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□ Clinical Research Article □

Effect of various anesthetic induction agents on blood magnesium and calcium concentration

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Background: Decrease in blood magnesium and calcium concentration is associated with an increase in the incidence of arrhythmia, especially during the induction period. Therefore, it is important to evaluate the effects of propofol, pentothal sodium, and sevoflurane on calcium and magnesium concentration.

Methods: Thirty-six premedicated, ASA grade I patients were selected and randomly allocated into 3 groups. Six percent sevoflurane inhalation (sevo group), propofol 1.5 mg/kg (propofol group), and 5 mg/kg of pentothal sodium (pento group) were administered for anesthetic induction and anesthetic maintenance was done with end-tidal sevoflurane concentration at 3.5%. Blood sampling was performed during the pre-induction period (pre-induction), just before tracheal intubation (pre-intubation), and 2 min after intubation (post-intubation). pH corrected ionized magnesium and calcium were calculated and analyzed simultaneously.

Results: Both total calcium and magnesium concentrations decreased significantly in all groups during the pre-intubation and post-intubation periods compared with the pre-induction period. Ionized calcium only decreased significantly during pre-intubation and post-intubation in the pento group, and did not change throughout the study period in the sevo and propofol groups. Ionized magnesium did not change throughout the study period in any of the groups. pH corrected ionized calcium decreased significantly only at post-intubation in the pento group.

Conclusions: All anesthetic induction agents administered in this study can be used safely in terms of magnesium-associated arrhythmia. However, ionized calcium concentration decreased in the pento group, but all values were within normal limits. This finding indicated that it is safe to use propofol, pentothal sodium, and sevoflurane for anesthetic induction. **(Korean J Anesthesiol 2009; 56: 254～8)**

Key Words: Calcium, Magnesium, Pentothal sodium, Propofol, Sevoflurane.

INTRODUCTION

Magnesium is the fourth most common cation in the body and the second most common intracellular cation after potassium. It is associated with regulation of ion channels and phosphorylation, and is important as a cofactor identified in the enzyme active site involving energy metabolism and nucleic acid synthesis [1]. Serum concentrations of magnesium have been reported to decrease during anesthesia, mostly likely because of the effects of hemodilution, renal loss, chelating with anions, and adrenergic stimulation [2-6].

Additionally, hypomagnesemia has been reported during anesthetic induction with thiamylal or propofol [7,8].
The cause of hypomagnesemia during induction was associated with intracellular shift of magnesium by a direct effect of the anesthetic agents on the cell membrane itself. But there is little information regarding the effects of thiopental and sevoflurane on serum magnesium concentration, which is widely used as an induction anesthetic.

Hypomagnesemia may cause cardiac arrhythmias, refractory hypokalemia or hypocalcemia, and neuromuscular excitability [1,9]. Both hypocalcemia and hypomagnesemia may give rise to a prolonged QT interval.

In addition, hypocalcemia has been associated with arrhythmia, myocardial depression, hypotension, muscle weakness, paresthesia, seizures and blood coagulation disorders [10].

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Thus, it is necessary to evaluate calcium concentrations in susceptible patients before anesthesia.

The purpose of this study was to investigate the effects of propofol, pentothal sodium, and sevoflurane upon blood total and ionized magnesium (TMg and Mg^{2+}, respectively) and calcium concentrations (TCa and Ca^{2+}, respectively).

MATERIALS AND METHODS

After obtaining institutional review board approval and informed consent, 36 patients undergoing elective minor surgery were enrolled.

Patients with preoperative electrolyte imbalance, abnormal albumin concentration, diabetes mellitus, hypertension, renal failure, or cardiac disease were excluded.

Venous cannulation and first blood sampling was performed when patients arrived at the pre-anesthetic room. All patients received premedication of 0.004 mg/kg of glycopyrrolate intravenously.

Patients were divided into 3 groups (sevoflurane group, propofol group, pentothal group) in the baseline of the randomization table. Anesthetic induction was done with 6% sevoflurane inhalation (sevo group), propofol 1.5 mg/kg (propofol group), and pentothal sodium 5 mg/kg (pento group).

Anesthetic maintenance was done with an end tidal concentration of sevoflurane of 3.5% of vol. Mask ventilation was performed to maintain $PaCO_2$ between 35－40 mmHg after the patient lost consciousness. Five minutes after anesthetic induction, rocuronium 0.6 mg/kg was administered for tracheal intubation.

A second blood sampling was taken just before tracheal intubation. Laryngoscopy and tracheal intubation was performed 2 min after rocuronium administration.

The end-tidal concentration of sevoflurane was reduced to around 3% of vol and positive pressure mechanical ventilation was utilized with the tidal volume set at 8 mL/kg, respiration rate at 12 times/min, and oxygen and air at a rate of 1 L/min. A third blood sampling was taken at 2 min after tracheal intubation.

Normal saline infusion was limited to a rate of 2 mL/kg/hr to minimize fluid effects during the study period.

Blood samples were collected with standard heparinized blood gas syringes and analyzed for plasma Mg^{2+}, Hematocrit (Hct), pH, and ionized calcium concentration (Ca^{2+}), using ion-selective electrodes (AVL988 to 4, AVL List, Medical instrument, Graz, Austria). An additive-free glass tuned with an automated dry-slide reflectance method (Vitros, Johnson & Johnson Rochester, USA) was used for measurement of total magnesium and calcium concentration.

Statistical analysis was performed using SPSS 12.0 (SPSS 12.0 for Windows, SPSS Inc, Chicago, IL, USA). All values were expressed as mean ± SD. Demographic data were analyzed among the 3 groups with the Chi-square or 1-way analysis of variance (ANOVA) as appropriate.

A One-way analysis of variance (ANOVA) was also used to compare the baseline values of total and ionized calcium and magnesium concentration at each time point among the 3 groups with Bonferroni adjusted p-value and Tukey's post-hoc test.

Differences within the groups were analyzed using a repeated-measure ANOVA. A P value of <0.05 was considered significant.

RESULTS

A total of 36 patients (12 in each group) completed the study. Demographic characteristics were similar in all 3 groups (Table 1).

Heart rate increased significantly in the sevo group at the pre-intubation and post-intubation period compared to the pre-induction period, but increased in the pento and propofol group only during the post-intubation period.

Mean blood pressure decreased significantly during anesthesia induction in all groups and only increased significantly during tracheal intubation in the propofol group compared to baseline values.

The pH increased significantly during the pre-intubation and post-intubation periods in all groups (Table 2). Serum sodium levels did not change throughout the study period, but serum potassium levels decreased significantly after anesthetic in-

Table 1. Characteristics of Patients

	Sevo group (n = 12)	Pento group (n = 12)	Propofol group (n = 12)	P value
Sex (M/F)	6/6	6/6	6/6	1.0
Age (yr)	40 ± 12	41 ± 10	41 ± 13	0.9
Height (cm)	167 ± 6	164 ± 8	167 ± 9	0.6
Weight (kg)	64 ± 13	64 ± 10	65 ± 9	0.9

Value are mean ± S.D. or number of persons (n).

Table 2. The Change in Hemodynamics, Sodium, Potassium and pH

	Group	Pre-induction	Pre-intubation	Post-intubation
Mean blood pressure (mmHg)	Sevo	96 ± 13	77 ± 12[a)]	101 ± 22
	Pento	105 ± 11	84 ± 9[a)]	111 ± 20
	Propofol	96 ± 13	74 ± 8[a)]	109 ± 9[a)]
Heart rate (rpm)	Sevo	82 ± 11	95 ± 13[a)]	109 ± 15[a)]
	Pento	77 ± 14	79 ± 12	104 ± 13[a)]
	Propofol	81 ± 12	83 ± 12	103 ± 8[a)]
Serum sodium (mmol/L)	Sevo	144.2 ± 2.2	144.4 ± 0.9	144.3 ± 1.2
	Pento	144.3 ± 2.9	145.1 ± 2.0	144.1 ± 1.8
	Propofol	146.2 ± 4.6	145.5 ± 3.1	145.1 ± 2.1
Serum potassium (mmol/L)	Sevo	4.4 ± 0.5	4.2 ± 0.3[a)]	4.2 ± 0.3[a)]
	Pento	4.6 ± 0.3	4.3 ± 0.2[a)]	4.3 ± 0.2[a)]
	Propofol	4.3 ± 0.5	3.9 ± 0.5[a)]	4.0 ± 0.6[a)]
pH	Sevo	7.36 ± 0.03	7.42 ± 0.02[a)]	7.42 ± 0.04[a)]
	Pento	7.37 ± 0.02	7.42 ± 0.03[a)]	7.43 ± 0.03[a)]
	Propofol	7.35 ± 0.03	7.40 ± 0.03[a)]	7.40 ± 0.04[a)]
pCO_2 (mmHg)	Sevo	49.9 ± 5.4	42.8 ± 4.4[a)]	42.0 ± 5.6[a)]
	Pento	51.3 ± 4.7	42.6 ± 4.9[a)]	41.1 ± 4.2[a)]
	Propofol	52.0 ± 3.4	47.6 ± 3.0[a)]	46.2 ± 4.4[a)]

Value is mean ± SD. [a)]$P < 0.05$ versus pre-induction period.

Table 3. The Change of Total and Ionized Calcium Concentration during Induction Period

	Group	Pre-induction	Pre-intubation	Post-intubation
Total calcium (mg/dL)	Sevo	9.20 ± 0.37	8.94 ± 0.29[a)]	8.89 ± 0.35[a)]
	Pento	9.3 ± 0.43	9.03 ± 0.35[a)]	8.93 ± 0.38
	Propofol	9.23 ± 0.49	8.91 ± 0.36[a)]	8.89 ± 0.43[a)]
Ionized calcium (mmol/L)	Sevo	1.19 ± 0.1	1.13 ± 0.05	1.11 ± 0.05
	Pento	1.23 ± 0.05	1.14 ± 0.05[a)]	1.11 ± 0.05[a)]
	Propofol	1.15 ± 0.08	1.11 ± 0.08	1.11 ± 0.09

Values are expressed as mean ± SD. [a)]$P < 0.05$ for versus Pre-induction.

Table 4. The Change of Total and Ionized Magnesium Concentration during Induction Period

	Group	Pre-induction	Pre-intubation	Post-intubation
Total magnesium (mg/dL)	Sevo	0.91 ± 0.07	0.87 ± 0.06[a)]	0.86 ± 0.06[a)]
	Pento	0.87 ± 0.05	0.83 ± 0.05[a)]	0.82 ± 0.05[a)]
	Propofol	0.91 ± 0.06	0.86 ± 0.05[a)]	0.87 ± 0.05[a)]
Ionized magnesium (mmol/L)	Sevo	0.574 ± 0.077	0.570 ± 0.059	0.570 ± 0.063
	Pento	0.585 ± 0.04	0.563 ± 0.039	0.574 ± 0.072
	Propofol	0.593 ± 0.058	0.584 ± 0.087	0.602 ± 0.077

Values are expressed as mean ± SD. [a)]$P < 0.05$ for versus Pre-induction.

duction and tracheal intubation in all groups. However, there were no potassium concentration values that were out of normal range.

Total calcium and magnesium concentration decreased significantly in all groups during the pre-intubation and post-intubation periods compared to the pre-induction period (Table 3, 4).

However, tracheal intubation did not decrease either total calcium or magnesium concentrations (Table 3, 4).

Ionized calcium only decreased significantly during pre-intubation and post-intubation in the pento group, but did not change throughout the study period in either the sevo or propofol groups (Table 3). In addition, ionized calcium values we-

Table 5. The Change of pH Corrected Ionized Magnesium and Calcium Concentration during Induction Period

	Group	Pre-induction	Pre-intubation	Post-intubation
Ionized magnesium (mmol/L)	Sevo	0.568 ± 0.077	0.573 ± 0.059	0.573 ± 0.063
	Pento	0.581 ± 0.04	0.566 ± 0.039	0.578 ± 0.072
	Propofol	0.589 ± 0.058	0.584 ± 0.087	0.602 ± 0.077
Ionized calcium (mmol/L)	Sevo	1.17 ± 0.1	1.14 ± 0.05	1.12 ± 0.05
	Pento	1.21 ± 0.05	1.15 ± 0.05	1.12 ± 0.05[a)]
	Propofol	1.13 ± 0.08	1.11 ± 0.08	1.11 ± 0.09

Values are expressed as mean ± SD. [a)]$P < 0.05$ for versus Pre-induction.
Ionized Ca concentration per pH unit was 0.50 mmol/L and ionized Mg concentration per pH was 0.16 mmol/L [11].

re all within normal limits.

Ionized magnesium did not change throughout the study period in any of the groups (Table 4).

There is no difference in total and ionized calcium and magnesium concentration at each time point among groups (Table 3, 4).

Both pH corrected ionized magnesium and calcium did not changed throughout the study period except ionized calcium concentration at post-intubation period in pento group (Table 5) [11].

DISCUSSION

Anesthetic induction with sevoflurane, pentothal sodium, and propofol decreased both total calcium and magnesium concentrations, but ionized magnesium did not decrease significantly in any of the groups and ionized calcium only decreased in the pentothal group.

Total magnesium concentration is the sum of 3 fractions: a protein-bound fraction (30%), a chelated fraction (15%), and an ionized fraction (55%). The ionized fraction is physiologically active and homeostatically regulated [12]. Changes in pH in the specimen affect the bindings of these ions to plasma proteins, mainly albumin, because hydrogen ions compete with calcium and magnesium protein binding sites [13].

Manual ventilation caused the blood to become a more alkaline environment in our study which can participate in decreasing ionized magnesium and calcium concentrations to some degree. Therefore, pH corrected ionized calcium concentrations decreased only at pre-intubation period in pento group in contrary to the results of the change of uncorrected ionized calcium concentration.

These results mean that non-ionized magnesium, a chelated fraction and a protein-bound fraction, did not changed with anesthetic induction but ionized calcium showed a decreasing tendency. Thus, further study is needed to verify how each magnesium fraction changes during anesthetic induction and an electrophysiologic study will be necessary to find the mechanism.

The discrepancy between of the change of ionized calcium concentration during induction was probably caused by the degree of decrease of ionized calcium upon pH change is approximately 3 times greater than those of ionized magnesium [13].

In addition, isoflurane caused a significant increase in serum parathyroid hormone which decrease the ionized calcium concentration [14]. Another studies showed that enflurane increased renal phosphorus clearance via parathyroid gland activity [15]. It can be postulated from the previous papers that sevoflurane may play a major role in decrease of ionized calcium concentration.

Although pentothal sodium decreased the ionized calcium at post-intubation, the value is similar to values from other two anesthetic agents.

Cohen et al. showed that in pediatric patients, ionized calcium levels decreased significantly, but ionized magnesium did not change during general anesthesia with propofol or sevoflurane [16]. They explained that decreased ionized calcium may be due to hyperventilation, which is common during general anesthesia.

Our study did not show a decrease of ionized calcium during propofol or sevoflurane induction probably because pediatric patients were more hyperventilated than adults. However, ionized calcium decreased significantly in the pentothal group, which is suggestive that it is not appropriate for patients with prolonged QT syndrome [17].

On the basis that the more patients were hyperventilated, the more ionized magnesium and calcium might decrease, it may

be necessary to be cautious of providing bag-mask ventilation in patients with prolonged QT intervals.

Clinical and experimental studies demonstrated that increased circulating catecholamine causes hypomagnesemia as the influx of magnesium into the intracellular compartment is under the influence of β-adrenergic activity [18,19].

Our study showed that tracheal intubation did not decrease plasma magnesium concentrations. Although tracheal intubation can cause sympathetic discharge, the anesthetic levels applied in our study were sufficient to blunt increases in blood pressure compared to baseline values, except for those in the propofol group. In addition, the sampling time may have been too short to detect changes in plasma magnesium concentrations.

A limitation of our study was that we did not check the effects of pentothal sodium and propofol on magnesium and calcium, but measured the effects of a bolus of these agents with adjunctive sevoflurane.

In conclusion, ionized magnesium concentrations did not change during induction with sevoflurane, pentothal sodium, and propofol.

Although pentothal sodium decreased ionized calcium concentrations, no values were out of normal range. All anesthetic induction agents administered in this study can be used safely in terms of serum magnesium and calcium associated arrhythmia.

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