Detection of arrhythmogenic cellular magnesium depletion in hip surgery patients

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Summary
The use of high-dose magnesium infusions in critically ill and surgical patients is increasing. This practice is associated with considerable risk of toxicity, as no reliable criteria are currently available to detect significant intracellular magnesium depletion. We have evaluated, before and after surgery, 33 elderly patients with hip fracture, by 24-h Holter ECG monitoring, Doppler echocardiography and serum chemistry; lymphocyte magnesium was measured using atomic absorption spectrophotometry. The severity of ventricular arrhythmias increased, and serum and mononuclear magnesium concentrations decreased significantly after surgery. Decreases in either serum magnesium concentrations \(< 0.125 \text{ mmol litre}^{-1}\) or cellular magnesium \(< 6 \text{ nmol mg}^{-1}\), but not serum or lymphocyte absolute magnesium concentrations, were associated with postoperative development of repetitive arrhythmias. Variations in serum magnesium concentrations correlated with intracellular decreases, and yielded good accuracy in predicting the postoperative worsening of arrhythmias. Thus perioperative differences in serum magnesium concentrations reflected intracellular variations and allowed us to identify patients with clinically relevant cellular magnesium depletion. (Br. J. Anaesth. 1997; 79: 776–781).

Key words

In recent years magnesium depletion has proved a common condition in patients with acute myocardial infarction\(^1\)–\(^3\) in the intensive care unit and after major surgery.\(^4\)–\(^12\) Magnesium deficiency has been associated with increased occurrence of cardiac arrhythmias, both after operation\(^8\)–\(^12\) and in acute myocardial infarction.\(^13\)–\(^15\) In addition, hypomagnesaemia has been associated with increased mortality both in postoperative and intensive care patients.\(^16\)–\(^17\) Thus routine magnesium therapy is expected to be used with increasing frequency in intensive care settings and operating rooms,\(^18\)–\(^19\) also because of increasing evidence of its beneficial effects on postoperative cardiac function and rhythm, muscle strength, vascular tone and central nervous system metabolism.\(^10\)–\(^22\)

In patients with myocardial infarction, systematic administration of magnesium has been shown to decrease the incidence of ventricular fibrillation, but with detrimental effects on survival.\(^23\)–\(^24\) This outcome was associated with an excess incidence of cardiogenic shock and heart failure;\(^25\) indeed, excessive intracellular magnesium concentrations can depress cardiac function.\(^26\)–\(^27\) It has been acknowledged that safe and effective magnesium treatment as a clinical routine is still hindered by the lack of correlation between serum and tissue magnesium concentrations; the value of other clinically available methods to detect magnesium deficiency, such as measurement of ultrafilterable magnesium or 24-h urinary excretion, is at best uncertain.\(^9\)–\(^11\)\(^\)–\(^12\)\(^\)–\(^13\)\(^\)–\(^14\)\(^\)–\(^15\)

Atomic absorption spectrophotometry is the most reliable method currently available to measure intracellular magnesium content.\(^30\) Mononuclear blood cell magnesium concentrations, as determined by this method, correlate well with myocardial concentrations in patients undergoing heart surgery.\(^11\) Nevertheless, this method is too expensive and difficult to implement to be used routinely.\(^10\)\(^\)–\(^11\)\(^\)–\(^12\)

We have studied a series of older patients undergoing hip surgery to identify any variables that may be useful in clinical practice to detect "relevant" intracellular magnesium depletion, that is independently associated with postoperative development of repetitive ventricular arrhythmias.

Patients and methods
We studied 52 older patients (mean age 80 (range...
Table 1 Perioperative characteristics of the population (mean (SEM) or number (%). SAP = Systolic arterial pressure; DAP = diastolic arterial pressure; LV = left ventricular. *P<0.05; ***P<0.0001

<table>
<thead>
<tr>
<th></th>
<th>Preoperative</th>
<th>Postoperative</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serum albumin (g litre$^{-1}$)</td>
<td>38 (1)</td>
<td>33 (1)*</td>
</tr>
<tr>
<td>Serum calcium (mmol litre$^{-1}$)</td>
<td>2.25 (0.02)</td>
<td>2.17 (0.02)*</td>
</tr>
<tr>
<td>Serum creatinine (mmol litre$^{-1}$)</td>
<td>83.98 (5.3)</td>
<td>99.9 (19.5)</td>
</tr>
<tr>
<td>Serum potassium (mmol litre$^{-1}$)</td>
<td>3.7 (0.5)</td>
<td>3.7 (0.4)</td>
</tr>
<tr>
<td>Serum sodium (mmol litre$^{-1}$)</td>
<td>138 (5)</td>
<td>138 (5)</td>
</tr>
<tr>
<td>Serum magnesium (mmol litre$^{-1}$)</td>
<td>0.97 (0.02)</td>
<td>0.85 (0.02)***</td>
</tr>
<tr>
<td>Cellular magnesium (nmol mg$^{-1}$)</td>
<td>60 (3.6)</td>
<td>54 (3.5)***</td>
</tr>
<tr>
<td>SAP (mm Hg)</td>
<td>144 (3.5)</td>
<td>140 (3.5)</td>
</tr>
<tr>
<td>DAP (mm Hg)</td>
<td>82 (1)</td>
<td>84 (1)</td>
</tr>
<tr>
<td>Diuretic users</td>
<td>10 (30)</td>
<td></td>
</tr>
<tr>
<td>Alcohol (&gt;0.20 oz day$^{-1}$)</td>
<td>2 (6)</td>
<td></td>
</tr>
<tr>
<td>Coffee</td>
<td>4 (12)</td>
<td></td>
</tr>
<tr>
<td>LV mass (g m$^{-2}$)</td>
<td>104 (3.6)</td>
<td></td>
</tr>
<tr>
<td>LV ejection fraction (%)</td>
<td>66 (1)</td>
<td>62 (1)*</td>
</tr>
</tbody>
</table>

61–100) yr with proximal femur fracture, consecu-
tively admitted to the orthopaedics ward of the Uni-
versity Hospital A. Gemelli from January 1 to June
30, 1994. Patients with pacemaker rhythm (three
cases), chronic atrial fibrillation (four cases),
pulmonary embolism (three cases), unreliable
mononuclear cell magnesium assay (six cases) or
those receiving antiarrhythmic drug therapy (three
cases) were excluded. Thus the study included 33
patients (two males, 31 females; mean age 82 (range
61–100) yr) whose characteristics are shown in table
1. Twelve patients suffered from coronary disease,
12 from hypertensive heart disease and four from
both conditions; however, no patient showed signs
or symptoms, or reported history of heart failure.

SURGERY

Femoral fractures were treated by compression
screw-plate in 18 patients and by cemented total hip
arthroplasty in 15. All patients received oral
diazepam and i.m. atropine as premedication.
General anaesthesia comprised induction with
thiopentone 3–4 mg kg$^{-1}$ and vecuronium 0.08 mg
kg$^{-1}$, and maintenance with isoflurane and nitrous
oxide in oxygen, with fentanyl 4 mg kg$^{-1}$ i.v.
During operation, the ECG, non-invasive arterial
pressure, pulse oximetry and end-tidal analysis of
expired gas were monitored throughout anaesthesia.
Postoperative pain was controlled by ketorolac i.v.
From the beginning of surgery to the postoperative
period, Holter monitoring and blood sample collec-
tion, patients received a mean of 5742
mg litre$^{-1}$ of i.v. fluids, with sodium 598 mmol litre$^{-1}$, potassium
37.5 mmol litre$^{-1}$, calcium 3 mmol litre$^{-1}$ and magnesium 6.25 mmol litre$^{-1}$.

DATA COLLECTION

All patients were evaluated by history, physical
examination, blood chemistry, chest x-ray, electro-
cardiography, Doppler echocardiography and
urinalysis. In addition, 24-h Holter monitoring was
performed (using a full-disclosure Oxford Medilog
RF/12 DR system) 48 h before, and from 18 to 20 h
after surgery. Two leads (CM1 and CM5) were
recorded and analysed independently by two
physicians who were blinded to all clinical data.
Ventricular arrhythmias were classified according to
Lown and co-workers: class 1 (less than 30 ectopic
beats per hour), 2 (30+ ectopic beats per hour),
3 (multifocal beats), 4A (couplets) and 4B (ventricular tachycardia). The fifth class (R-on-T
phenomenon) was not recorded in our patients.
Doppler echocardiograms were obtained at the
beginning of each Holter monitoring; all investiga-
tions were performed by a phased-array system,
equipped with a 3.5-MHz probe (2.5 MHz during
pulsed Doppler sampling). The left ventricular
mass was calculated by a validated method.

Mononuclear blood cells were obtained for
measurement of intracellular magnesium content
within the first hour of each Holter monitoring from
duplicate 10-ml samples of heparinized blood,
obtained from the antecubital fossa after removing
the tourniquet. Lymphocytes were obtained from
whole blood by separation on a discontinuous
density gradient (Lymphoprep, Nycomed, Oslo). The
mononuclear cell layer was washed in isotonic saline
and the cell pellet lysed by resuspending in 1.2
ml of distilled water. Immediately after lysis, 0.5-ml aliquots were diluted 1:1 with sodium
phosphate buffer 20 mmol litre$^{-1}$, pH 7.4, for
protein analysis, or nitric acid 0.2 mol litre$^{-1}$ for
magnesium assay, and stored at $-20^\circ$C. Protein
analysis was carried out using the Bradford method,
with 1 mg ml$^{-1}$ of albumin solution as standard.
Cell magnesium was measured by atomic absorption
spectroscopy.

As it is difficult to measure accurately lymphocyte magnesium concentrations, we obtained
duplicate specimens for each patient from a single venepunc-
ture, and these were processed independently.
Magnesium mononuclear cell values were used in
the study only if the results in the two specimens
differed by less than 15% of the mean value of
the two specimens. This standard was not met in six
(15%) of the duplicate specimens.

STATISTICAL ANALYSIS

Data for continuous variables are presented as mean
(SEM). Statistical analysis was performed using
EpilInfo III and SPSS for Windows 6.0.1 statistical
softwares; differences were considered significant at
$P<0.05$. The variations in Lown classification
induced by surgery were evaluated by the Wilcoxon
matched pairs rank test. Comparisons between pre-
and postoperative variables were performed by the
two-tailed paired Student’s $t$ test. Analysis of vari-
ance for normally distributed variables in relation to
both postoperative Lown classification and perioper-
ative variations in Lown classes of arrhythmias was
performed by ANOVA comparisons; otherwise,
non-parametric tests, such as Kruskal–Wallis H,
were adopted.

Because no established cut-offs are available to
diagnose magnesium depletion, linear discriminant
analysis was used to test in separate models the
association of perioperative differences in serum and cellular magnesium concentrations with postoperative worsening of ventricular arrhythmias.36

Logistic regression analysis with forward stepwise selection of covariates, based on conditional variable estimates, was used to assess the association of cellular and serum magnesium variations with postoperative worsening of Lown classification. As cellular and serum magnesium differences were collinear measures, these variables were analysed in separate models. In the regression models patients with serum and cellular magnesium decreases $>0.125$ mmol litre$^{-1}$ and $>6$ mmol mg$^{-1}$, respectively, were compared with those with lower degrees of magnesium depletion. According to linear discriminant analysis, these thresholds yielded the best accuracy in predicting worsening of ventricular arrhythmias.36 The following covariates were also examined as potential confounders in the regression models: age; sex; pre- and postoperative serum creatinine, sodium, calcium and potassium concentrations, and their perioperative differences; type and duration of surgery; preoperative Lown classification; amount of fluids and electrolytes administered; occurrence of intraoperative hypotension; occurrence of severe blood loss with necessity of transfusion; presence of cardiovascular disorders; and preoperative cellular and serum magnesium concentrations.

Finally, the Pearson’s correlation coefficient for perioperative variations in serum and cellular magnesium was calculated. Also, stepwise linear regression analysis was used to build an equation that predicted the variations in intracellular magnesium from a series of clinically available variables. The covariates entered in this model included: age; sex; presence of cardiovascular disorders; type and duration of surgery; amount of fluids and electrolytes administered; occurrence of intraoperative hypotension; occurrence of severe blood loss with subsequent transfusion; preoperative cellular magnesium concentrations; and the perioperative differences in serum concentrations of magnesium, sodium, calcium, potassium and creatinine.

Results

VENTRICULAR ARRHYTHMIAS

No patient developed significant arrhythmias during surgery. The average frequency of ventricular ectopic beats did not differ between preoperative and postoperative Holter recordings (206 (76) vs 214 (102) beat h$^{-1}$, respectively; $P=0.9$). However, postoperative worsening of Lown classification of ventricular arrhythmias (table 2) was detected by Holter monitoring in 18 patients (55%), while the severity of arrhythmias was unchanged in 13 and decreased in two (6%); the perioperative difference for all patients, as evaluated by the Wilcoxon rank test, was significant ($z=2.77$, $P=0.005$). After operation, nine (27%) patients showed repetitive ventricular arrhythmias that were not detectable before surgery. Among these, two (6%) had runs of sustained ventricular tachycardia (from 12 to 30 beats); one died suddenly approximately 24 h after Holter monitoring. There were no signs of pulmonary embolism or myocardial infarction at necropsy, thus supporting the hypothesis of arrhythmic death.

BLOOD CHEMISTRY

After surgery, significant reductions in serum albumin, calcium, and in both cellular and serum magnesium concentrations occurred. There were no differences in serum potassium, sodium, chloride, ureic nitrogen, creatinine or phosphate concentrations (table 1).

CORRELATES OF POSTOPERATIVE ARRHYTHMIAS

There were no significant differences in clinical or Doppler echocardiographic variables with respect to postoperative Lown classification of arrhythmias or perioperative variations.

Preoperative Lown classification ($P=0.0015$) and extent of intracellular magnesium loss ($P=0.04$) were the only variables associated with postoperative Lown classification. When postoperative worsening of Lown

<table>
<thead>
<tr>
<th>Class</th>
<th>Preoperative ($n$ (%))</th>
<th>Postoperative ($n$ (%))</th>
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<tbody>
<tr>
<td>0</td>
<td>8 (25)</td>
<td>6 (18)</td>
</tr>
<tr>
<td>1</td>
<td>14 (42)</td>
<td>10 (30)</td>
</tr>
<tr>
<td>2</td>
<td>2 (6)</td>
<td>4 (12)</td>
</tr>
<tr>
<td>3</td>
<td>4 (12)</td>
<td>2 (6)</td>
</tr>
<tr>
<td>4a</td>
<td>5 (15)</td>
<td>9 (28)</td>
</tr>
<tr>
<td>4b</td>
<td>2 (6)</td>
<td></td>
</tr>
</tbody>
</table>

Table 2 Lown classes of ventricular arrhythmias

Figure 1 Individual variations in lymphocyte magnesium content according to the postoperative increase in severity of ventricular arrhythmias. The solid lines represent group means; broken line indicates the threshold value (calculated with linear discriminant analysis) above which worsening was most likely to occur. Also shown are sensitivity (se), specificity (sp), positive predictive value (ppv), negative predictive value (npv) and predictive accuracy (a) for this threshold.
Serum magnesium models adjusted for variations in serum calcium

Serum magnesium models not adjusted for variations in serum calcium

Cellular magnesium

Table 3

<table>
<thead>
<tr>
<th></th>
<th>Odds ratio</th>
<th>95 % CI</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Models not adjusted for variations in serum calcium</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Serum magnesium</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(decrease &gt; 1.25 mmol mg⁻¹)</td>
<td>9.62</td>
<td>1.95–47.4</td>
<td>0.005</td>
</tr>
<tr>
<td>Cellular magnesium</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(decrease &gt; 6 mmol mg⁻¹)</td>
<td>7.50</td>
<td>1.49–37.7</td>
<td>0.014</td>
</tr>
<tr>
<td>Models adjusted for variations in serum calcium</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Serum magnesium</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(decrease &gt; 1.25 mmol litre⁻¹)</td>
<td>8.36</td>
<td>1.37–50.9</td>
<td>0.021</td>
</tr>
<tr>
<td>Cellular magnesium</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(decrease &gt; 6 mmol mg⁻¹)</td>
<td>29.5</td>
<td>2.37–368.3</td>
<td>0.008</td>
</tr>
</tbody>
</table>

3 refer to partial models, not adjusted for difference in serum calcium. It is noteworthy that while the odds ratio for the decrease in serum magnesium was not affected substantially by adjustment for serum calcium difference (model 3), the statistical significance of cellular magnesium depletion was enhanced markedly when serum calcium variation was entered into the model (model 4).

CORRELATES OF CELLULAR MAGNESIUM DEPLETION

While pre- and postoperative absolute serum concentrations of magnesium did not correlate with intracellular concentrations, a significant correlation was found between perioperative differences in serum and lymphocyte concentrations ($r=0.62$; $P=0.0001$). The perioperative difference in serum magnesium was the only variable that entered the final linear regression model, and was therefore independently associated with variations in intracellular magnesium.

The resulting regression equation was

$$
\Delta_{\text{cell}} \text{Mg} = 1.59 + \Delta_{\text{serum}} \text{Mg} \times 35.26
$$

where $\Delta_{\text{cell}} \text{Mg} =$ perioperative difference in lymphocyte magnesium content (expressed as nmol mg⁻¹), and $\Delta_{\text{serum}} \text{Mg} =$ difference in serum magnesium (mmol litre⁻¹).

Discussion

We have found that postoperative arrhythmogenic cellular magnesium depletion corresponded with a >10% reduction in intracellular concentrations, rather than with a simply “low” total cellular content. In addition, while absolute serum and cellular magnesium concentrations did not correlate, perioperative intracellular variations were associated with differences in serum concentrations by a simple equation, so that patients at risk of development of repetitive ventricular arrhythmias may be identified accurately by monitoring serum magnesium concentrations. Knowledge of variations in intracellular magnesium content from serum assays may be crucial for safe and effective management of high-dose magnesium therapy in patients at risk of magnesium depletion.

Our study focused on detection of postoperative arrhythmogenic cellular magnesium depletion in hip surgery; the clinical value of this study model was confirmed by the significant postoperative increase in repetitive ventricular arrhythmias (table 2). This observation is in agreement with previous observations on the arrhythmogenic role of major surgery; in some studies, magnesium depletion has been identified as the main culprit.

In our patients, magnesium depletion was the major determinant of the postoperative increase in severity of arrhythmias (table 3). The independent association of magnesium depletion with postoperative ventricular ectopic activity was significant, even after adjustment for potential confounders, such as potassium and calcium serum concentrations, or their perioperative variations.
The results of this study suggest that postoperative magnesium depletion should be considered in terms of perioperative variations in intracellular concentrations, rather than as "low" total cellular content. This finding is in agreement with experimental studies on magnesium mobilization from cardiac myocytes. These studies showed that most intracellular magnesium is complexed (i.e. inactive) and that only rapid outward magnesium fluxes (ranging from 10 to 15% of total content) yield significant effects on cellular metabolism and electrophysiology through redistribution of subcellular magnesium fractions. Noticeably, the threshold level for the decrease in intracellular magnesium that best predicted postoperative worsening of ventricular arrhythmias in our patients corresponded with approximately 10% of the mean preoperative cellular content (table 1). Other studies also found no relation between total serum or cellular magnesium content and arrhythmias. Even though simultaneous serum and monocyte magnesium concentrations did not correlate, perioperative differences in serum concentrations reflect intracellular variations, and allow simple prediction of postoperative worsening of ventricular arrhythmias with reasonable accuracy (fig. 2). Indeed, a correlation between changes in serum and myocardial magnesium has been reported in a longitudinal study. According to the final regression equation, a decrease in serum magnesium concentration of 0.125 mmol litre⁻¹ would correspond to a reduction in intracellular concentrations of 5.99 nmol mg⁻¹. These values correspond to threshold levels that in separate models of discriminant analysis best predicted postoperative worsening of arrhythmias (figs 1, 2).

It is unclear why the association between cellular magnesium depletion and worsening arrhythmias was increased after adjusting for serum calcium variations, compared with the unadjusted analysis (table 3). The interrelations between magnesium and calcium variations are complex and not completely understood. Low serum calcium concentrations may enhance cellular magnesium depletion and, conversely, hypocalcaemia can result from magnesium depletion. In this study, 20 (61%) patients were hypomagnesaemic after surgery; this is similar to the reported prevalence of hypomagnesaemia (69%) after cardiac surgery. The loss of magnesium after surgery has been attributed to perioperative administration of magnesium-free fluids, and to increased serum catecholamine concentrations. Similarly, magnesium depletion in patients with acute myocardial infarction has been associated with increased serum noradrenaline concentrations. Indeed, massive magnesium release from myocytes has been demonstrated after stimulation with noradrenaline; such an efflux is independent of extracellular magnesium concentrations. In surgical settings, increased noradrenaline serum concentrations have been observed for several days after interventions. These observations are in keeping with the reported persistence of magnesium loss during the early postoperative period, and the transient efficacy of single magnesium infusions. Therefore, protracted, high-dose magnesium supplementation has been recommended in patients with acute myocardial infarction or in those undergoing major surgery. However, in large studies in patients with acute myocardial infarction (such as the LIMIT-2 and ISIS-4 studies) treatment with high-dose magnesium has been found either to decrease or increase mortality. Sustained monitoring of serum concentrations of magnesium in these patients might allow us to identify subjects with significant intracellular depletion in whom magnesium administration would yield the best risk–benefit ratio.

References


