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ORIGINAL ARTICLE

Are the perioperative changes of serum magnesium in lung surgery arrhythmiogenic?

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Summary

Purpose: *To prospectively study the perioperative changes in serum magnesium (sMg) after major lung resections and their effect to the generation of cardiac dysrhythmias, and to present a brief review of the literature surrounding this phenomenon.*

Patients and methods: *We studied 33 patients with non small cell lung cancer (NSCLC), scheduled for major pulmonary resection. Three patients were excluded from the study due to preoperative medication with β-blocker and calcium (Ca) antagonists. Pneumonectomy was performed in 10 patients and lobectomy in 20. Heparinized arterial blood samples for the assessment of sMg, potassium (K) and Ca concentration were obtained before surgery, on arrival to the High Dependency Unit (HDU), and on the morning of the first and the second postoperative day. No patient had evidence of cardiac disease.*

Results: *Atrial fibrillation occurred in 3 (10%) patients. There was no statistically significant association between sMg and dysrhythmias. A statistically significant difference after adjusting for age was found between sMg concentration, just after the operation and the first postoperative day and the baseline measurement (before the operation). The type of surgical procedure was not found to be associated with the sMg concentration or the appearance of dysrhythmia. The serum K and Ca concentration for all samples was within normal range.*

Conclusion: *Serum concentration of Mg decreases significantly within the first 24 hours of major lung resection. Although our study didn't demonstrate a relationship between decreases in sMg and the generation of arrhythmias, this link is well established in other fields and thus we support the prophylactic $MgSO_4$ administration in their prevention in such cases whilst we await further larger studies.*

Key words: atrial fibrillation, hypomagnesemia, lung cancer, major lung resection, serum magnesium, supraventricular dysrhythmia

Introduction

Supraventricular dysrhythmias (SVD) after thoracic surgery were first described in 1940 [1]. They happen in the first 24-72 hours postoperatively and represent a main cause of prolonged hospital stay. Atrial fibrillation (AF) is the most frequent dysrhythmia - about 90% of the total observed [2].

The cause is unknown, while many factors have been implicated. Previous studies showed that sMg deficiency was responsible for a variety of supraventricular or ventricular dysrhythmias [3]. We prospectively studied the perioperative changes of sMg after major lung resection till the second postoperative day and their effect to the generation of cardiac dysrhythmias.

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Patients and methods

Patients

We prospectively studied the perioperative con-

centrations of sMg in 33 non-diabetic patients who were scheduled for a major lung resection due to NSCLC during the 2-year period 2000-2001. There were 31 males and 2 females with a mean age of 62.5 (±12) years (range 33-77). Preoperative cardiologic evaluation included physical examination, ECG and 2-D echocardiography. Three patients were excluded from the study due to preoperative medication with β-blocker and Ca antagonists. There was no evidence of arrhythmia, hypertension, coronary disease or heart failure in the remaining patients. Preoperative spirometry showed adequate respiratory reserve for planned resection in all patients. Pneumonectomy was performed in 10 and lobectomy in 20 patients. Extended mediastinal lymph node dissection was performed in each case.

Following surgery all patients were immediately extubated and transferred to the HDU, where they were monitored. Portable chest x-ray showed no atelectasis. There was no air leakage. Patients received a combination of opiate and non-steroid anti-inflammatory drugs and postoperative physiotherapy. Arterial blood gases were examined regularly, based on which there was a correction of patients' electrolyte balance and oxygen concentration. The serum Mg, K, Ca concentrations were recorded for comparison.

Method

Heparinized arterial blood samples for the assessment of Mg, K and Ca serum concentration were obtained before surgery (PRE), on arrival to the HDU just after the surgery (HDU), on the morning of the first (POD), and the second postoperative day (FIN).

Statistics

A Longitudinal Data Analysis was performed to explore if there was any association between the appearance of SVD (in our study all patients developed AF) and the sMg concentration. We applied a logistic regression model, with the binary outcome "dysrhythmia or no-dysrhythmias", using as explanatory variables the sMg concentration, after adjusting for age and/or the type of operation (pneumonectomy or lobectomy). The binary responses for individual patient were assumed to be equally correlated and thus exchangeable correlation structure was used. We also investigated if the type of the procedure influenced the levels of the sMg and, consequently, the occurrence of dysrhythmias. A mixed linear model, which contains fixed-effects parameters with unstructured covariance matrix, was used in this case.

The Repeated Measurements Statistical Analysis was balanced irregular without missing values. Estimations and inference were based on Restricted Maximum Likelihood. Generalized Estimating Equations (GEE) method was used to check for the possible association between potential dysrhythmias and sMg concentration. All reported values were based on two – sided tests and compared to a significance level of 5%. SAS version 9.00 was used for all statistical calculations.

Results

Mean serum concentration of Mg, K and Ca are presented in Table 1. Only 3 out of the 30 patients (10%) developed SVD, and more specifically AF (2 of them on the first postoperative day and one on the day of operation). Two patients had undergone lobectomy and one pneumonectomy. Intravenous administration of amiodarone was used for the treatment of AF in all cases, restoring sinus rhythm. Patient characteristics are shown in Table 2. We did not notice any recurrence of the AF in the 30-day postoperative period.

sMg concentration was not found to have a statistically significant association with AF, after adjusting for

Table 1. Mean serum Mg^{+2}, K^{+} and Ca^{+2} concentrations

	PRE	*PICU*	*POD*	*FIN*
Mg^{+2}	1.46	1.26	1.29	1.36
(1.3-2.1 mEq/lt)	(1.3-1.5)	(1-1.5)	(1.1-1.4)	(1.2-1.6)
K^{+}	3.95	3.95	4	3.9
(3.5-4.5 mEq/lt)	(3.7-4.1)	(3.7-4.2)	(3.9-4.1)	(3.8-4)
Ca^{+2}	8.5	7.7	7.9	8.35
(8.0-10.2 mEq/lt)	(8.2-8.9)	(7.2-8)	(7.6-8.4)	(8-8.6)

Values in median (interquartile rate)
For abbreviations see text

Table 2. Characteristics of the patients presenting with SVD

	Patient 1	*Patient 2*	*Patient 3*
Gender	Male	Male	Male
Age (years)	66	67	70
Operation	Rt lower lobectomy	Lt lower lobectomy	Rt upper lobectomy
SVD	AF	AF	AF
Day of SVD	1st post-op day	Operation day	1st post-op day
sMg (mEq/lt)			
PRE	1.4	1.5	1.3
HDU	1.2	1.2	1.7
POD	1.1	1.1	1.2
FIN	2.3	1.5	1.4

For abbreviations see text

Table 3. Statistical analysis of GEE Parameter Estimates of age and sMg

Parameter	*Odds ratio*	*95% Confidence interval*	*p-value*
Age (years)	0.9	0.83-0.97	0.008
Mg^{+2} (mEq/lt)	0.53	0.077-3.67	0.518

Each odds ratio is of the form "no-dysrhythmia / dysrhythmia"

patients' age (p=0.52). In the model presented in Table 3, age was found to be significantly associated with AF, meaning that one year increase of the age (within the range of our patients), having stable the sMg concentration, increases the probability of developing AF by almost 10% ($p < 0.05$). The incidence of AF was not enough to generate a corresponding statistical analysis adjusting also for the type of operation. However, we found a statistically significant difference, again after adjusting for age, between sMg concentrations, just after the operation (HDU, p= 0.001) and on the first postoperative day (POD, p=0.039), compared with the baseline measurements (PRE) (Table 4). There was no relation between the type of the operation and the sMg concentration or the appearance of AF. The serum concentration of K and Ca for all samples was within normal range.

Discussion

The incidence of SVD after thoracic operations ranges from 9 to 37%, while it is markedly influenced by the extent of resection. The incidence of SVD has been reported to be 1% following segmental or wedge resection, 13% following esophagectomy, 12-16% following lobectomy, 20-30% following pneumonectomy, and as high as 40% following extrapleural pneumonectomy [2]. It represents AF in 90% of cases and atrial flutter or other supraventricular tachycardia in the rest [2]. SVD is present at the second postoperative day in the majority of the cases [4]. Indeed, AF was the only kind of dysrhythmia in our patients but it presented during the first 24 hours after the operation in all cases.

Table 4. Solution for fixed effects at every measurement time point, adjusted by age, after modeling sMg levels compared with the baseline measurements

Fixed effects	*Estimate*	*Standard error*	*p-value*
Age (years)	-0.003	0.004	0.485
PICU (mEq/lt)	-0.2	0.056	0.001
POD (mEq/lt)	-0.17	0.078	0.039
FIN (mEq/lt)	-0.107	0.074	0.163

For abbreviations see text

The mechanisms are not well understood. Described causal factors are the enhanced vagal tone, atrial inflammation, hypoxemia, hypovolemia, sepsis, electrolyte imbalances, increased right-heart pressure and right ventricular dilatation after the reduction of the pulmonary vascular bed due to major lung resection, pulmonary hypertension; but a general consensus is still lacking. Reported risk factors are intrapericardial ligation of pulmonary vessels, extent of resection, age and lung cancer [4,5]. We prospectively studied the perioperative sMg concentration changes in such 30 patients to determine if they were correlated with the appearance of SVD. Although we found a statistically significant difference between sMg just after surgery and the first postoperative day comparing to the baseline preoperative measurements, but not with the second postoperative day, we did not find a significant relation of those changes to the appearance of SVD. Our results differ from those of Amar et al., who found that there was no difference among perioperative sMg measurements. Moreover, we were not able - like them - to establish a relationship between sMg and the generation of SVD [6].

The majority of SVD occurs during the first 48 hours postoperatively. Although our study is the only prospective one that examines the possible association between sMg and the generation of perioperative SVD until the second postoperative day, our sample is not big enough, and has too few events (observed dysrhythmias) to produce a statistical analysis of sufficient power. However, exploratory data analysis and longitudinal analysis have been applied and resulted in not only a possible trend of the studied variables, in our attempt to model the outcome of occurrence of dysrhythmias, but also in a general approach of the methodology of our research. Furthermore, these data and data from other relevant studies could be aggregated in a future pooled meta-analysis, providing a more robust analysis.

Zwillinger, in 1935, reported the relation between Mg and cardiac dysrhythmias [7]. Mg causes arrhythmia acting either to K metabolism or as a Ca blocking agent [8,9]. It is a necessary co-factor for membrane adenosine-triphosphatonuclease (ATP-ase), which is critical for the transport of K into the cell and Na out from the cell. Thus, in the event of a Mg deficiency, the cell cannot keep its high intracellular level of K intact, despite an abundant supply of K in the extracellular space. Instead, this K is excreted in the urine. The interference from a Mg deficiency on the equilibrium of K may result in the resting membrane potential, changes in K conductance across the cell membrane, as well as disturbances in the repolarization phase. Mg may also act as a Ca blocking agent, as they share a common

intracellular transport mechanism. Therefore, Mg infusion causes peripheral vasodilatation, flushing, decrease in blood pressure and decrease in contractile strength of the heart. Mg affects the basic function of the cellular membrane and reacts directly but also indirectly with Ca and K metabolism [8,9]. We noticed that the serum K was within normal limits in all measurements of our study. We observed serum Ca concentrations following changes to sMg at every measurement time point.

It must be admitted that sMg disturbances may not be followed by clinical signs and symptoms because only 5% of total body Mg is found in serum, while the rest is intracellular [10]. Therefore, low sMg may coexist with normal intracellular Mg level, while normal sMg may coexist with tissue Mg deficiency [4]. Table 5 illustrates the variety of undesirable cardiac manifestations resulting from low levels of sMg [3,11].

Researchers have suggested the use of several drugs from all classes of antiarrhythmic drugs in the treatment of SVD. Although amiodarone involves danger of acute respiratory distress syndrome (ARDS), it is the most frequently drug used because of its direct action and the low incidence of recurrence [12-14]. We used amiodarone in the treatment of AF and we did not notice any side effect or any recurrence in the 30-day postoperative period.

Furthermore digoxin, flecainide, verapamile, as well as amiodarone have been administered with good results in the prevention of SVD, but unfortunately they have many side effects [13, 15-18]. The more recently introduced Ca channel blocker diltiazem has been met with enthusiasm, because it has a high efficacy in preventing SVD after major lung resections [19]. Moreover, researchers have reported the effectiveness of $MgSO_4$ administration either in the treatment, or in the prevention of SVD after cardiac and non-cardiac thoracic surgery [4,5,20,21]. Although our data demonstrated postoperative decrease of sMg concentration during the first 24 hours after major lung resection without significant relation to SVD generation, we support its prophylactic administration in the prevention of SVD in such cases.

Table 5. Hypomagnesemia-induced cardiac effects

Ventricular premature contractions and ventricular tachyarrhythmia
Prolonged PR and QT intervals
T-wave flattening
Atrial fibrillation and supraventricular tachycardia
Torsades de pointes
Coronary artery spasm
Increased sensitivity to digitalis
More extensive myocardial infarction
Possibly increased sensitivity to ventricular fibrillation and sudden death in ischemic heart disease

Conclusion

We observed that the incidence of postoperative SVD was 10% and occurred during the first 24 hours after major lung resection. Although our study demonstrated that sMg concentration changes significantly within the first 24 hours after major thoracic surgery, we could not support an association between the decrease in sMg to the generation of dysrhythmias. Also, the type of the operation was not found to be related with the sMg concentration or the appearance of arrhythmia. However, further studies are certainly required to detail this important clinical problem.

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