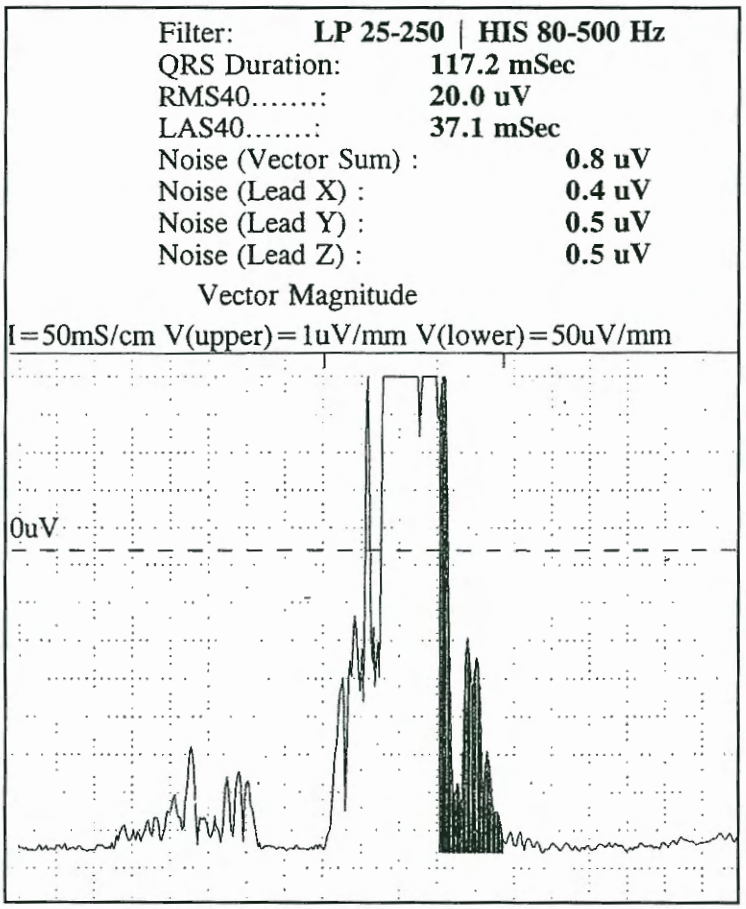

Figure 2. Illustration of the signal-averaged electrocardiogram in the same patient within Figure 1at 6th day after magnesium treatment.

the LP is viable ischemic myocardium, which is adjacent to the infarcted myocardium. Electrically asynchrony in viable ischemic myocardium may cause a late potential with low amplitude and long duration. Magnesium infusion may correct the electrical instability and the focal ischemic induced late potentials. As mentioned above it was shown that Mg increases the absolute refractory period, and decreases the vulnerable period by correction of the electrical instability especially in the ischemic tissue. Whether ventricular arrhythmia presents or not, reducing the LP with Mg infusion has a clinical importance. Because, presence of LP itself may cause ventricular arrhythmias as a strong predictor especially in patients with acute myocardial infarction.

The infarcted myocardium constitutes an anatomic arrhythmogenic substrate, a zone of delayed conduction which can be detected as late potentials on signal averaged ECG [26]. The triggering of a ventricular arrhythmia is closely correlated to the occurrence of a severe ventricular arrhythmia in the months following infarction. Prevention and early therapy of potentially deleterious arrhythmias may limit infarct size, improve the short-term prognosis of patients with myocardial infarction, and decrease the incidence of late sudden death [27]. The administration of intravenous Mg to patients in the immediate postinfarction period is cardioprotective and decreases the incidence of arrhythmia, pump dysfunction, and death [28]. As mentioned above, antiarrhythmic and cardioprotective effect of Mg infusion in acute myocardial infarction makes Mg a valuable choice in acute myocardial infarction. However, it is not possible to say that the decrease in the incidence of arrhythmia is not solely related to Mg infusion. Success of the thrombolysis, infarction size, left ventricular ejection fraction, and beta blocker therapy are important predictors of the ventricular arrhythmia.

Although the possible mechanisms that Mg increase the absolute refractory period and decrease LP incidence, the exact mechanism is not clear. Long standing Holter monitoring and a multivariate analysis could have been better to say the beneficial effect of Mg on LP as an independent factor. However, our study population is not large enough for such an analysis.

CONCLUSION

Magnesium infusion not only significantly suppresses the ventricular arrhythmias, but also reduces presence of LP. At the study dosages side effects due to hypermagnesemia are almost impossible in patients with normal renal function and the cost of the treatment is very low.

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