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Effect of magnesium on restenosis after percutaneous transluminal coronary angioplasty: a clinical and angiographic evaluation in a randomized patient population

A pilot study

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Restenosis is a major clinical problem following successful percutaneous transluminal coronary angioplasty. Since magnesium has vasodilator and antithrombotic effects, this study was designed to evaluate its potential to decrease the rate of restenosis.

In an open-labelled, randomized controlled study, 148 patients underwent successful coronary angioplasty. Ninety-eight patients were treated with 46–52 mmol/18–20 h intravenous magnesium sulphate (groups M1 and M2), and 49 of them continued with oral supplements of magnesium hydroxide 600 mg . day^{-1} (group M2). The other 50 patients served as controls (group C). Coronary angiography was performed before, immediately after and at 6 months follow-up or earlier if clinically indicated. Clinical, laboratory, ergometric and radionuclide evaluations were also carried out.

One hundred and thirty-nine patients (94%) with 163 dilated segments completed the study. Intravenous magnesium was well tolerated. The cross-sectional area at the site of angioplasty increased by 3·55 ± 2·01 mm^2 in groups M1 and M2 compared with an increase of 2·90 ± 1·63 mm^2 in the control group, (P=0·03). A trend towards a lower rate of restenosis (>50% reduction in luminal diameter) was noticed in the magnesium groups (28/110, 25%) compared with the control group (20/53, 38%) P=0·10. Oral administration of magnesium was well tolerated, did not have an additive effect on restenosis, but an improved clinical course was noted.

It is concluded that intravenous administration of magnesium in patients undergoing coronary angioplasty is feasible and safe and that the beneficial trend of magnesium to prevent acute recoil and late (within 6 months) restenosis is encouraging and should promote further investigation in a larger patient population.

Introduction

Since its introduction in 1977[1], percutaneous transluminal coronary angioplasty has proved to be a successful method in the treatment of coronary artery disease. However, restenosis, which constitutes the major problem following successful angioplasty, occurs in 30–40% of patients (range 20–70%) within 3–6 months[2–12], despite extensive efforts to reduce its incidence[13–16]. These include the administration of drugs such as warfarin[17,18], calcium channel-blocking agents[19–21], aspirin[22], ticlopidine[23], prostacyclin[24], thromboxane A_2-receptor blocker[25], colchicine[26], corticosteroids[27] and lipid-lowering regimens[3,4,6,7,28–32].

Restenosis may be viewed as a multifactorial response of the vascular tissue to balloon injury. Several interactive processes are involved: mechanical factors (medial dissection and intimal flap formation, elastic recoil and vasospasm), haemostatic factors (thrombus formation and platelet deposition) and cellular proliferation[14]. These processes are concordant with both pathological and clinical studies which assess their role in the occurrence of restenosis[2,33–37].

An association between hypomagnesaemia and atherosclerosis, hypertension, cerebral ischaemic attacks and coronary spasm has recently been described[38–41]. There is epidemiological evidence that soft water and diets with high Ca/Mg ratios increase vulnerability to cardiovascular disease[42,43]. Higher mortality rates from coronary disease were reported in North America, Finland and Britain (by 15–76%) in comparison to hard water areas[44].

Magnesium lowers systemic vascular resistance[40], decreases platelet aggregation[45], improves myocardial metabolism[46] and decreases mortality in acute myocardial infarction[47]. It is also associated with lower prevalences of cardiovascular disease and sudden death[48–50].

Since magnesium deficiency increases intra-arterial coagulation[51,52], it may have a role in the management of mural thrombi at sites of arterial damage. Moreover,

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local application of high concentrations of magnesium and repeated intravenous infusions of magnesium solutions in animals suppressed thrombus formation at intimal lesions[45,53]. Thus, the antivasospastic[54] and antithrombotic[55–58] effects of magnesium, together with reduction of smooth muscle contraction at the angioplasty site, might minimize ongoing endothelial trauma and platelet deposition in the early hours after the procedure and have a beneficial effect on restenosis.

The current study was designed to evaluate the effectiveness of magnesium in decreasing the rate of restenosis in patients undergoing successful percutaneous transluminal coronary angioplasty.

Methods

STUDY POPULATION AND RANDOMIZATION

The study was designed as an open-labelled randomized and controlled trial. The patients were randomized in a 2:1 fashion to maximize the number of patients treated with intravenous magnesium and to encourage patient enrolment while preserving the statistical advantage of a randomized design. One hundred and forty-eight consecutive patients with either stable or unstable anginal syndrome, who underwent successful coronary angioplasty without complications during the following 24 h (death, acute myocardial infarction, coronary artery bypass grafting, repeat angioplasty or recurrence of angina), were included. After completing the entry angiogram, 98 patients were randomized to receive magnesium intravenously (groups M1 and M2), of whom 49 continued oral supplements of magnesium (group M2). The other 50 patients received no magnesium and served as the control group (group C).

Exclusion criteria included: age <18 or >80 years, unreliable or noncooperative patient, active drug or alcohol abuse, inaccessibility for follow-up, antimalignancy or immunosuppressant therapy, a history of or an existing clinical condition which may lead to hypomagnesaemia (ileal resection, etc.), myocardial infarction within the 5 days preceding the procedure, uncontrolled hypertension or diabetes, severe allergy to contrast media, contraindication to aspirin (active peptic ulcer, allergy, etc.), evidence of chronic renal disease or failure (urolithiasis or serum creatinine >2·0 mg%), systolic arterial blood pressure <90 mmHg, atrioventricular or sinoatrial block of second or third degree, a totally occluded vessel, previous angioplasty in the artery to be dilated or any coronary bypass surgery.

STUDY PROTOCOL

The experimental protocol was approved by the Human Subjects Review Committee of the Sourasky Medical Center and all patients gave written informed consent.

Angioplasty procedures and quantitative analysis

All patients received sublingual nitroglycerin (0·6 mg) before angiography (at baseline and at follow-up angiography) to avoid coronary spasm. Intravenous morphine was administered as required for chest pain. After placement of a vascular sheath, 5000 U heparin was administered intravenously. Once it was determined that a patient was suitable for angioplasty, an additional 10 000 U intravenous heparin was given. Intracoronary nitroglycerin (0·1 mg) was administered during coronary angioplasty to all patients in all groups before performing the angiogram, which was to be analysed following the procedure.

Coronary angioplasty was performed using standard available balloon catheters sized to the normal lumen diameter of the artery to be dilated. Inflation duration and pressure was left to the discretion of the angioplasty operator. Upon completion of the procedure, 10 min were allowed to pass before resuming angiograms of the dilated vessel. The performance of an angiogram of the contralateral vessel for the purpose of assessing the presence or absence of collaterals concluded the session. A final angiogram was carried out 6 months later unless the patient's clinical condition necessitated earlier intervention. If no restenosis was present and the follow-up time was <2 months, the patient was requested to undergo a further coronary angiogram at 6 months.

Qualitative analysis of coronary morphology was obtained by consensus at a blinded review of the angiograms by a panel of three experienced cardiologists. Angiographic projections and cine frames were selected to visualize vessel segments as nearly perpendicular as possible to the imaging axis to minimize shortening, and an end-diastolic frame was selected for analysis. Quantitative analysis of the lesions before and after angioplasty and at follow-up was performed in identical angiographic projections by means of manual edge detection and computer-assisted calculations previously described elsewhere[59]. The catheter was used as an object of known dimensions providing calibration for measurements of coronary vessels. The actual outside diameter of the catheter was manually entered into the computer for calculation of the magnification factor. The diameters for the 7F and 8F Judkins catheters used were 2·25 mm and 2·45 mm, respectively. Successful angioplasty was defined as at least 20% reduction in luminal stenosis diameter of the dilated segment and <50% diameter stenosis immediately after angioplasty. Restenosis was defined as a narrowing >50% at the site of previous dilation measured from the same angiographic view.

Drug regimen

In groups M1 and M2, a bolus of 1 g (4 mmol) magnesium sulphate ($MgSO_4$) was infused intravenously over a 10 min period prior to the initiation of angioplasty, followed by an infusion of 0·04 mmol . min^{-1} throughout the procedure and for 18–20 h thereafter. In group M2, the first oral dose of magnesium hydroxide [$Mg(OH_2)$] 300 mg b.i.d. was initiated 3 h before discontinuation of the intravenous drip. A continuous heparin infusion (begun during angioplasty) was administered for 12 to 18 h and stopped routinely 4 h before the

intravascular sheath was removed. Other individual medications (beta-blockers, anti-arrhythmics, etc.) were continued or administered as warranted. All patients were discharged under a regimen of aspirin 125–250 mg . day^{-1} and diltiazem 90–180 mg . day^{-1}.

Patient management and follow-up

After coronary angioplasty, patients were transferred to the cardiology ward where they were monitored, with vital signs being frequently taken for at least 24 h. When a haematoma developed at the location of the intravascular sheath, heparin was discontinued earlier. A 12-lead electrocardiogram was obtained immediately in the event of any chest discomfort and, if ischaemia was suspected, creatine kinase levels were measured and cardiac catheterization was performed again. Patients were routinely discharged 1 to 2 days after coronary angioplasty. A 12-lead electrocardiogram was recorded upon discharge. Patients were seen at the outpatient clinic at 1, 2, 3, and 6 months for a check-up including laboratory tests, 12-lead electrocardiogram and a tablet count and a new supply of trial medication for those in group M2. Left ventricular function was assessed by two radionuclide studies which the patients underwent 24–72 h following angioplasty and immediately before the follow-up angiogram.

A modified Bruce protocol was performed at 1 week and at 3 and 6 months following angioplasty. Twelve-lead electrocardiographic recordings and blood pressure measurements (cuff) were obtained at rest and at the end of each stage during exercise, at the point of 1 mm ST segment depression, at peak exercise and at 3 and 6 min into the recovery period. A positive exercise test indicative of myocardial ischaemia was defined as horizontal or downsloping ST segment depression ≥ 1 mm (0·1 mV) measured 60 ms after the J point or ST segment elevation in Q wave leads in which there was enough preservation of R waves. The exercise test was stopped in the event of chest pain of moderate severity, or the patient's inability to exercise further. For purposes of final analysis, only those who had at least two comparable stress tests at follow-up were included.

Laboratory tests

These were obtained at baseline and at follow-up clinic visits and included determination and measurement of: full blood chemistry (Beckman Synchron CX3, Beckman Instruments Inc, Brea, CA, U.S.A.) including magnesium levels (determined by atomic absorption spectrophotometry Perkin-Elmer 3100, Norwalk, Connecticut, U.S.A.), full blood count, prothrombin time and partial thromboplastin activity, serum lipidophoresis [determination of total cholesterol, triglycerides and high- (HDL) and low- (LDL) density lipoprotein using a Bohringer-Hitachi 737 analyser, Mannheim, Germany] and urinalysis. In addition, a 24 h collection of urine was obtained each time for the measurement of magnesium, calcium, phosphorous, sodium, potassium and creatinine.

Drug compliance

Patients were questioned about capsule intake at the follow-up visits and requested to collect the empty medication containers and bring them for counting. Compliance was also assessed by subsequent analysis of the fractional excretion of magnesium, calculated as follows: (urine magnesium/plasma magnesium) × (plasma creatinine/urine creatinine) × 100. In addition, blood samples were drawn for magnesium levels immediately before discontinuation of magnesium drip.

DATA REVIEW

The following variables were analysed. Clinical: age, gender, current smoking habits, diabetes mellitus, hypertension, hyperlipidaemia, duration of angina, type of angina or recent myocardial infarction, location of infarction, recent (up to 30 days) use of an intravenous thrombolytic agent, and clinical status during follow-up and upon completion of the study. Angiographic: the pre- and post-angioplasty as well as follow-up features of the dilated artery included the following variables assessed at an end-diastolic frame: dilated artery, proximal mid- or distal stenosis location, single-, double- or triple-vessel disease using the 50% diameter stenosis definition, length of the stenosis, location of the stenosis at a bend >45°, branch point location, the pre-angioplasty presence of contrast staining or a filling defect suggestive of thrombus and collateral circulation to the dilated artery.

REPRODUCIBILITY AND INTEROBSERVER VARIABILITY

The stenosis morphology and quantitation was assessed independently at random by three experienced cardiologists. The reproducibility of these measurements was assessed by complete reanalysis of the angiograms of 50 of the lesions by the same team and a good level of agreement was obtained (Table 1).

STATISTICAL ANALYSIS

All results of continuous variables are expressed as mean ± 1 standard deviation. Differences between continuous variables were compared using the Student's t-test for two groups and multiple analysis of variance for the repeated measurements. Differences between discrete variables were compared by using univariate chi-squared analysis. A value of $P<0·05$ was considered significant.

Results

PATIENT POPULATION

Starting in May 1990 and ending in December 1992, 160 patients were randomized with the 2:1 randomization scheme to receive magnesium. Within this group, 105 were randomized for magnesium and 55 for control. Of these, two patients in each group refused to continue the study shortly after they had given their consent.

Table 1 Reproducibility of selected angiographic parameters in studied segments

Variable	Analysis 1	Analysis 2	r value	*P* value	SEE value
		Interobserver (n=25)			
Normal artery CSA (mm^2)	8·3 ± 3·5	7·8 ± 3·8	0·881	<0·001	1·66
Lesion CSA (mm^2)	2·8 ± 2·1	2·7 ± 2·3	0·967	<0·001	0·54
Lesion % stenosis	44 ± 21	44 ± 23	0·951	<0·001	6·50
		Intra-observer (n=25)			
Normal artery CSA (mm^2)	7·5 ± 3·1	6·9 ± 3·2	0·870	<0·001	1·70
Lesion CSA (mm^2)	2·4 ± 2·0	2·3 ± 2·1	0·964	<0·001	0·52
Lesion % stenosis	45 ± 21	45 ± 24	0·956	<0·001	6·38

CSA=cross-sectional area; SEE=standard error of estimate.

Table 2 Baseline characteristics of three patient groups randomized to control (group C), intravenous magnesium (group M1) and to both intravenous and oral magnesium (group M2)

	Group C (n=46)	Group M1 (n=45)	Group M2 (n=48)	*P* value
Age (years)	57 ± 9	53 ± 9	57 ± 10	ns
Males (%)	83	80	85	ns
Current MI (%)	56	56	42	ns
Previous MI (%)	39	18	27	0·08
Hypertension (%)	26	26	21	ns
Current smokers (%)	55	73	69	ns
Diabetes mellitus (%)	13	21	13	ns
S/P recent thrombolytic treatment (%)	35	31	33	ns
LVEF (%)	50 ± 9	51 ± 8	47 ± 10	ns
Triglycerides ($mg \cdot dl^{-1}$)	164 ± 69	187 ± 78	164 ± 70	ns
HDL cholesterol ($mg \cdot dl^{-1}$)	39 ± 12	39 ± 8	39 ± 9	ns
LDL cholesterol ($mg \cdot dl^{-1}$)	128 ± 36	135 ± 24	139 ± 30	ns
Serum magnesium ($mg \cdot dl^{-1}$)	1·8 ± 0·2	1·9 ± 0·5	1·9 ± 0·3	ns
FE of magnesium (%)	3·2 ± 1·5	3·7 ± 1·8	4·3 ± 1·4	ns
Previous treatment with:				
Nitrates (%)	70	78	56	0·08
Beta-blockers (%)	54	58	51	ns
Calcium blockers (%)	43	44	60	ns
Aspirin (%)	83	78	81	ns
Heparin (%)	10	14	11	ns

FE=fractional excretion; LVEF=left ventricular ejection fraction calculated by isotope ventriculography; MI=myocardial infarction; S/P=status post.

Coronary angioplasty failed in two of the control group and in three of the magnesium group. One patient in the control group underwent urgent coronary bypass (due to coronary dissection) and magnesium infusion was stopped prematurely (after 3 and 5 h from initiation) by mistake in two patients of the magnesium group. Thus, of the remaining 148 patients, 98 patients (66%) were randomized to intravenous magnesium and 50 patients (34%) served as control. Forty-nine patients who received intravenous magnesium continued on a regimen of oral magnesium capsules for 6 months until the final angiogram. A total of 139 patients (94%) completed the study with a follow-up angiogram while nine patients (most of them having had a complete clinical follow-up) refused the final angiogram (they included four patients in the control group, four in group M1 and one in group M2). These nine patients were excluded from the final analysis. The demographic, selected laboratory and angiographic characteristics were similar in the three patient groups and these data are presented in Tables 2 and 3.

EFFECTS OF INTRAVENOUS MAGNESIUM ADMINISTRATION

Intravenous magnesium was well tolerated and no serious adverse effects were observed during administra-

Table 3 Comparison of lesion morphology and angioplastic procedure parameters of three patient groups randomized to control (group C), intravenous magnesium (group M1) and to both intravenous and oral magnesium (group M2)

Variable lesion morphology	Group C (n=46)	Group M1 (n=45)	Group M2 (n=48)	*P* value
No of lesions	53	53	57	ns
Length (mm)	8·7 ± 3·6	8·8 ± 4·1	9·2 ± 3·6	ns
Eccentric lesion (%)	74	79	67	ns
Filling defect	26	21	33	ns
Ectasia (%)	19	21	18	ns
Angioplasty parameters				
Extent of coronary artery diseased (%)				
1 vessel	54	58	69	ns
2 or more	46	42	31	ns
Vessels involved (%)				
Left anterior descending	55	46	51	ns
Circumflex	15	24	34	ns
Right coronary artery	30	30	19	ns
Site (%)				
Proximal	94	94	92	ns
Mid or distal	6	6	8	ns
Left ventricular EF (%)	62 ± 11	62 ± 11	63 ± 11	ns
Visible collaterals (%)	12	21	15	ns
Inflations (n)	4 ± 1	4 ± 2	4 ± 1	ns
Maximal inflation P (atms)	8 ± 2	8 ± 2	8 ± 2	ns
Maximal inflation D (s)	142 ± 107	170 ± 129	167 ± 121	ns
Before PTCA				
Normal artery CSA (mm^2)	7·4 ± 3·8	6·8 ± 3·7	7·5 ± 2·3	ns
Stenotic segment CSA (mm^2)	1·0 ± 0·8	0·8 ± 0·6	1·0 ± 0·6	ns
Segment % stenosis	65 ± 9	67 ± 8	66 ± 9	ns
After PTCA				
Normal artery CSA (mm^2)	7·4 ± 3·9	7·4 ± 3·7	8·4 ± 3·6	ns
Dilated segment CSA (mm^2)	3·90 ± 1·8	4·4 ± 2·4	4·5 ± 1·8	0·09
Segment % stenosis	24 ± 12	24 ± 12	24 ± 12	ns
Dissection (%)	19	11	13	ns

tion. Systolic blood pressure dropped in two patients shortly after initiation of intravenous magnesium. The magnesium infusion was discontinued, fluids were administered and the magnesium infusion was later resumed. The clinical course of these two patients was uneventful thereafter. Flushing was observed in 8/98 (8%) patients, but only two complained about it. In the magnesium groups, serum magnesium levels increased significantly after completion of magnesium infusion (dosage 46–52 mmol over 18–20 h) compared with baseline (from 1·98 ± 0·47 to 3·13 ± 0·55 mg%, $P=0·001$).

In the magnesium-treated groups, coronary angioplasty resulted in an increase from 0·9 ± 0·6 to 4·5 ± 2·1 mm^2 in the cross-sectional area at the site of dilatation and a reduction in percent diameter stenosis from 66 ± 9 to 24 ± 12%. The corresponding improvement in cross-sectional area in the control group was from 1·0 ± 0·8 to 3·9 ± 1·8 mm^2 and from 65 ± 9% to 24 ± 12% in percent diameter stenosis. The increase in the cross-sectional area was more pronounced in the magnesium-treated groups (3·55 ± 2·01 mm^2) than in the control group (2·90 ± 1·63 mm^2, $P=0·031$). The vasodilatory properties were also evident in the reference segment where intravenous magnesium induced an increase of 0·74 ± 2·97 mm^2 in cross-sectional area compared with a minimal change (− 0·02 ± 2·16, $P=0·067$) in the control group (Fig. 1). Magnesium effects were not related to the dilated artery, shape or location of stenosis or to any of the clinical or laboratory parameters examined. It should be noted that in the entire study population, the mean cross-sectional area of the dilated segments which did not restenose (n=115) after angioplasty, was significantly larger than those segments which restenosed (4·5 ± 2·1 mm^2 vs 3·6 ± 1·7 mm^2, $P=0·01$). This was not related to the degree of diameter stenosis after angioplasty which was identical for patients who either did or did not restenose (24 ± 12%).

EFFECTS OF ORAL MAGNESIUM ADMINISTRATION

Oral magnesium was well tolerated with only few side effects. Table 4 demonstrates selected clinical and angiographic parameters in the studied population during follow-up.

Coronary angiography was performed on schedule (6 months) in 33/45 (73%) of patients in group M1, 42/48 (87%) in M2 and 34/46 (74%) in the control population. Thus, although not statistically significant, urgent early catheterization occurred less in group M2 because of recurrence of symptoms. In addition, onset of severe chest pain on days 3 and 4 after angioplasty necessitated re-catheterization in two control patients. Early closure

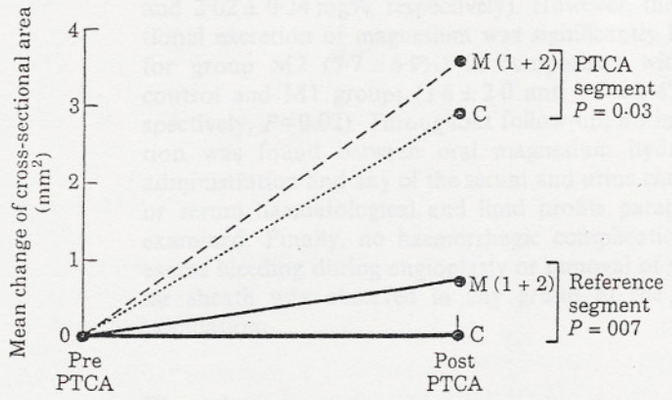

Figure 1 Effects of intravenous magnesium administration on segmental cross sectional area after percutaneous coronary angioplasty. —— C=normal reference segments of control group; —— M1 and M2=normal reference segments of magnesium groups; ···· C=dilated segments of control group; – – – – M1 and M2= dilated segments of magnesium groups [n for C=53, n for M (1+2)=110].

Table 4 Clinical and angiographic follow-up of the three patient groups randomized to control (group C), intravenous magnesium (group M1) and to both intravenous and oral magnesium (group M2)

Variable	Group C (n=46)	Group M1 (n=45)	Group M2 (n=48)	*P* value
No of lesions	53	53	57	ns
Follow-up (weeks)	22 ± 8	22 ± 5	24 ± 5	ns
Early angiography (%)	26	26	13	ns
Lipid lowering drugs (%)	9	10	9	ns
Symptoms (%)	46	56	36	ns
Exercise stress test (n)	39	37	43	—
Chest pain (%)	15	14	7	ns
ECG changes (%)	18	22	23	ns
Both (%)	5	5	5	ns
Undetermined (%)	8	11	12	ns
Silent restenosis (%)	19	17	22	ns
LVEF (%)	54 ± 8	55 ± 8	51 ± 8	ns
Dilated segment CSA (mm²)	2·3 ± 1·8	2·6 ± 3·0	2·7 ± 1·8	ns
Segmental % stenosis	44 ± 27	41 ± 23	39 ± 25	ns
Restenosis (no of lesions with >50% stenosis) (%)	38	26	25	ns
Recurrent treatment				
PTCA (%)	19	27	25	ns
CABG (%)	12	2	0	ns

CABG=coronary artery bypass grafting, all others as for Tables 1 and 2.

of the dilated segment was demonstrated, and these patients were referred for emergency coronary bypass surgery. Four more control patients and one group M1 patient were referred for surgery during follow-up, in comparison to none of the patients who received oral magnesium.

The rate of restenosis (defined as >50% reduction in the luminal diameter at site of angioplasty) tended to be lower in groups M1 and M2 (14/53: 26% and 14/57: 25%, respectively) compared with group C (20/53: 38%). This difference was not statistically significant. However, if both magnesium-treated groups in combination are compared to the control group, a trend toward a lower occurrence rate of restenosis is noticed for those who received intravenous magnesium (28/110, 25%), in comparison with the control group (20/53, 38%), $P=0·10$.

GENERAL EFFECTS OF MAGNESIUM AND PATIENT COMPLIANCE

Oral administration of magnesium was well tolerated and no adverse gastrointestinal effects were reported throughout follow-up. Interestingly, more patients in group M2 reported improved 'well-being' than those not receiving oral magnesium.

At the end of the study, no difference was observed in serum magnesium levels in group M2 (2·04 ± 0·21 mg%) compared with the control and M1 groups (1·97 ± 0·18

and 2·02 ± 0·24 mg%, respectively). However, the fractional excretion of magnesium was significantly higher for group M2 (5·7 ± 6·9%) in comparison with the control and M1 groups (3·6 ± 2·0 and 3·1 ± 1·4%, respectively, $P=0·02$). Throughout follow-up, no interaction was found between oral magnesium hydroxide administration and any of the serum and urine chemical or serum haematological and lipid profile parameters examined. Finally, no haemorrhagic complications or excess bleeding during angioplasty or removal of vascular sheath was observed in any group of the study population.

Discussion

WHY MAGNESIUM?

There is continued improvement in both initial success rates of coronary angioplasty and in the introduction of new devices to complement balloon angioplasty, in addition to a reduced initial complication rate. Nevertheless, a physiologically significant stenosis recurs within 6 months at the site of angioplasty in approximately 30–40% of patients. This rate of restenosis has remained constant despite multiple pharmacological approaches directed towards the prevention of vascular responses which underlie restenosis[60–62]. Warfarin, for example, was initiated to affect the haemostatic mechanism, aspirin to affect thrombocytes and calcium channel blockers to modify mechanical factors (vasospasm) and cellular proliferation. Magnesium has unique characteristics: it is a vasodilator [38–40] and has a profound effect on haemostasis[45].

In vitro studies have shown that magnesium deficiency constricts isolated dog[40] and human[63] coronary arteries and that magnesium repletion dilates them. Reduction of Mg^{+2} in smooth muscle preparations increases vascular tone and potentiates the pressor action of angiotensin II[64]. In addition, it was shown that increased concentration of extracellular Mg^{+2} reduced platelet aggregation and the release reaction[65]. Some authors have suggested that magnesium deficiency might adversely influence the healing and reendothelialization of vascular injuries[66]. This could contribute to thrombosis[45] and, therefore, to excessive subintimal proliferation of smooth muscle cells[48,67], changes that could lead to the development of atheromatous plaques. Thus, the antithrombotic and antivasospastic effects of magnesium were expected to improve the problem of restenosis.

DOES MAGNESIUM PROTECT AGAINST RESTENOSIS?

In this study, the overall segmental restenosis rate was 29·4% (48/163 segments). Patients treated with intravenous magnesium tended to have a lower rate of restenosis (28/110 segments) compared to the control group (20/53 segments, $P=0·10$. This distinction in our study was based on a definition of restenosis as the stenosis being greater than 50% of the diameter. As previously shown in animals, this degree of stenosis is functionally and physiologically relevant and causes blunting of coronary flow reserve[68,69].

Both coronary spasm and elastic recoil, which occurs immediately after angioplasty at the angioplasty site[70], have been associated with recurrent stenosis, since the early days of coronary angioplasty[35]. It was shown[71] that 4 h after coronary angioplasty, transient spontaneous vasoconstriction of the dilated and distal segments occurs, and to a level so intense that the cold pressor test does not cause any further constriction. These abnormalities resolve within 8 days of coronary angioplasty. It was demonstrated also that ergonovine-induced coronary artery vasoreactivity at the angioplasty site was associated with more than twice the recurrent stenosis rate[72]. Stretching of the coronary artery and elastic recoil of the dilated segments as a mechanism involved in angioplasty were recently demonstrated by intravascular ultrasound[73]. Despite this firm correlation, several randomized trials of calcium antagonists given after coronary angioplasty have failed to demonstrate a decrease in recurrent stenosis, either because these drugs are not powerful enough to change local coronary tone or because the spasm is merely a marker for a lesion likely to recur, i.e. spasm is associated with recurrence but does not cause it.

We have shown that magnesium exerted a marked additive coronary vasodilatory effect (Fig. 1) on the vessels already dilated by pre-angioplasty administration of nitrates. This response was noticed proximally and distally to the angiographically narrowed segments but was more pronounced at the angioplasty site. Thus, the injured dilated segment responds to the vasoreactive stimuli of magnesium in a profound manner. Given the significantly greater luminal diameter achieved post-angioplasty in the magnesium groups, one could suppose that a more aggressive approach was taken in this treatment arm, although as is obvious from Table 3, no difference in the technical approach was exerted between the groups. It is possible that the addition of a fourth arm to the study in which patients receive magnesium after dilatation to demonstrate the net vasodilator effect of magnesium perhaps would be optimal. Nevertheless, prevention of elastic recoil and the increased cross-sectional area of the dilated segments may be the underlying mechanism for the tendency towards a lower restenosis rate in the magnesium-treated patients (25%) compared to controls (38%).

Magnesium taken orally did not result in any additive beneficial effect throughout follow-up. Presumably, only the relatively high plasma levels attained with intravenous administration are of value. These blood levels could not be attained during a 6-month period of oral treatment. This conclusion is corroborated by the small fraction absorbed and rapid clearance of the intravenous magnesium after cessation of infusion.

In this study, the changes observed in the dilated vessels during the acute and the long-term phase of magnesium administration did not correlate statistically with lesion characteristics or with, age, sex, smoking,

diabetes, angina duration and severity, and previous myocardial infarction. This contrasts with findings reported by others where associations between patient-related variables and restenosis were described[4,6,11,30,31,74]. No patient or lesion characteristics predicted which dilated segment is susceptible to restenosis.

Although the rate of restenosis was 34% lower for the magnesium-treated group compared with control (25% vs 38%), it was not statistically significant. This beneficial trend of magnesium to prevent acute recoil and late (within 6 months) restenosis is encouraging. Moreover, the inverse relationship we found between the tendency to restenosis in the whole study population and the size of the cross-sectional area achieved after angioplasty further emphasize the importance of reaching a maximally wide lumen of the vessel, in which the coronary vasodilatatory properties of magnesium may play an important role.

HOMEOSTASIS OF MAGNESIUM

Over the past decade, several reviews have focused on the relevance of magnesium in cardiac disease[49,67,75]. Magnesium, the fourth most abundant metal in living organisms and the second most prevalent intracellular cation, is distributed in three major compartments in the body: 65% in the mineral phase of the skeleton, 34% in the intracellular space, and only 1% in the extracellular fluid[76].

Magnesium concentration in various organs[77–79] does not correlate with serum magnesium level, and normal serum magnesium levels may exist in the presence of low tissue levels[38,80,81].

The recommended daily allowance of magnesium for a healthy adult is 5 mg . kg^{-1}[67]. Urinary excretion is approximately 3 to 5% of filtered magnesium. With a rise in magnesium loading, the fraction of filtered magnesium excretion increases, as was also demonstrated in our study, during oral supplementation. On the other hand, a decreased concentration of serum magnesium, which occurs when a low-magnesium diet is ingested for a few days, leads to the near disappearance of magnesium from the urine.

Dietary surveys have shown that not even the modest, officially recommended magnesium intakes are met by most Americans and Canadians[82]. This causes concern when considering the straightline correlation of increased incidence of ischaemic heart disease death rates in countries with high dietary Ca/Mg ratios[83,84].

SAFETY OF INTRAVENOUS MAGNESIUM ADMINISTRATION DURING AND AFTER ANGIOPLASTY

This study established the safety of magnesium administration during coronary angioplasty and the following 20 h. The entire dose (11·8–13·0 g) was administered for 18 to 20 h and was well tolerated. Blood magnesium did not increase to toxic levels nor were any haemodynamic or electrocardiographic abnormalities noted. Upon cessation of intravenous administration, no rebound tachycardia, hypertension or chest discomfort were observed. No excessive bleeding through venous or arterial access sites was observed during infusion or at the time of intravascular sheath removal. However, although one of the presumed effects of magnesium is to decrease platelet aggregation, with this being a clinico-angiographic study, no platelet function or other coagulation test was performed (except for thrombin time and partial thromboplastin time, the results of which were normal for the whole patient population throughout the study).

CLINICAL IMPLICATION AND CONCLUSIONS

Intravenous administration of magnesium in patients undergoing coronary angioplasty is feasible and safe when applied to patients with systolic blood pressure >90 mmHg. Adverse effects are seldom encountered and can easily be treated by the administration of fluids and temporary cessation of magnesium infusion. The rationale for the use of intravenous magnesium as adjuvant treatment during percutaneous coronary angioplasty seems to be promising. Oral administration of 600 mg magnesium per day does not have an additive effect on restenosis, but may result in an improved clinical course. Large-scale studies with a higher dose of magnesium applied during angioplasty and for a longer period thereafter seems warranted.

Appendix

THE ICHILOV MAGNESIUM STUDY GROUP (CO-INVESTIGATORS)

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