Antiarrhythmic Effects of Magnesium Infusions in Patients with Acute Myocardial Infarction

F. Bertschat*, H. Ising**, T. Günther***, J. Sorgenfrei*, M. Wollitz*, Karla Ibe*

Zusammenfassung

In einer randomisierten Therapiestudie an 42 Patienten mit akutem Myokardinfarkt (AMI) wurde die antiarrhythmische Wirkung von 3tägigen MgSO4-Infusionen gegenüber NaCl-Infusionen geprüft. Pro Person wurde innerhalb von 20 Tagen nach dem Myokardinfarkt an 7 Tagen je ein 24-Stunden-EKG aufgezeichnet und analysiert. Am 3. und 5. Tag war die Zahl der ventrikulären Extrasystolen (VES) in der Mg-Gruppe signifikant niedriger als in der Kontrollgruppe. Am 1. Tag nach dem AMI bestanden zwischen den beiden Gruppen keine signifikanten Unterschiede bezüglich der untersuchten Arrhythmieformen. Vom 2. bis 20. Tag war das Auftreten von ventrikulären Extrasystolen sowie Couplets (paarweise auftretende VES) und/oder ventrikulären Tachykardien in der Mg-Gruppe signifikant reduziert, was auf eine länger anhaltende antiarrhythmische Wirkung von Mg-Infusionen schließen läßt.

Summary

In a randomized therapy study involving 42 patients suffering from acute myocardial infarction (AMI), the antiarrhythmic effect of 3-day MgSO4 infusions was tested against NaCl infusions as controls. Seven 24 h ECG recordings per person were performed within 20 days after the AMI. On days 3 and 5, the number of ventricular extrasystoles (VES) was significantly lower in the Mg group than in the controls, whereas both groups had had similar arrhythmias at day 1. The occurrence of VES as well as of couplets and/or ventricular tachycardia during days 2 to 20 was significantly reduced in the Mg group, indicating a longer lasting antiarrhythmic effect of Mg infusions.

Résumé

Au cours d'une étude incluant 42 patients atteints d'infarctus aigu du myocarde (IDM), les auteurs ont comparé les effets anti-arythmiques de perfusions de MgSO4 pendant 3 jours à ceux de perfusions de NaCl, administré comme témoin. Dans les 20 jours qui ont suivi l'infarctus aigu du myocarde chaque patient a subi sept ECG de 24 heures. Les troisième et cinquième jours, le nombre des extrasystoles ventriculaires (ESV) était significativement moindre dans le groupe sous Mg que dans le groupe témoin, bien qu'il n'y ait eu aucune différence significative du nombre des arythmies entre les deux groupes le premier jour de l'étude. Du 2ème au 20ème jour, l'incidence des extrasystoles ventriculaires, des extrasystoles bigéminées et/ou des tachycardies ventriculaires a été significativement réduite dans le groupe sous Mg, démontrant ainsi les effets anti-arythmiques plus prolongés de perfusions de magnésium.

Introduction

In patients with acute myocardial infarction (AMI), serum Mg concentrations are reduced [1, 2, 3]. In patients with hypomagnesemia, caused e.g. by chronic treatment with diuretics, cardiac arrhythmia is often observed [2]. Cardiac arrhythmia is a serious complication of AMI. Cardiac arrhythmia can be successfully treated by i.v. Mg injection [4,5].

As yet, only a few studies of Mg infusion in AMI have been conducted. Beneficial effects were demonstrated: Mg infusion resulted in lower requirements of antiarrhythmics [6] and a lower rate of arrhythmia and death [7, 8, 17]. In these studies, however, no quantitative analysis of the arrythmias was performed. In the Mg group and the controls only the percentages of patients who needed antiarrhythmic treatment were compared. Furthermore, the ECG monitoring applied in these studies was already terminated 3 to 7 days after the AMI.

After a decrease of arrhythmias in the first days after the AMI, the arrhythmias increase quite often 2 to 3 weeks later.

Therefore, we planned to quantify the arrhythmias during 3 weeks after the AMI. For reasons discussed later, the following hypothesis will be tested:

Mg infusion therapy during the first 3 days after the AMI decreases quantitatively the arrhythmias during the first 3 weeks after the AMI.

Method

The study involved 42 patients with AMI. The patients were randomized: 20 (16 males and 4 females, age 56 ± 9 years) were infused with 80 mval NaCl/day (control) and 22 (15 males and 7 females, age 56 ± 11 years) were infused with 81 mval MgSO$_4$/day.

Exclusion criteria were:

1. kidney failure (serum creatine $2 \geq$ mg/dl)

* Reanimationszentrum der Medizinischen Klinik und Poliklinik der Freien Universität Berlin im Klinikum Rudolf Virchow Bereich Charlottenburg, Spandauer Damm 130, D 1000 Berlin 19, Tel. 0 30/ 3 03 58 82

** Institut für Wasser-, Boden- und Lufthygiene des Bundesgesundheitsamtes, Berlin

***Institut für Molekularbiologie und Biochemie der Freien Universität Berlin

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2. any kind of AV block
3. systolic blood pressure < 100 mm Hg
4. Myasthenia gravis, pareses and plegia

The patients gave their informed consent. 13 ± 9 hours after the onset of severe pain (day 1), the infusions were started and continued for 3 days.

Tab. 1 shows the number of patients in both groups who received thrombolytic treatment after AMI and the dosage of antiarrhythmic drugs (lidocaine) during the first 3 days. There were no significant differences between the 2 groups. Before the start of infusion and later at daily intervals, blood was taken at 8 a.m. by venous puncture into evacuated glass tubes containing lithium-heparin. The blood was centrifuged within 1 hour and Mg was analyzed by atomic absorption spectrophotometry (Perkin Elmer model). On days 1, 2, 3, 5, 10, 15 and 20 of AMI treatment, from all patients ECG recordings were made over 24 hours using Medilog 4000 — III recorders and analysed automatically by means of a two-channel Oxford Medilog 4000 system. Serious arrhythmia, i.e. couplets and ventricular tachycardia (VT), were verified visually. For statistical analysis, nonparametric tests were used and medians are presented in the figures.

Tab. 1: Number of patients with and without thrombolytic (L) treatment on the day of AMI and dosage of antiarrhythmics (mean values ± standard deviations).

	Number of patients		Dosage of Lidocaine (mg)		
	with L	without L	day 1	day 2	day 3
Controls	15	5	343 ± 654	240 ±475	165 ±489
Mg group	19	3	340 ± 738	235 ±605	75 ±308

Tab. 2a: Frequencies of ventricular extrasystoles per 24 h (VES/24 h) in myocardial infarction patients on the day of AMI (day 1).

VES/24 h	0	1 to 24	25 to 240	241 to 2400	> 2400	Total number of measurements
Controls	–	2 11 %	12 63 %	4 21 %	1 5 %	19 100 % (1 missing value)
Mg group	–	3 14 %	12 57 %	4 19 %	2 10 %	21 100 % (1 mis. value)

$\chi^2 = 0.3$: no significant group difference

Tab. 2b: Frequencies of VES/24 h per patient on days 2, 3, 5, 10, 15 and 20 after AMI.

VES/24 h	0	1 to 24	25 to 240	241 to 2400	> 2400	Total number of measurements
Controls	19 17 %	45 41 %	28 25 %	14 13 %	3 3 %	109 100 % (11 mis. values)
Mg group	38 31 %	45 37 %	22 18 %	16 13 %	–	121 100 % (11 mis. values)

$\chi^2 = 9.59$: significant group difference ($\alpha < 1$ %)

Results

During i.v. Mg infusion, serum Mg concentration (SMg) was increased from 0.78 mmol/l to 1.21 mmol/l (see Fig. 1). Upon termination of Mg infusion, serum Mg concentration dropped to the same values as measured in the control group. As was found in an earlier study (1), serum Mg on days 5 to 20 after the AMI was somewhat higher than shortly after the event. The distribution of ventricular extrasystoles (VES) for both groups on day 1, is listed in Tab. 2a. All patients had at least a few VES. There was no significant difference between the 2 groups. Fig. 2 compares the medians of VES per 24 hours of both groups during a period of 20 days after the event.

From day 1 to day 2 there was a decrease of VES in both groups with no significant group difference. On the 3. day of Mg treatment, the Mg group showed a significantly lower number of VES ($\alpha < 5$ %). Also on day 5, 2 days after the termination of the Mg treatment, this difference was still significant ($\alpha = 5$ %, Mann-Whitney U-test). Later, the number of VES increased in both groups with no significant group difference. The distribution of all VES per 24h from day 2 to day 20 for the Mg group as compared to the controls is
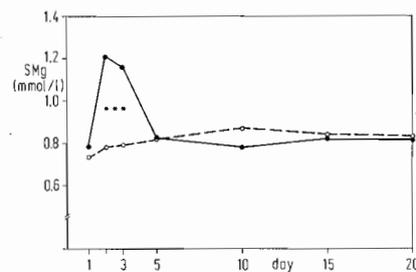

Fig. 1: Time course of serum Mg concentrations (medians) in two groups of patients with AMI at day 1.
- •—• 22 patients with MgSO4 infusions during days 1–3,
- o–o 20 patients with NaCl infusions during days 1–3.
  (Significance level of group differences (Mann-Whitney U-test), ***: $\alpha < 0.1$ %).

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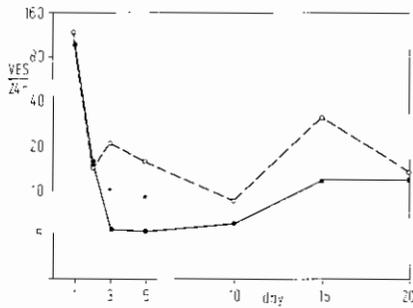

Fig. 2: Time course of ventricular extra-systoles per 24 hours (medians) in 2 groups of patients with AMI at day 1
•——• 22 patients with Mg infusions,
o— —o 20 patients with NaCl infusions.
(Significance level of group differences (Mann-Whitney U-test), *: $\alpha < 5$ %).

shown in Tab. 2b. The VES results of one 24h ECG recording on each patient were considered as one single measurement. Taking into account the entire VES measurement results, the reduction of VES in the Mg group was found to be significant ($\alpha < 1$ %, χ^2- test) in the first 3 weeks after the AMI. In Tab. 3a, the numbers of patients without salvos, with couplets and without VTs and with VTs on day 1 are given for both groups. Tab. 3b gives the corresponding figures for the days 2 to 20. Also in this case, we took the results of each single 24h ECG per patient as one individual measurement. The χ^2-test showed no significant difference between the salvos on day 1, whereas between days 2 to 20, the salvos in the control group were significantly more frequent than in the Mg group ($\alpha < 5$ %). Also for salvos the hypothesis was confirmed, that the applied Mg infusion therapy quantitatively reduced arrhythmias during 3 weeks after the AMI.
In the control group one patient died.

Table 3b: Occurrences per patient and 24 h ECG of couplets (C) and ventricular tachycardias (VT) at days 2, 3, 5, 10, 15 and 20 after AMI.

	No salvos	C (no VT)	VT	Total number of measurements
Controls	83 (76 %)	14 (13 %)	12 (11 %)	109 (100 %) (11 mis. values)
Mg group	107 (88 %)	7 (6 %)	7 (6 %)	121 (100 %) (11 mis. values)

$\chi^2 = 6.06$: significant group difference ($\alpha < 5$ %)

Discussion

Our results indicate a longer lasting antiarrhythmic effect of Mg infusions. Among heterotopic ventricular dysrhythmia, couplets and VTs are considered to have a serious prognostic importance with regard to sudden cardiac death. The significant reduction of these dangerous arrhythmias by Mg, which does not show toxic side effects like the other antiarrhythmics, is the most important result of this study. This result is in agreement with other studies [7, 8, 17].

The antiarrhythmic effect of Mg became obvious on day 3, the 3. and last day of the Mg infusion therapy and it outlasted the period of therapy. At days 15 and 20, the number of VES increased in both groups. At day 20, the controls had almost the same VES median as the Mg group, indicating that the antiarrhythmic effect of Mg infusions during 3 days after the AMI had decreased 16 days after the termination of the Mg treatment.

The delayed manifestation of the antiarrhythmic Mg effect (it did not become obvious before the 3. day) leads to the question whether a higher dosage at the beginning of the treatment could be beneficial. Even bolus injection of Mg should be discussed. Future studies are necessary to optimize the Mg treatment of AMI.

To understand the antiarrhythmic effect of Mg some Mg-dependent mechanisms will be discussed.

Besides other mechanisms, the reduction of the extracellular concentration of free Mg^{2+} ions, which is the active fraction of serum $Mg([Mg^{2+}] o)$, may be involved in the development of arrhythmias in AMI or may, at least, aggrivate arrhythmias [5] which are induced by other mechanisms in AMI.

Since a reduction of VES did not occur until the 3. day of the Mg therapy, a direct pharmacological effect of a moderate increase of extracellular Mg upon cardiac arrhythmias might be excluded. The delayed effect of the therapy was probably due to a slowly progressing normalization of intracellular electrolytes. This could also explain the prolonged effect of the Mg treatment.

Abraham et al. [8], who started the Mg treatment with a quick infusion of 20 mmol Mg, reported significant reductions of arrhythmias already in the first 24h after the begin of Mg treatement.

Such a single dose of Mg-sulfate may lead for a short time to maximal SMg of about 2 to 3 mmol/l. Mg concentrations of that magnitude seem to have a direct pharmacological antiarrhythmic effect. A possible negative inotropic effect of such high SMg should be taken into account and investigated in further studies.

Table 3a: Occurrences of couplets (C) and ventricular tachycardias (VT) at day 1 of AMI.

	No salvos	C (no VT)	VT	Total number of measurements
Controls	5 (26 %)	7 (37 %)	7 (37 %)	19 (100 %) (1 mis. value)
Mg group	7 (33 %)	3 (14 %)	11 (52 %)	21 (100 %) (1 mis. value)

$\chi^2 = 2.73$: no significant group difference

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The beneficial effect of slow Mg infusions in our study may be mediated by:

1. a direct effect of $[Mg^{2+}]o$ on the membrane permeability for Na^+ and Ca^{2+} [5]. Increased membrane permeability after AMI may be normalized by increased $[Mg^{2+}]o$. At significantly increased $[Mg^{2+}]o$, the permeability of Na^+ and Ca^{2+} may be reduced, supporting effective pumping of Na^+ and Ca^{2+} out of the cardiamyocytes. The restoration of normal ion distribution and membrane potentials may support the prevention of arrhythmia. These effects could last longer than the increase of $[Mg^{2+}]o$ by Mg infusions.

2. an indirect effect of $[Mg^{2+}]o$. At reduced $[Mg^{2+}]o$, the release of catecholamines [9], biogenic amines (serotonin, histamine [10, 11] and prostaglandins (thromboxane A2 [12] is increased.

In AMI, the release of catecholamines [13], histamine [14] and prostaglandins [15] is increased. Particularly in AMI patients with cardiac arrhythmia, TXB2 in plasma was drastically increased [15]. Histamine is known to induce cardiac arrhythmia [14, 16] and its liberation may be enhanced by noradrenaline [14].

Thus, these hormones may act together in producing cardiac arrhythmia. A drastic increase in $[Mg^{2+}]o$ — e.g. by Mg infusions may inhibit their liberation.

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(For the authors: Dr. F. Bertschat, Freie Universität Berlin, Universitätsklinikum Charlottenburg, Reanimationszentrum, Spandauer Damm 130, D-1000 Berlin/FRG)