Magnesium as a neuroprotectant in cardiac surgery: A randomized clinical trial

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Read at the Eighty-fifth Annual Meeting of The American Association for Thoracic Surgery, San Francisco, Calif, April 10-13, 2005.

Received for publication April 4, 2005; revisions received Oct 20, 2005; accepted for publication Nov 21, 2005.

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J Thorac Cardiovasc Surg 2006;131:853-61
0022-5223/\$32.00

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doi:10.1016/j.jtcvs.2005.11.018

Objective: We sought to evaluate magnesium as a neuroprotectant in patients undergoing cardiac surgery with cardiopulmonary bypass.

Methods: From February 2002 to September 2003, 350 patients undergoing elective coronary artery bypass grafting, valve surgery, or both were enrolled in a randomized, blinded, placebo-controlled trial to receive either magnesium sulfate to increase plasma levels 1½ to 2 times normal during cardiopulmonary bypass (n = 174) or no intervention (n = 176). Neurologic function, neuropsychologic function, and depression were assessed preoperatively, at 24 and 96 hours after extubation (neurologic) and at 3 months (neuropsychologic, depression). Neurologic scores were analyzed using ordinal longitudinal methods, and neuropsychologic and depression inventory data were summarized by principal component analysis, followed by linear regression analysis using component scores as response variables.

Results: Seven (2%) patients had a postoperative stroke, 2 (1%) in the magnesium and 5 (3%) in the placebo group ($P = .4$). Neurologic score was worse postoperatively in both groups ($P < .0001$); however, magnesium group patients performed better than placebo group patients ($P = .0001$), who had prolonged declines in short-term memory and reemergence of primitive reflexes. Three-month neuropsychologic performance and depression inventory score were generally better than preoperatively, with few differences between groups ($P > .6$); however, older age ($P = .0006$), previous stroke ($P = .003$), and lower education level ($P = .0007$) were associated with worse performance.

Conclusions: Magnesium administration is safe and improves short-term postoperative neurologic function after cardiac surgery, particularly in preserving short-term memory and cortical control over brainstem functions. However, by 3 months, other factors and not administration of magnesium influence neuropsychologic and depression inventory performance.

Neurologic and neuropsychologic dysfunction are major causes of mortality and morbidity after cardiac surgery^{1,2} and are associated with prolonged hospital stay and use of intermediate- or long-term care facilities.³ Neuropsychologic dysfunction is evident in 50% to 80% of patients at hospital discharge,

Abbreviations and Acronyms

CABG	= coronary artery bypass grafting
CPB	= cardiopulmonary bypass
NMDA	= <i>N</i> -methyl-D-aspartate
WPNS	= Western Perioperative Neurologic Scale

20% to 50% at 6 weeks, and 10% to 30% at 6 months postoperatively⁴⁻⁷; thus, early neuropsychologic dysfunction is implicated in late cognitive deterioration.⁸

Although measures to prevent brain injury have been studied,^{9,10} strategies to minimize injury, as advocated for stroke victims,¹¹ have received less attention. After an ischemic neurologic insult, glutamate is released, activating *N*-methyl-D-aspartate (NMDA), leading to increased sodium and calcium ion conduction across cell membranes and exacerbation of neurologic injury. Magnesium sulfate, a noncompetitive NMDA antagonist with clinical benefit in acute stroke,¹¹ has not been investigated as a neuroprotectant in cardiac surgery. Therefore, we conducted a single-institution randomized clinical trial to determine whether increased magnesium during cardiac surgery and in the first 24 hours postoperatively is neuroprotective.

Patients and Methods**Study Design**

From February 2002 to September 2003, 350 patients (mean age 64 ± 12 years) undergoing elective on-pump coronary artery bypass grafting (CABG), valve surgery, or combined CABG and valve surgery were enrolled in a randomized, blinded, placebo-controlled clinical trial at Cleveland Clinic to receive either magnesium to increase plasma levels to between 3.6 and 4.8 mg · dL⁻¹ during the operation and for 24 hours thereafter (magnesium group, *n* = 174)¹²⁻¹⁴ or no intervention (placebo group, *n* = 176; Appendix E1). Patients with preoperative atrial fibrillation or renal impairment were excluded (Figure E1). Patients were randomized 1:1 at operation, with a block size of 2 and 4, independently for each of 11 operating rooms. Preoperative and operative characteristics of the 2 groups were well balanced (Table 1). The Pharmacy Department (J.P.) prepared study medications, the anesthetic team administered the 24-hour infusion, and the perfusion teams dosed the cardiopulmonary bypass (CPB) circuit. All were blinded to the study except perfusion teams, who were required to monitor and maintain magnesium levels during CPB.

This study was approved by the institutional review board, and patients provided written informed consent.

Magnesium Dosing

Patients randomized to the magnesium group received 780 mg (32 mmol) of MgSO₄ in 100 mL of normal saline intravenously over 15 minutes during anesthesia induction, followed by 3160 mg (130 mmol) in 100 mL of normal saline over 24 hours; the CPB circuit was primed with MgSO₄ to a concentration of 3.6 mg · dL⁻¹. The plasma magnesium level was measured every 15 minutes during CPB. If it decreased to less than 3.6 mg · dL⁻¹,

MgSO₄ was administered to achieve levels between 3.6 and 4.8 mg · dL⁻¹ (Figure 1).

Patients randomized to the placebo group received normal saline intravenously in the CPB circuit and over 24 hours in bags and syringes indistinguishable from those used for the magnesium group.

Conduct of Operations

Anesthesia was induced intravenously with a combination of midazolam, 3 to 5 mg; fentanyl, up to 0.25 mg; and sodium thiopental, 3 to 5 mg · kg⁻¹ (in patients with mitral or aortic valve stenosis or left ventricular ejection fraction $\leq 30\%$, etomidate, 0.3-0.5 mg · kg⁻¹, was used instead of sodium thiopental). It was maintained with inhaled isoflurane, 1% to 2%, supplemented with fentanyl up to 1 mg.

CPB was instituted with a conventional roller-pump system and vacuum-assisted venous return¹⁵ using a heparin-coated circuit that included a 25- μ m arterial filter. Arterial flow rate was 2.0 to 2.4 L · min⁻¹ · m⁻², with mean arterial pressure maintained between 50 and 70 mm Hg. Body temperature was either kept at 37°C or allowed to drift to 32°C to 34°C. Blood-gas management was by alpha-stat strategy.

Assessments

Safety. Postoperative mortality and morbidity data were collected by research nurses and entered into the Cardiovascular Information Registry concurrently with patient care. This registry is approved for use in research by the institutional review board.

Neurologic assessment. The Western Perioperative Neurologic Scale (WPNS)¹⁶ was used to assess neurologic performance preoperatively and at 24 and 96 hours after extubation. Fourteen tests were performed by an individual certified to administer them (S.K.B.) and were grouped into 4 domains:

- Mentation (4 tests): level of consciousness; orientation to time, place, and person; short-term memory; and speech
- Motor function (5 tests): motor strength in right and left upper and lower limbs, cranial nerves (facial motor function)
- Sensory (4 tests): sensation in right and left upper and lower limbs
- Cerebellar function (4 tests): movement, gait, reflexes, primitive reflexes (glabellar tap, snout response, suck response, palmomental reflex, grasp reflex). For clinical reasons, gait was not assessed 24 hours after extubation.

Neuropsychologic and depression assessment. A neuropsychologic assessment battery and depression inventory were administered by a neuropsychologist (R.I.N.) or neuropsychology technician (E.W.) preoperatively and 3 months postoperatively. Tests included the following:

- Hopkins Verbal Learning Test (HVLT; total, discrimination index, and delayed recall) to measure memory
- Controlled Oral Word Association Test (COWAT) and Boston Naming Test (BNT) to measure word fluency and confrontation naming
- Digit Symbol and Symbol Search, subtests of the Wechsler Adult Intelligence Scale, third edition, to produce the Pro-

TABLE 1. Patient characteristics and procedure details

Characteristic	Magnesium group (n = 174), No. (%)	Placebo group (n = 176), No. (%)	P value
Demography			
Female	41 (24)	39 (22)	.8
Age (y), mean $\pm$ SD	64 $\pm$ 12	64 $\pm$ 13	.7
Body mass index (kg $\cdot$ m ⁻²)	29 $\pm$ 5	30 $\pm$ 6	.4
Education			
Years	14 $\pm$ 3	14 $\pm$ 3	.3
WRAT-3 reading score			
Raw	46 $\pm$ 6	47 $\pm$ 6	.5
Grade level	10.4 $\pm$ 2.9	10.5 $\pm$ 2.8	.6
Standardized (Z) score*	-0.8, 0.2, 0.87	-0.86, 0.2, 0.87	>.9
Preoperative neurologic morbidity			
CVA	1 (0.6)	5 (3)	.2†
TIA	10 (6)	10 (6)	>.9
Syncope	13 (7)	12 (7)	.8
Cardiac morbidity			
Previous MI	69 (40)	62 (35)	.4
Atrial fibrillation	4 (2)	3 (2)	.7†
Previous cardiac operation	35 (20)	33 (19)	.7
NYHA class			.07
I	44 (25)	42 (24)	
II	101 (58)	118 (67)	
III	22 (13)	15 (9)	
IV	7 (4)	1 (0.6)	
Aortic regurgitation (moderate or greater)	50 (29)	38 (22)	.1
Aortic stenosis (moderate or greater)‡	36 (21)	57 (34)	.01
Mitral regurgitation (moderate or greater)§	68 (40)	73 (42)	.7
Mitral stenosis (moderate or greater)	2 (1.1)	5 (3)	.4†
Coronary disease			
LMT stenosis (>50%)¶	23 (14)	27 (16)	.6
LAD stenosis (>70%)#	89 (53)	87 (51)	.7
LCx stenosis (>70%)#	77 (46)	63 (37)	.09
RCA stenosis (>70%)¶	79 (48)	84 (49)	.7
Three-system disease	77 (46)	67 (39)	.2
Noncardiac comorbidity			
Hypertension	120 (69)	126 (72)	.5
Diabetes mellitus	37 (21)	39 (22)	.8
Peripheral vascular disease	77 (44)	59 (34)	.04
Carotid disease	69 (40)	54 (31)	.08
COPD	30 (17)	23 (13)	.3
History of smoking	93 (53)	92 (53)	.9
Procedure			
Isolated CABG	71 (41)	57 (32)	.1
CABG + valve procedure	44 (25)	54 (31)	.3
Aortic valve repair	5 (3)	2 (1)	.3†
Aortic valve replacement	56 (32)	74 (42)	.06
Mitral valve repair	44 (25)	45 (26)	.1
Mitral valve replacement	8 (5)	12 (7)	.4
Tricuspid valve repair	4 (2)	6 (3)	.8†
Support			
Perfusion time (min)	92 $\pm$ 35	93 $\pm$ 36	.8
Ischemic time (min)	74 $\pm$ 28	74 $\pm$ 31	>.9

SD, Standard deviation; WRAT-3, Wide Range Achievement Test, third edition; CVA, cerebrovascular accident; TIA, transient ischemic attack; MI, myocardial infarction; NYHA, New York Heart Association; LMT, left main trunk; LAD, left anterior descending coronary artery; LCx, left circumflex coronary artery; RCA, right coronary artery; COPD, chronic obstructive pulmonary disease; CABG, coronary artery bypass grafting. *15th, 50th, and 85th percentiles. †Fisher's exact test. ‡Six unknown in each group. §Two unknown in magnesium group, 1 unknown in placebo group. ||Three unknown in magnesium group, 4 unknown in placebo group. ¶Eight unknown in magnesium group, 6 unknown in placebo group. #Seven unknown in magnesium group, 6 unknown in placebo group.

Figure 1. Perioperative magnesium levels. *Open circles* (placebo group) and *filled circles* (magnesium group) are mean values within different time intervals. *Solid lines* are evolution of predicted mean values over time for each group.

cessing Speed Index, and Trail-Making Test (Forms A and B) to measure timed visual-motor speed

- Grooved Pegboard (for dominant and nondominant hand) to measure timed manual dexterity
- Beck Depression Inventory, second edition, to measure depressive symptomatology.

Level of education and intelligence were determined preoperatively by total completed years of education and reading ability, as assessed by the Wide Range Achievement Test (WRAT, third edition).

Two hundred seventy-three (78%) patients completed the 3-month neuropsychologic reassessment (the study was powered for 300 patients). Patient and procedure variables of those who were assessed were well balanced between the magnesium and placebo groups (Table E1), but those who refused reassessment were more likely to be female or to have had noncardiac surgery during follow-up (Table E2). Five (1%) patients died before reassessment.

Data Analysis

All analyses were performed with SAS statistical software (version 8.2; SAS Institute, Inc, Cary, NC).

Neurologic assessment. Longitudinal ordinal logistic regression was used to analyze 24- and 96-hour WPNS scores, with preoperative score, randomization group, and time of testing forced into the model as previously described.¹⁷ Only a few patients had low scores, and therefore scores were collapsed into 3 categories to meet the proportional odds assumption of the model.

Neuropsychologic assessment. Twelve test scores (Digit Symbol and Symbol Search were used instead of the Processing Speed Index) were available for analysis at both preoperative and postoperative assessment. WRAT-3 reading score, preoperative scores, and randomization group, were included in all analyses.

Because neuropsychologic tests are somewhat correlated, we used principal component analysis to condense the information into a few

TABLE 2. Safety

Hospital morbidity	Magnesium group (n = 174), No. (%)	Placebo group (n = 176), No. (%)	P value
Return to OR for bleeding	4 (2)	3 (2)	.7*
Packed RBC transfusion (units)			.6
0	108 (62)	118 (67)	
1	16 (9)	16 (9)	
2	23 (13)	14 (8)	
3	11 (6)	11 (6)	
4	7 (4)	8 (5)	
≥5	9 (5)	9 (5)	
Myocardial infarction	0 (0)	1 (0.6)	1*
Renal insufficiency	0 (0)	0 (0)	
Respiratory insufficiency	5 (3)	3 (2)	.5*
Septicemia	3 (2)	4 (2)	1*
Atrial fibrillation	57 (33)	64 (36)	.5
Length of stay (d)			
ICU†	1, 2, 3	1, 2, 3	>.9
Postoperative†	5, 6, 9	5, 6, 9	>.9
Hospital†	5, 7, 11	5, 7, 10	.3

OR, Operating room; RBC, red blood cells (includes both intraoperative and postoperative transfusions); ICU, intensive care unit. *Fisher's exact test.

†15th, 50th, and 85th percentiles.

uncorrelated variables (components), one of which was the depression inventory by itself, with minimal loss of information.¹⁸ We applied this technique (PROC PRINCOM, SAS) to preoperative test scores of all 350 patients, identifying 4 principal components that accounted for 72% of total variation (Table E3), and used the component coefficients to calculate preoperative component scores and those at 3-month follow-up. We then performed multivariable linear regression using component scores as response variables to assess the effect of magnesium. All preoperative and intraoperative variables (Table 1) were considered in these analyses, along with interaction between age and randomization group.

Other variables. Plasma magnesium levels were measured preoperatively, during CPB, at 2 to 6 AM on postoperative day 1, and at 24 ± 6 hours. During CPB, blood flow, mean arterial pressure, temperature, and hematocrit levels were recorded. Temporal trends of these variables were similar for each group ($P > .08$). In addition, Cardiovascular Information Registry personnel collected preoperative, operative, and postoperative data concurrently with patient care.

Presentation. Continuous variables are presented as mean ± standard deviation and as 15th, 50th (median), and 85th percentiles when values were skewed; comparisons were made using the Wilcoxon rank-sum test. Categorical data are described using frequencies and percentages; comparisons were made using the χ^2 test or Fisher's exact test when the frequency was less than 5. Actual and estimated percentages of patients with the highest neurologic scores are presented with 68% confidence limits, equivalent to ±1 standard error.

Figure 2. Overall and domain scores of the Western Perioperative Neurologic Scale preoperatively and at 24 and 96 hours after extubation in the magnesium (filled circles) and placebo (open circles) groups. Shown are percentages of patients reaching the maximum overall and domain scores (scores indicated on vertical axes). Unadjusted percentages with 68% confidence bars are given for patients with complete scores. **A,** All 16 neurologic tests. **B,** Mentation (5 tests). **C,** Motor (4 tests). **D,** Sensory function (4 tests). **E,** Cerebellar function (3 tests).

TABLE 3. Factors associated with better neurologic performance (higher Western Perioperative Neurologic Scale Scores)*

Factor	Coefficient $\pm$ SD	P value
Magnesium group	1.6 $\pm$ 0.42	.0001
Higher preoperative score	3.0 $\pm$ 0.40	<.0001
Time†	−2.5 $\pm$ 4.5	.5
Time and magnesium group†	−21 $\pm$ 10	.04
Younger‡	−0.51 $\pm$ 0.19	.007
Shorter myocardial ischemic times§	−0.79 $\pm$ 0.42	.06
Lower bilirubin	−0.36 $\pm$ 0.20	.07
Lower BUN	−0.81 $\pm$ 0.46	.08

SD, Standard deviation; BUN, blood urea nitrogen. *Higher score is better. †(1/time), inverse transformation, where time is the interval between 24- and 96-hour assessments. ‡Exp(age/50), exponential transformation. §Ln(myocardial ischemic time), logarithmic transformation. ||Ln(BUN), logarithmic transformation.

Results

Safety

There were 2 (1%) hospital deaths, 1 in each group ($P = 1$). However, 5 (1%) patients died within their 3-month enrollment, none from stroke or neurologic injury. Mortality was similar in the magnesium (1 death) and placebo (4 deaths) groups ($P[\log \text{rank}] = .2$), as were other in-hospital morbidities, including transfusion requirements (Table 2). Length of intensive care unit, postoperative, and total hospital stays were similar.

Neurologic Assessment

Seven (2%) patients had a postoperative cerebrovascular accident, 2 (1%) in the magnesium group and 5 (3%) in the placebo group ($P[\log \text{rank}] = .3$). Preoperative WPNS scores were similar in both groups (Figure 2).

WPNS scores decreased by 24 hours postoperatively in both groups ($P < .0001$); by 96 hours, the magnesium group had recovered nearly to preoperative performance, but the placebo group had not ($P = .003$). Thus, neurologic decline or death from neurologic injury (which did not occur within 3 months in either group), the study's composite primary end point, was less at 96 hours in the magnesium group than the placebo group ($P = .01$).

Other factors associated with improved WPNS were higher preoperative score, younger age, and shorter ischemic time (Table 3).

Of the WPNS domains, sensory and motor functions appeared to be relatively unaffected in the magnesium ($P > .3$) and placebo ($P = .07$) groups. The mentation score (consciousness, orientation, short-term memory, and speech) decreased in both groups by 24 hours ($P < .0005$); by 96 hours, it had returned to preoperative levels ($P = .1$) in the magnesium group but remained depressed in the placebo group. Cerebellar function (movement, gait, re-

Figure 3. Estimated percentage of patients with total cerebellar function score of 9 (best possible score) as a function of age. The nomogram represents a solution of the multivariable equation in Table 4 (date of operation set to June 2003). Dashed lines are estimated 68% confidence intervals.

flexes, and primitive reflexes) remained at preoperative levels in the magnesium group ($P > .5$), but decreased in the placebo group by 24 hours and was not restored by 96 hours ($P < .002$); the difference between groups was unlikely to be due to chance ($P = .003$). Decrease in cerebellar function score was mainly due to reappearance of primitive reflexes, such as snout and suck responses and grasp reflexes (see the Methods section). The older the patient in the magnesium group, the better the cerebellar function score; in contrast, the older the patient in the placebo group, the worse the score (Figure 3 and Table 4).

Neuropsychologic and Depression Assessment

Neuropsychologic scores in multiple domains and depression inventory scores were generally somewhat better 3 months postoperatively than preoperatively because of familiarity with test procedures during retesting (Figure E2 and Table E4), and changes were similar between groups ($P > .6$). However, older patients ($P = .006$) and those with previous stroke ($P = .003$), extensive coronary disease ($P = .02$), or lower education level ($P = .0007$) performed worse at 3-month follow-up than preoperatively (Tables E5-E8).

Discussion

There is great interest in developing strategies to prevent neurologic dysfunction in patients undergoing cardiac surgery.^{1,2,19-21} However, rather than focusing on prevention of neurologic insult, this study addresses the issue of minimizing injury from such insults. To our knowledge, magnesium has not been used previously as a neuroprotectant in cardiac surgery. The rationale for its use is that neuronal damage

TABLE 4. Factors associated with better cerebellar function score

Factor	Coefficient $\pm$ SD	P value
Magnesium group	-3.5 ± 1.7	.04*
Higher preoperative cerebellar score	2.4 ± 0.83	.003
Time†	0.00001 ± 0.0013	>.9
Older age in magnesium group‡	1.1 ± 0.51	.04
Younger age in placebo group§	-0.54 ± 0.27	.04
More recent date of operation	-0.21 ± 0.12	.07

SD, Standard deviation. *Because of interaction terms, this value does not represent group difference. Rather, the difference is age related (Figure 3). †Interval between 24- and 96-hour assessments. ‡Interaction: magnesium group $\cdot \exp(\text{age}/50)$. §Interaction: placebo group $\cdot \exp(\text{age}/50)$. || $[1/(\text{interval from 1/1/2002 to date of operation})]$, inverse transformation.

after injury is attributable to release of glutamate from neurons and glia,²² and magnesium is a noncompetitive NMDA receptor antagonist.²³ Glutamate receptor modulation has shown promise in animal and clinical studies. Remacemide, an NMDA antagonist, reduced neuropsychologic dysfunction after cardiac surgery but at the cost of important side effects (ataxia, dizziness, drowsiness, fatigue, headache, nausea, and abdominal pain).²⁴ Magnesium shows no such toxicity. In addition, magnesium modulates the ischemic brain injury cascade at other levels. These include abilities to inhibit neurotransmitter release²³ and cerebral vasospasm,²⁵ antagonize voltage-gated calcium ion channels,²⁶ and attenuate production of reactive oxygen species.²⁷

During CPB, serum magnesium levels might be depleted, and hypomagnesemia can persist for 24 hours postoperatively.²⁸ In animal models, brain magnesium deficiency before injury exacerbates functional deficits,²⁹ and limiting postinjury magnesium decline attenuates functional deficit after brain injury.³⁰ The level of serum magnesium required for neuroprotection is not well established, but animal studies indicate that a concentration of $3.62 \text{ mg} \cdot \text{dL}^{-1}$ reduces histologic infarct volume in ischemic brain injury.¹² In acute stroke, increasing serum magnesium levels to 1½ to 2 times normal is beneficial.¹¹

Key Findings

Safety. No adverse effects of elevated magnesium levels were observed in this study.

Neurologic assessment. The primary end point of the study was achieved, with the better overall neurologic function in the magnesium group unlikely to be due to chance. Interestingly, the WPNS demonstrated that magnesium reduced cerebellar complications, especially return of primitive reflexes. After perioperative stroke or subtle brain injury, these primitive reflexes reappear in up to 39% of patients.⁴ Their reappearance is considered a sensitive marker of brain injury in “silent” brain ischemia,³¹ advanced human

immunodeficiency disease,³² neuropsychiatric disorders,³³ Alzheimer disease (where it is a poor prognostic sign),^{34,35} and after cardiac surgery,^{4,36} particularly in the elderly.³⁷ The phenomenon is complex and perhaps best interpreted as nonspecific loss of cortical control over brainstem functions.³⁸

Mentation, which includes short-term memory, was better preserved in patients receiving magnesium, with older patients benefiting more than younger ones. This might reflect greater brain reserve in younger patients.

We hypothesize, without supporting data, that rehabilitation of cardiac surgical patients might be enhanced if these subtle but sensitive and important deficits are reduced.

Neuropsychologic and depression assessment. Magnesium did not influence neuropsychologic function or depressive symptomatology 3 months postoperatively, but other systemic factors, including older age, did. Neuropsychologic dysfunction and depression after cardiac surgery are highly variable. Timing of assessment is crucial, with more variability in dysfunction observed early after surgery. In this study, neuropsychologic performance was generally better at 3 months than preoperatively, probably a manifestation of the test–retest phenomenon.³⁹

Limitations

Typical of randomized clinical studies, only a small fraction of this center's cardiac surgical population was included (Figure E1), which might introduce bias. A major deterrent to participation was need to return for 3-month follow-up neuropsychologic and depressive symptom testing. Also, because pretesting was required, patients undergoing emergency and urgent operations were not included; such patients are particularly vulnerable to neurologic injury. Recognizing this limitation, we designed the study to include not only patients undergoing CABG, as has been the case in most studies of neurologic injury after cardiac surgery,³⁻⁸ but also patients undergoing heart valve surgery, in whom opportunity for neurologic injury from particulate matter might be even greater. CABG and valve surgery account for the majority of cardiac operations performed.

Another limitation is that neuropsychologic assessment was made only at 3 months and not earlier (when it is less stable) or longitudinally over years.⁸ Despite prior agreement, a substantial number of patients refused postoperative neuropsychologic testing, which could introduce bias (Table E2). Neurologic assessment was made by using a formal, sensitive, and validated instrument.¹⁶ However, neurologic assessment was not performed 3 months postoperatively. Thus, we do not know whether patients who manifested neurologic abnormalities before hospital discharge improved.

Finally, the study was designed to discover a possible short-term neuroprotective effect of magnesium elevation.

It was not designed to assess duration of the effect or effects on convalescence or long-term outcomes.

Conclusions

Increasing serum magnesium levels during CPB and for 24 hours thereafter is safe. It offers short-term neurologic benefits, particularly in preserving short-term memory and preventing reemergence of primitive reflexes. However, patient factors primarily influenced 3-month neuropsychologic function and depressive symptomatology, not use of magnesium.

The trial suggests that future research be directed toward ascertaining duration of detectable neurologic benefit and determining whether the observed short-term benefits of elevated magnesium levels translate into helping patients recover more quickly and completely after cardiac surgery or confer long-term neurologic benefit.

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Discussion

Dr Ralph J. Damiano (St Louis, Mo). Congratulations on a beautifully designed, prospective randomized study. Studies like this are sorely needed in our specialty to allow us, as surgeons, to optimize patient management. And I congratulate you on undertaking a prospective study in what has become an even more difficult and perhaps confusing area.

I have a number of questions for you, and I will ask them one at a time to give you a chance to respond.

First of all, why do you think the principal effect of magnesium was on cerebellar function? It had very little effect certainly on motor and sensory function, and even its effect on mentation was not dramatic. Is this due to some anatomic variability in the distribution of NMDA receptors? How do you explain that from a mechanistic standpoint?

Dr Bhudia. Thank you, Dr Damiano. I think the main effect of magnesium was to minimize any insult. If one was to experience any motor dysfunction, then the likelihood of a huge brain insult, as in stroke, is high. It is similar for the sensory function.

What we are picking up in the cerebellar dysfunction are subtle changes, for example the primitive reflexes. This cerebellar dysfunction was more obvious in those receiving the placebo. These subtle changes are not obvious if we do not look for them. We believe that the magnesium helps reduce the effect of these small insults to the brain rather than the larger insults, which manifest as stroke.

One of the possible mechanisms for magnesium as a neuroprotectant is through its antagonist property on the NMDA receptor. The distribution of NMDA receptors is different across the brain, but I do not think the reason for reduction in cerebellar dysfunction is related to the NMDA receptor distribution.

Dr Damiano. Is there any clinical relevance to your findings? Because there were no changes between the groups at 3 months, does the small difference in cerebellar function have any real effect in terms of patient recovery?

As a second part of this question, in your manuscript you suggested that the early benefits of magnesium on cerebellar function might accelerate patient recovery, yet length of stay in this randomized study was exactly the same. Were there any objective measures of accelerated recovery in the magnesium group?

Dr Bhudia. As for the short-term benefit, although the difference was mainly in the primitive reflexes, short-term memory was also better in those receiving magnesium. We therefore argue that although the length of stay of patients was similar in both groups, these subtle changes can influence other factors. If short-term memory is better, then getting back to routine tasks and going back to work might occur sooner, even though at 3 months we did not see any difference between the 2 groups.

Dr Damiano. But is that something you are supposing and have no objective data to support?

Dr Bhudia. No, we did not have any objective data to support it.

Dr Damiano. Also it might be of interest to the audience to point out that you are looking at fairly subtle differences in neurocognitive testing.

Dr Bhudia. That's right.

Dr Damiano. And even though there is a difference in cerebellar function, did you notice a difference in gait in these patients or anything objective that would make that subtle difference actually have a clinical effect?

Dr Bhudia. The testing of cerebellar function, and all the other modalities, was very objective. Although the changes might be subtle, they could make a difference to the overall well-being of the patient.

Dr Damiano. There certainly is a lot of literature that says that magnesium prevents atrial fibrillation, yet in your study you mentioned that there was no difference in atrial fibrillation between groups. How do you explain how this finding relates to the rest of the literature, which is fairly supportive that magnesium administration prevents atrial fibrillation?

Dr Bhudia. We were puzzled about this as well. Patients in the magnesium group had a similar incidence of atrial fibrillation as those in the placebo group, although this was not what we set out to look for as the primary outcome. Also, other postoperative outcomes, such as incidence of bleeding, infection, renal impairment, and respiratory insufficiency, were similar in the 2 groups, implying that it was safe to give magnesium at these higher levels.

One speculation as to why magnesium did not reduce the incidence of atrial fibrillation is that the highest level of serum magnesium occurred during aortic clamping. The magnesium

would therefore distribute to the body, including the brain, and not the myocardium.

Dr Damiano. Finally, just quickly, at the Cleveland Clinic, is everybody receiving magnesium right now?

Dr Bhudia. That is the next step.

Dr Guo-Wei He (Hong Kong, China). Congratulations for your elegant study. I have 2 questions.

Regarding the plasma concentration of magnesium, how did you decide your magnesium level of plasma concentration should be increased to 1.5 to 2 times? How did you decide on this index?

Second, in your placebo group, do you also use the magnesium cardioplegia? I believe if you use blood cardioplegia, it contains 8 to 10 mEq of magnesium that would be absorbed into the blood also. Therefore, the question is this: Did you measure the plasma concentration of magnesium in those placebo group patients as well to make a fair comparison?

Dr Bhudia. Thank you for your comments. The question about how much magnesium to give and what level to bring it up to was one we had to answer early on. Some animal studies have shown that a serum magnesium level of $3.6 \text{ mg} \cdot \text{dL}^{-1}$, approximately 1.5 times normal range in human subjects, is the neuroprotective dose. That is how we decided on $3.6 \text{ mg} \cdot \text{dL}^{-1}$ to $4.8 \text{ mg} \cdot \text{dL}^{-1}$. The upper limit, $4.8 \text{ mg} \cdot \text{dL}^{-1}$, was high, but not high enough to cause side effects.

Regarding whether we measured magnesium levels in the placebo group, the answer is yes. One of our graphs showed that the 2 curves of magnesium levels were significantly different.

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Appendix E1. Details of Trial Design

Hypothesis

Keeping serum magnesium levels greater than 1½ times adult normal range during CPB and 24 hours thereafter in patients undergoing cardiac surgery has no neuroprotective effect.

Trial Design

Randomized, blinded, placebo-controlled, single-site clinical study in which patients undergoing elective cardiac surgery were randomized to have serum magnesium levels increased to 1½ to 2 times normal level versus placebo. The trial included the following interactions with patients, interventions, and assessments:

1. Three to 4 days before surgery: consent, followed by neurologic, neuropsychologic, and depressive assessment
2. Day of operation: randomization to treatment or placebo
3. Induction of anesthesia: intravenous bolus of magnesium sulfate or placebo over 15 minutes, followed by infusion over 24 hours
4. Off CPB: possible magnesium sulfate bolus of 1 g (surgeon practice); this is given occasionally to prevent cardiac arrhythmias, with the surgeon making the decision
5. 24 hours after surgery: magnesium sulfate or placebo discontinued
6. 24 hours after extubation: neurologic assessment
7. Extubation: neurologic assessment
8. 96 hours after surgery: neurologic assessment
9. 90 days after surgery: neuropsychologic and depressive inventory assessment.

Patient Population

Patients were recruited from the 7-county Cleveland region if they were admitted to Cleveland Clinic for elective on-pump cardiac surgery. Other patients from outside this region who were willing to come back for 3-month assessment were also recruited.

Inclusion Criteria

Patients 18 years or older scheduled to undergo elective CABG, valve surgery, or both, on CPB who consented for the trial.

Exclusion Criteria

1. Preoperative atrial fibrillation.
2. Preoperative renal impairment, defined as plasma creatinine level greater than 2.0 or on chronic renal dialysis.
3. Participation in another trial.
4. Inability to read, write, or comprehend English.
5. Refusal to consent.

In toto, other than refusal to consent, 29 patients were excluded: 1 with diabetic retinopathy was unable to read, 1 was unable to understand instructions, 2 discontinued the assessment (withdrew consent), 2 had a baseline assessment but then withdrew consent, 5 had baseline assessment but either had no operation or a percutaneous procedure, and 18 underwent an operation more

extensive than the one contemplated at the time of baseline assessment that did not meet inclusion criteria.

Sample Size

Neurologic decline or death from neurologic injury was anticipated to be 35% in the control group. Assuming this would be 20% in the treatment group, a 2-group test of independent proportions, a type I error of 0.05, and a 2-tailed alternative, a total sample size of 300 would achieve at least 80% power to detect this difference. This was augmented by 50 patients to guard against overly optimistic anticipated differences and the possibility that not all consenting patients would complete all tests.

Magnesium Dose

Magnesium dosing was derived from the knowledge that (1) serum magnesium concentrations 1½ times normal ($3.62 \text{ mg} \cdot \text{dL}^{-1}$) were associated with reduced histologic infarct volume in ischemic injury animal models,^{E1} (2) concentrations 2 to 3 times normal ($4.2 \text{ mg} \cdot \text{dL}^{-1}$ to $6.8 \text{ mg} \cdot \text{dL}^{-1}$) with reduced occurrence of preeclamptic and eclamptic seizure,^{E2} and (3) concentrations 1½ to 2 times normal with important clinical benefit in acute stroke.^{E3}

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Appendix E2. Analyses of Neuropsychologic and Depressive Inventory Scores

Principal components analysis of preoperative test scores identified 4 components accounting for 72% of total variation: principal component 1 for 42%, 2 for 13%, 3 for 9%, and 4 for 8%. These 4 components can be interpreted as follows (Table E3):

1. Weighted average of all tests except Beck Depression Inventory, second edition. A lower score signifies worse performance.
2. Mainly represents average of 3 trials of the Hopkins Verbal Learning Test scores. A lower score signifies worse performance.
3. Represents Beck Depression Inventory, second edition. A higher score signifies higher levels of depressive symptomatology.
4. Mainly represents the Boston Naming Test and Controlled Oral Word Association Test (word fluency). A lower score signifies worse performance.

Figure E1. CONSORT flow chart of patients assessed for eligibility in this randomized trial.

Figure E2. Unadjusted preoperative and 3-month follow-up neuropsychologic test scores presented for magnesium and placebo groups. *Top whisker*, Maximum score; *bottom whisker*, minimum score; *top line in box*, 85th percentile; *middle line*, median; *bottom line*, 15th percentile; +, mean. **A**, Hopkins Verbal Learning Test (HVL). **B**, HVL delayed recall. **C**, HVL discrimination index. **D**, Controlled Oral Word Association Test (COWAT). **E**, Boston Naming Test. **F**, Digit Symbol. **G**, Symbol Search. **H**, Grooved Pegboard, dominant hand (D). **I**, Grooved Pegboard, nondominant hand (ND). **J**, Trail-Making Test Form A. **K**, Trail-Making Test Form B. **L**, Beck Depression Inventory second edition.

TABLE E1. Characteristics of patients who completed 3-month follow-up neuropsychologic study

Characteristic	Magnesium group (n = 132), No. (%)	Placebo group (n = 141), No. (%)	P value
Demography			
Female	26 (20)	25 (18)	.7
Age (y), mean $\pm$ SD	62 $\pm$ 12	63 $\pm$ 13	.6
Body mass index (kg $\cdot$ m ⁻²)	29 $\pm$ 5	29 $\pm$ 6	.5
Preoperative neurologic morbidity			
CVA	1 (0.8)	2 (1)	1*
TIA	8 (6)	5 (4)	.4*
Syncope	8 (6)	11 (8)	.6
Cardiac morbidity			
Previous MI	53 (40)	45 (32)	.2
Atrial fibrillation	4 (3)	3 (2)	.7*
Previous cardiac operation	30 (23)	26 (18)	.4
NYHA class			.1
I	35 (27)	34 (24)	
II	76 (58)	97 (69)	
III	18 (14)	9 (6)	
IV	3 (2)	1 (0.7)	
Aortic regurgitation (moderate or greater)	37 (28)	31 (22)	.2
Aortic stenosis (moderate or greater)†	26 (20)	42 (31)	.04
Mitral regurgitation (moderate or greater)‡	55 (42)	55 (39)	.6
Mitral stenosis (moderate or greater)§	1 (0.8)	4 (3)	.4*
Coronary disease			
LMT stenosis (>50%)	20 (16)	23 (17)	.9
LAD stenosis (>70%)¶	69 (55)	68 (50)	.4
LCx stenosis (>70%)¶	56 (45)	50 (37)	.2
RCA stenosis (>70%)	58 (47)	68 (50)	.6
Three-system disease	59 (47)	60 (44)	.9
Noncardiac comorbidity			
Hypertension#	88 (67)	103 (74)	.2
Diabetes mellitus	27 (20)	29 (21)	>.9
Peripheral vascular disease	61 (46)	47 (33)	.03
Carotid disease	57 (43)	42 (30)	.02
COPD	22 (17)	17 (12)	.3
History of smoking	66 (50)	78 (55)	.4
Procedure			
Isolated CABG	53 (40)	49 (35)	.4
CABG + valve procedure	33 (25)	42 (30)	.4
Aortic valve repair	5 (4)	2 (1)	.3*
Aortic valve replacement	41 (31)	58 (41)	.08
Mitral valve repair	35 (27)	34 (24)	.6
Mitral valve replacement	5 (4)	10 (7)	.2
Tricuspid valve repair	2 (2)	6 (4)	.3*
Support			
Perfusion time (min)	91 $\pm$ 36	91 $\pm$ 35	.8
Ischemic time (min)	73 $\pm$ 29	73 $\pm$ 30	>.9

SD, Standard deviation; CVA, cerebrovascular accident; TIA, transient ischemic attack; MI, myocardial infarction; NYHA, New York Heart Association; LMT, left main trunk; LAD, left anterior descending coronary artery; LCx, left circumflex coronary artery; RCA, right coronary artery; COPD, chronic obstructive pulmonary disease; CABG, coronary artery bypass grafting. *Fisher's exact test. †Three unknown in magnesium group, 6 unknown in placebo group. ‡Two unknown in magnesium group, 1 unknown in placebo group. §Two unknown in magnesium group, 4 unknown in placebo group. ||Eight unknown in magnesium group, 4 unknown in placebo group. ¶Seven unknown in magnesium group, 4 unknown in placebo group. #One unknown in placebo group.

TABLE E2. Characteristics of patients who completed 3-month neuropsychologic battery compared with patients who did not

Characteristic	Completed (n = 273), No. (%)	Not completed (n = 77), No. (%)*	P value
Demography			
Female	51 (19)	29 (38)	.0005
Age (y), mean $\pm$ SD	63 $\pm$ 12	65 $\pm$ 13	.05
Body mass index (kg $\cdot$ m ⁻²)	29 $\pm$ 6	31 $\pm$ 7	.1
Preoperative neurologic morbidity			
CVA	3 (1)	3 (4)	.3†
TIA	13 (5)	7 (9)	.1
Syncope	19 (7)	6 (8)	.8
Cardiac morbidity			
Previous MI	98 (36)	33 (43)	.3
Atrial fibrillation	7 (3)	0 (0)	.4†
Previous cardiac operation	56 (21)	12 (16)	.3
NYHA class			.2
I	69 (25)	17 (22)	
II	173 (63)	46 (60)	
III	27 (10)	10 (13)	
IV	4 (1)	4 (5)	
Aortic regurgitation (moderate or greater)	68 (25)	20 (26)	.8
Aortic stenosis (moderate or greater)‡	68 (26)	25 (34)	.2
Mitral regurgitation (moderate or greater)§	110 (41)	31 (40)	>.9
Mitral stenosis (moderate or greater)	5 (2)	2 (3)	.6†
Coronary disease			
LMT stenosis (>50%)¶	43 (16)	7 (10)	.1
LAD stenosis (>70%)#	137 (52)	39 (52)	>.9
LCx stenosis (>70%)#	106 (40)	34 (45)	.4
RCA stenosis (>70%)¶	126 (48)	37 (49)	.9
Three-system disease	112 (43)	32 (43)	>.9
Noncardiac comorbidity			
Hypertension**	191 (70)	55 (71)	.8
Diabetes mellitus	56 (21)	20 (26)	.3
Peripheral vascular disease	108 (40)	28 (36)	.6
Carotid disease	99 (36)	24 (31)	.4
COPD	39 (14)	14 (18)	.4
History of smoking**	144 (53)	41 (54)	.8
Procedure			
Isolated CABG	102 (37)	26 (34)	.6
CABG + valve procedure	75 (27)	23 (30)	.7
Aortic valve repair	7 (3)	0 (0)	.4†
Aortic valve replacement	99 (36)	31 (40)	.5
Mitral valve repair	69 (25)	20 (26)	.9
Mitral valve replacement	15 (5)	5 (6)	1†
Tricuspid valve repair	8 (3)	2 (3)	1†
Support			
Perfusion time (min)	91 $\pm$ 36	97 $\pm$ 34	.08
Ischemic time (min)	73 $\pm$ 30	78 $\pm$ 28	.04

SD, Standard deviation; CVA, cerebrovascular accident; TIA, transient ischemic attack; MI, myocardial infarction; NYHA, New York Heart Association; LMT, left main trunk; LAD, left anterior descending coronary artery; LCx, left circumflex coronary artery; RCA, right coronary artery; COPD, chronic obstructive pulmonary disease; CABG, coronary artery bypass grafting. *Patients who died were excluded. †Fisher's exact test. ‡Nine unknown in completed group, 3 unknown in incomplete group. §Three unknown in completed group. ||Six unknown in completed group, 1 unknown in incomplete group. ¶Twelve unknown in completed group, 2 unknown in incomplete group. #Eleven unknown in completed group, 2 unknown in incomplete group. **One unknown in completed group.

TABLE E3. Principal components of neuropsychologic and depression inventory tests

Test	PC #1	PC #2	PC #3	PC #4
Hopkins Verbal Learning Test				
Total of 3 trials	0.282	0.436		
Delayed recall	0.272	0.484		
Discrimination index	0.214	0.471		
Controlled Oral Word Association Test	0.234		0.456	
Boston Naming Test	0.198		0.751	
Digit Symbol	0.361			
Symbol Search	0.348			
Grooved Pegboard				
Dominant hand	−0.320			
Nondominant hand	−0.322			
Trail-Making Test				
Form A	−0.337			
Form B	−0.366			
Beck Depression Inventory, second edition	—		0.720	

PC, Principal component.

TABLE E4. Neuropsychologic and depression inventory performance 3 months postoperatively compared with preoperatively in entire study population

Test	Performance at 3 mo*	P value
Hopkins Verbal Learning Tests		
Total of 3 trials	Better	<.0001
Delayed recall	Better	.002
Discrimination index	Better	.004
Controlled Oral Word Association Test	No change	>.9
Boston Naming Test	Better	<.0001
Digit Symbol	No change	.08
Symbol Search	Better	.05
Grooved Pegboard		
Dominant hand	Better	.0008
Nondominant hand	Better	.003
Trail-Making Test		
Form A	No change	.2
Form B	Better	.05
Beck Depression Inventory, second edition	Better	<.0001

*Compared with preoperative performance.

TABLE E5. Factors associated with lower PC #1 score

Factor	Coefficient ± SD	P value
Unadjusted		
Lower preoperative PC #1 score	−0.91 ± 0.03	<.0001
Magnesium group	−0.019 ± 0.14	.9
Adjusted		
Lower preoperative PC #1 score	−0.78 ± 0.035	<.0001
Magnesium group	−0.067 ± 0.12	.6
CVA	1.74 ± 0.57	.003
History of TIA	0.57 ± 0.30	.06
Older*	0.33 ± 0.096	.0006
Diabetes	−1.2 ± 0.75	.1
Interaction: older patients with diabetes†	0.42 ± 0.20	.04
Higher BUN‡	0.14 ± 0.029	<.0001

Note: Primary component #1 is a weighted average of all tests, except the Beck Depression Inventory. PC, Principal component; SD, standard deviation; CVA, cerebrovascular accident; TIA, transient ischemic attack; BUN, blood urea nitrogen. *Exp(age/50), exponential transformation. †Exp(age/50) × diabetes, interaction term. ‡Exp(BUN/20), exponential transformation.

TABLE E6. Factors associated with lower PC #2 score

Factor	Coefficient ± SD	P value
Unadjusted		
Lower preoperative PC #2 score	−0.67 ± 0.05	<.0001
Magnesium group	−0.063 ± 0.12	.6
Adjusted		
Lower preoperative PC #2 score	−0.64 ± 0.05	<.0001
Magnesium group	0.07 ± 0.05	.6
Lower WRAT-3 reading score*	−0.30 ± 0.086	.0007
Left main trunk disease (>70% stenosis)	0.57 ± 0.24	.02
Mitral valve repair	0.37 ± 0.14	.01
Higher Canadian angina class	0.14 ± 0.06	.03
More recent date of operation†	0.14 ± 0.05	.008

Note: Principal component #2 is an average of all 3 Hopkins verbal learning tests. PC, Principal component; SD, standard deviation; WRAT-3, Wide Range Achievement Test, third edition. *Standardized (Z) score. †Exp(interval from 1/1/2002), exponential transformation.

TABLE E7. Factors associated with higher PC #3 score

Factor	Coefficient $\pm$ SD	P value
Unadjusted		
Higher preoperative PC #3 score	0.56 ± 0.05	$<.0001$
Magnesium group	-0.031 ± 0.097	.8
Adjusted		
Higher preoperative PC #3 score	0.59 ± 0.05	$<.0001$
Magnesium group	0.007 ± 0.09	$>.9$
Older*	0.15 ± 0.058	.01
Preoperative ventricular arrhythmia	0.30 ± 0.16	.06
Severe mitral valve stenosis	0.19 ± 0.08	.03
Shorter myocardial ischemic time†	0.21 ± 0.12	.08

Note: Represents Beck Depression Inventory, second edition. *PC*, Principal component; *SD*, standard deviation. *Exp(age/50), exponential transformation. †Myocardial ischemic time/70, inverse transformation.

TABLE E8. Factors associated with lower PC #4 score

Factor	Coefficient $\pm$ SD	P value
Unadjusted		
Lower preoperative PC #4 score	-0.76 ± 0.04	$<.0001$
Magnesium group	-0.05 ± 0.08	.6
Adjusted		
Lower preoperative PC #4 score*	-8.2 ± 0.49	$<.0001$
Magnesium group	0.098 ± 0.08	.8
Lower WRAT-3 reading score†	-0.19 ± 0.054	.0005
Lower BUN‡	-0.04 ± 0.02	.02
No COPD	-0.26 ± 0.11	.02

Note: Mainly represents word fluency. *PC*, Principal component; *SD*, standard deviation; *WRAT-3*, Wide Range Achievement Test, third edition; *BUN*, blood urea nitrogen; *COPD*, chronic obstructive pulmonary disease. *Ln(PC #4 score), logarithmic transformation †Standardized (Z) score. ‡Exp(BUN/20), exponential transformation.