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Intravenous Administration of Acetated Ringer's Solution Containing Magnesium and 1% Glucose during Neurosurgery

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Abstract

Lactated Ringer's solution and acetated Ringer's solution are used for extracellular fluid replacement during neurosurgery. Since these solutions are glucose- and Mg-free, they may precipitate potentially serious complications partly due to hypomagnesemia. We compared newly-available Mg- and 1% glucose-containing acetated Ringer's solution with conventional Ringer's solution by measuring ionized Mg concentration, glucose metabolism, rate of occurrence of arrhythmia and hypertension, and neurological outcome during neurosurgery. Sixty patients scheduled for neurosurgery were randomly assigned into three equal groups; those who received acetated Ringer's solution containing 1% glucose and Mg (Group 1), lactated Ringer's solution (Group 2), and acetated Ringer's solution (Group 3).

The ionized Mg blood concentration was maintained in Group 1 while gradual falls were observed in both Group 2 and Group 3. Although a slight rise in blood glucose was observed in the Group 1, no profound hyperglycemia was noted. The incidence of arrhythmia and hypertension, and the neurological outcome, were not different among the groups. We conclude that acetated Ringer's solution containing Mg and 1% glucose seems effective in maintaining blood Mg concentration without causing profound hyperglycemia, hypertension, or lethal arrhythmia during neurosurgery.

Key words; magnesium, glucose, neurosurgery, pyruvate, fatty acid

Introduction

Although magnesium (Mg) is an essential mineral for the human body, there is little information on the effects and roles of Mg during neurosurgery.

Lactated Ringer's solution and acetated Ringer's solution are currently used for extracellular fluid replacement in patients undergoing neurosurgery. These solutions are slightly hyponatremic (sodium concentration, approximately 130mEq/L) and glucose- and Mg-free. Accordingly, perioperative administration of large amounts of these solutions could cause abnormally high blood pressure[1~3], cardiac arrhythmia[4~6], neurological symptoms such as depression and hallucinosis[7,8], and allodynia (lowered threshold)[9,10], partly due to hypomagnesemia mainly by blood dilution.

In the present study, we compared the acetated Ringer's solution containing Mg and glucose with two conventional solutions; acetated Ringer's solution and lactate Ringer's solution, in terms of the effects on changes in ionized Mg concentration, glucose metabolism, the incidence of cardiac arrhythmia and hyper-

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tension, neurological outcome during the perioperative period in neurosurgical patients.

Methods

This study was conducted with the approval of the Institutional Review Board and after obtaining a written consent from each patient or family member. Detailed explanation regarding the objectives and the contents of the study was provided. The subjects were 60 adult patients with an ASA physical status of I-II who were admitted for major elective neurosurgery lasting at least 6 hours. Subjects with chronic conditions that could alter blood Mg concentrations, e.g., those with liver dysfunction, kidney dysfunction, endocrine disorders, or metabolic disorders, and those receiving steroids or loop diuretics, were excluded from the study.

The patients were randomly assigned to three groups; those to receive acetated Ringer's solution containing 1% glucose and Mg (Physio 140™) (Group 1, with Mg), lactated Ringer's solution (Hartmann's solution pH: 8™) (Group 2, Mg-free), and acetated Ringer's solution (Veen F™) (Group 3, Mg-free). The ingredients of these three solutions are listed in **Table 1**. The study solutions were administered at a flow rate of 10mL/kg/hr during the first hour after general anesthesia. Then, the infusion rate was adjusted to within the range of 5～10mL/kg/hr, depending on the patient's condition. Propofol (2mg/kg) and vecuronium (0.1mg/kg) was used for the induction of anesthesia, and fentanyl, propofol, and/or isoflurane was used for maintenance throughout surgery.

During surgery, arterial pressure, central venous pressure, electrocardiogram, SpO_2, and end-expiratory carbon dioxide partial pressure were monitored in all patients. Blood electrolyte concentrations and blood gases were evaluated at the preinfusion of each solution, and at 30, 60, 120, 360 minutes, and 24 hours after starting the infusion of each solution. Stat Profile M (NOVA Biomedical, Waltham, MA) was used for evaluation of blood electrolytes and blood gases. In addition, blood concentrations of pyruvic acid and free fatty acids were measured at preinfusion, and at 360min and 24 hours after the first evaluation using an automatic analyzer (7170, Hitachi, Tokyo, Japan). The consciousness status was evaluated by the GCS (Glasgow Coma Scale) at the preinfusion, 24 hours after starting the infusion of each solution, and at the time of discharge from the hospital. Cardiac arrhythmia was defined as more than a single premature contraction per minute. Hypertension was defined as mean arterial blood pressure of more than 100mmHg.

Statistical analysis

Results are expressed as mean ± SD. Demographic data and baseline values, GCS, proportion of patients who developed arrhythmia and hypertension were analyzed by the unpaired t-test or chi-square analysis. Differences between groups were evaluated by ANOVA followed by the Student-Newman-Keuls test. $P < 0.05$ was considered to represent

Table 1 Ingredients of three extracellular solutions used in the present study

	Group 1 (Physio 140™) acetated Ringer's solution containing 1% glucose and Mg	Group 2 (Hartmann's pH 8™) lactated Ringer's solution (glucose- and Mg-free)	Group 3 (Veen F™) acetated Ringer's solution (glucose- and Mg-free)
pH	5.9-6.2	7.8-8.2	6.5-7.5
Na^+	140mEq/l	131mEq/l	131mEq/l
K^+	4mEq/l	4mEq/l	4mEq/l
Cl^-	115mEq/l	110mEq/l	109mEq/l
Ca^{2+}	3mEq/l	3mEq/l	3mEq/l
Mg^{2+}	2mEq/l	0mEq/l	0mEq/l
Glucose	10g/l	0g/l	0g/l
Acetate	$Acetate^-$ 25mEq/l	0mEq/l	$Acetate^-$ 28mEq/l
Lactate	0mEq/l	$Lactate^-$ 28mEq/l	0mEq/l

Table 2 Patients' profiles

	Group 1	Group 2	Group 3
Male/Female (number of patients)	11/9 (n=20)	12/8 (n=20)	11/9 (n=20)
Age (years) *	45.8±18.2	49.9±16.6	52.6±15.8
Weight (kg) *	60.5±13.5	56.2±11.9	59.3±13.0
Operation time (min) *	419±191	385±113	371±102
Anesthesia time (min) *	585±196	499±141	502±110
Quantity of solution (mL) *	3118±1134	2784±1293	2500±951
Quantity of urine (mL) *	2213±1023	1833±908	1735±1331
Anesthesia (TIVA/isoflurane)	6/14 (n=20)	5/15 (n=20)	6/14 (n=20)
Disease: brain tumor	11	12	14
cerebral aneurysm	4	5	4
moyamoya disease	3	1	1
internal carotid stenosis	2	2	1

*Values are mean±SD.

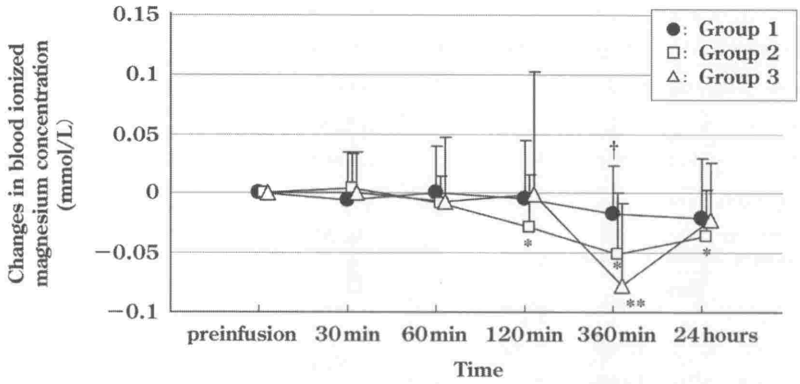

Figure 1 Time-course of changes in blood ionized magnesium concentrations.
Values are mean±SD. In Group 1 (with Mg), ionized Mg blood concentrations were maintained until 24 hours after induction of anesthesia compared to Group 2 and Group 3 (Mg-free). †$P<0.05$, compared with Group 3, *$P<0.05$ compared with preinfusion value. **$P<0.01$ compared with the control value.

statistical significance.

Results

A. Patients' characteristics

Table 2 lists the patient characteristics, methods of anesthesia, and background conditions. There were no significant differences between groups regarding age, sex, body weight, duration of surgery and anesthesia, infusion volume, urine output, and diseases.

B. Changes in blood Mg and glucose concentrations

Differences in ionized blood Mg concentrations between the three groups of patients during perioperative periods are shown in **Fig. 1**. Blood ionized Mg concentrations decreased significantly inpatients who received Mg-free solutions following the beginning of anesthesia. In Group 2, blood Mg concentrations at 120min, 360min and 24 hours were significantly lower than the respective values of the control ($P<0.05$). In Group 3, blood Mg concentration at 360min was significantly lower than respective value of the control ($P<0.01$). The decrease in Mg in Group 1 (with Mg) was significantly less compared to that of Group 3 (Mg-free) at 360min ($P<0.05$). Therefore, blood ionized Mg concentration was maintained during anesthesia in Group 1 (with Mg) compared with Groups 2 and 3 (Mg-free). A gradual self-recovery of ionized Mg blood concentrations was observed in all three groups 24 hours later. The total amount of ionized magnesium received by patients of

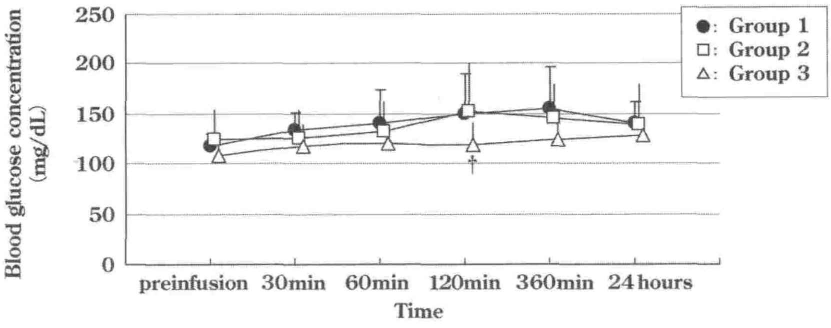

Figure 2 Time-course of changes in blood glucose concentration.

Values are mean±SD. Blood glucose concentration tended to increase in all three groups. Only at the 120min, blood glucose concentration of Group 3 was significantly lower than that of Groups 1 and 2 ($P<0.01$). †$P<0.01$, compared with Group 1.

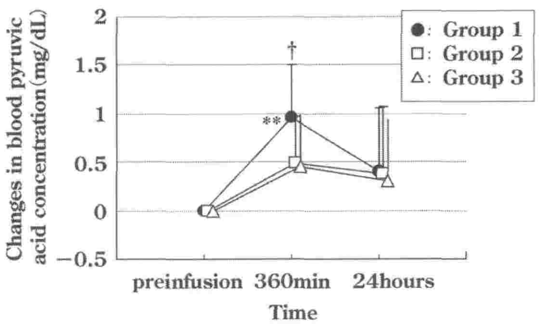

Figure 3 Time-course of changes in blood pyruvic acid concentration.

Values are mean±SD. At 360mins, the mean pyruvic acid concentration of Group 1 (with glucose) was significantly higher than those of Groups 2 and 3 (glucose-free). Pyruvic acid concentration of Group 1 at 360min was significantly higher than the preinfusion value of the same group. †$P<0.01$, compared with Groups 2 and 3. **$P<0.01$, compared with the preinfusion value for the same group.

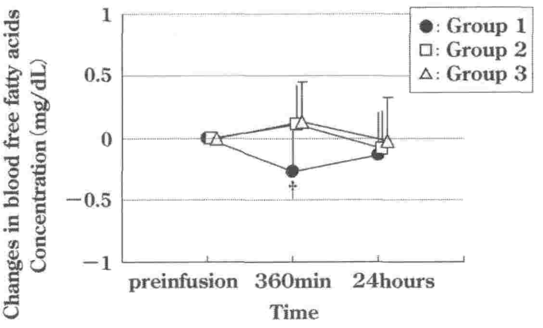

Figure 4 Time-course of changes in blood free fatty acids concentration.

Values are mean±SD. At 360min, the mean free fatty acid concentration of Group 1 (with glucose) was significantly lower than those of Groups 2 and 3 (glucose-free). †$P<0.01$, compared with Groups 2 and 3.

Group 1 was 6.24±2.27mEq.

Fig. 2 shows changes in perioperative blood glucose concentrations. Blood glucose concentration tended to increase in all three groups. Only at 120min, blood glucose concentration of Group 3 was significantly lower than the respective values of Groups 1 and 2 ($P<0.01$). The total amount of glucose provided to patients of Group 1 was 31.2±16.3g.

C. Changes in blood pyruvic acid and free fatty acid concentrations

Fig. 3 summarizes the changes in perioperative pyruvic acid concentrations. Pyruvic acid concentration at 360min was significantly higher in patients of Group 1 than the respective values of Groups 2 and 3 ($P<0.01$). In Group 1, pyruvic acid concentration at 360min was significantly higher than that measured at preinfusion ($P<0.01$).

Changes in perioperative free fatty acid concentrations are shown in **Fig. 4**. Free fatty acid concentration at 360min was significantly lower in Group 1 than in Groups 2 and 3 ($P<0.01$). There were no significant differences among groups regarding free fatty acid and pyruvic acid concentrations at 24 hours. Furthermore, there was no significant difference among groups regarding the ratio of pyruvic acid to lactate acid concentration (data not shown).

D. Other changes

Table 3 lists the effect of perfusion fluids on arterial blood gases. There were no significant differences

Table 3 Arterial blood gases

		preinfusion	60min	120min	360min
pH	Group 1	7.45±0.06	7.44±0.05	7.44±0.05	7.46±0.05
	Group 2	7.48±0.05	7.47±0.03	7.46±0.04	7.47±0.04
	Group 3	7.44±0.06	7.45±0.05	7.46±0.06	7.46±0.05
$PaCO_2$	Group 1	38.6±4.6	39.0±4.9	39.4±4.7	37.9±5.1
	Group 2	36.5±4.0	37.5±4.5	37.2±5.5	38.5±4.4
	Group 3	38.5±6.8	36.9±4.2	37.6±5.7	37.4±4.7
HCO_3^-	Group 1	26.0±3.5	26.5±3.5	26.5±3.5	26.5±3.5
	Group 2	27.2±3.0	27.2±3.1	26.5±3.8	28.1±2.7
	Group 3	25.8±3.5	25.8±3.2	26.5±3.0	26.3±3.2
BE	Group 1	3.4±3.7	2.9±3.5	2.8±3.5	3.4±3.4
	Group 2	4.6±2.8	4.4±2.5	4.0±3.3	4.8±2.6
	Group 3	1.9±3.4	2.4±2.8	3.1±3.2	2.8±3.2
Na	Group 1	141.7±1.9	141.8±3.1	140.7±3.3	140.2±3.2
	Group 2	141.5±2.3	140.8±2.8	140.1±4.1	139.4±2.8
	Group 3	140.1±3.7	139.5±3.9	137.8±4.5	138.5±3.6

Values are mean±SD.

Table 4 Glasgow Coma Scale in each group of patients at three time periods

	Group 1	Group 2	Group 3
Pre-operation	14.8±0.92	14.9±0.24	15
Post-operation	14.8±0.42	14.8±0.43	14.7±0.58
Hospital Discharge	15	15	15

Values are mean±SD.

among the groups regarding changes in pH, $PaCO_2$, HCO_3^-, and BE. There were also no significant differences among the three groups regarding blood sodium and calcium concentrations. The postoperative consciousness status scores evaluated by GCS are shown in **Table 4**. There was no significant difference in GCS among the three groups.

E. Changes in blood pressure and appearance of cardiac arrhythmias

Regarding the mean arterial blood pressure, although there was no significant difference among the groups, 3 patients of Group 2 (Mg-free) and 2 patients of Group 3 (Mg-free) required continuous administration of anti-hypertensive agents, whereas this was not necessary in any of the patients of Group 1 (with Mg). These 5 patients consisted of two patients with brain aneurysm who were diagnosed of hypertension, and three patients who had brain tumor with no previous history of hypertension.

In this study, arrhythmia appeared in 4 patients who received Mg-free solution (three from Group 2 and one from Group 3, all were supra-ventricular premature contractions), and 2 patients who received Mg-containing Ringer solution (Group 1, one developed supra-ventricular premature contraction and the other one had ventricular premature contraction). However, no lethal arrhythmia was observed, and there was no significant difference among the groups.

All patients recovered postoperatively without worsening neurological status compared to the preoperative status.

Discussion

In the present study, we found the new solution: 1) maintained ionized Mg blood concentrations, 2) increased blood pyruvic acid concentrations, 3) decreased free fatty acid blood concentrations without any detrimental effects on outcomes. These results suggest that the solution could be used during neurosurgery to avoid hypomagnesemia along with adequate glucose metabolism.

The goals of fluid management for patients undergoing neurosurgery include replacement of intravascular volume deficits, preservation of cerebral blood flow and metabolism. Although various solutions are recommended during neurosurgery, the search for appropriate fluid therapy is still a challenging issue.

Falls in perioperative ionized Mg blood concentrations are thought to occur for the following reasons 1) Blood dilution resulting from the administration of intravenous solution, 2) poor perioperative supplementation of Mg, 3) increased excretion of Mg, 4) effects of blood albumin concentration, and 5) transfer of Mg from the extracellular space to the intracellular space (elevated catecholamine secretion stimulates β_2 receptors in the liver or skeletal muscle, followed by increased uptake of Mg into the cells)[11,12].

The ionized Mg blood concentrations gradually decreased in the Mg-free groups. However, the levels were maintained in patients who received Mg-containing acetated Ringer's solution during neurosurgery. These results were consistent with previous reports that Mg-containing solution was effective for maintenance of perioperative ionized Mg blood concentrations by supplying sufficient Mg without causing hypermagnesemia and by preventing blood dilution upon administration of intravenous solutions. In our study, the fall in ionized Mg concentration tended to recover within 24 hours after surgery.

The maintenance of stable blood Mg concentration is important based on the inhibitory roles of intracellular Mg on Ca influx and Ca release, and those of extracellular Mg on voltage-gated Ca channel followed by vasodilation[13~15]. Based on these roles, Mg is considered to be a physiological antagonist of Ca. In clinical practice, a rise in blood pressure due to low blood Mg concentration might be problematic. However, in our study, there was no significant difference in blood pressure among the three groups. Nevertheless, no patients who received Mg-containing solution required anti-hypertensive agent.

Previous studies indicated that hypomagnesemia could trigger cardiac arrhythmia[4,5]. While the exact underlying mechanism of supraventricular tachycardia and ventricular arrhythmia is not well known, it could be mediated by a rise in intracellular ionized Ca concentration caused by inhibition of the Na-K pump or increased sensitivity of ionized Ca channel[4,5]. Furthermore, Zuccala et al[16] reported that a decrease of ≥ 0.125mmol/L in ionized Mg blood concentration could lead to arrhythmia. Shils et al[17] also reported that arrhythmia might occur even if the decrease was only 10 to 30% of normal levels. Therefore, administration of magnesium sulfate to cardiac surgical patients reduces the risk of cardiac arrhythmia[18~22]. Clinically, intravenous administration of Mg is a safe and effective method as it reduces the frequency of arrhythmias and mortality in acute myocardial infarction[23]. In this study, arrhythmia (not lethal) were observed in some patients of every group. Although prophylactic magnesium treatment for cardiac arrhythmia has remained controversial[24], further studies are needed to elucidate the anti-arrhythmic properties of the currently available acetated Ringer's solution used in neurosurgery.

Supplying sufficient energy is recommended not only in the intensive care unit but also in the operating room. There are various merits regarding perioperative glucose supplementation. For example, glucose may prevent hypoglycemia, provide a protein-sparing effect, and may inhibit ketosis due to endogenous fat mobilization. Although the 1% glucose solution used in our study could potentially cause hyperglycemia, which could aggravate brain damage, only a slight rise in glucose concentration was observed compared to patients treated with acetated Ringer's solution, and no significant difference was observed with patients on lactated Ringer's solution. Furthermore, none of the patients who received 1% glucose-containing solution showed less GCS throughout the perioperative period. Taken together, the new solution does not seem to cause neuronal damage and can be useful during neurosurgery. Thus, the 1% glucose-containing acetated Ringer's solution does not seem to cause profound hyperglycemia or worsening of Glasgow Coma Scale.

A rise in free fatty acid suggests endogenous fat mobilization[25]. In the present study, free fatty acid concentration was decreased in patients of Group 1 (with glucose) and increased in those of Groups 2 and 3 (glucose-free). Regarding pyruvic acid concentration, the level was significantly increased in patients of Group 1 (with glucose), but remained unchanged in those of Groups 2 and 3 (glucose-free) at 360min. These results suggest that sufficient aerobic metabolism progressed in patients who received glucose and Mg[26,27]. In other words, the 1% glucose-containing acetated Ringer's solution could promote glucose metabolism and inhibit endogenous fat mobilization.

In summary, acetated Ringer's solution containing Mg and 1% glucose effectively maintained blood Mg concentration and activated aerobic metabolism without causing profound hyperglycemia, hypertension, or lethal arrhythmia during neurosurgery.

References

1) Gums JG: Magnesium in cardiovascular and other disorders. Am J Healthy Syst Pharm 2004; 61:1569-76.
2) Kawano Y, Matsuoka H, Takishita S, et al: Effects of magnesium supplementation in hypertensive patients: assessment by office, home, and ambulatory blood pressures. Hypertension 1998; 32: 260-5.
3) Iseri LT, French JH: Magnesium: Nature's physiologic calcium blocker. Am Heart J 1984; 108: 188-93.
4) Song Y, Lui QY, Vasolle M: On the antiarrhythmic actions of magnesium in single guinea-pig ventricular myocytes. Clin Exp Pharmacol Physiol 1996; 23: 830-8.
5) Ceremuzynski L, Gebalska J, Wolk R, et al: Hypomagnesemia in heart failure with ventricular arrhythmias. Beneficial efforts of magnesium supplementation. J Intern Med 2000; 247: 78-86.
6) Teo KK, Yusuf S, Collins R, et al: Effects of intravenous magnesium in suspected acute myocardial infraction: overview of randomized trials. Br Med J 1991; 303: 1499-503.
7) Gambling DR, Birmingham CL, Jenkins LC: Magnesium and the anesthetist. Can J Anesth 1988; 35: 644-54.
8) Elin RJ: Magnesium metabolism in health and disease. Dis Mon 1988; 34: 161-218.
9) Nowak L, Bregestovski P, Ascher P, et al: Magnesium gates glutamate-activated channels in mouse central neurons. Nature 1984; 307: 462-5.
10) Tramer MR, Schneider J, Marti RA, et al: Role of magnesium sulfate in postoperative analgesia. Anesthesiology 1996; 84: 340-7.
11) Joborn H, Akerström G, Ljunghall S: Effects of exogenous catecholamines and exercise on plasma magnesium concentrations. Clin Endocrinol (Oxf) 1985; 23: 219-26.
12) Nastou H, Sarros G, Palta M, et al: Fluctuations in serum magnesium levels during total intravenous anaesthesia with propofol. Magnes Res 1996; 9: 47-53.
13) Rotevatn S, Sårheim H, Murphy E: Intracellular free magnesium concentration: relevance to cardiovascular medicine. Acta Physiol Scand Suppl 1991; 599: 125-33.
14) Romani A, Scarpa A: Regulation of cell magnesium. Arch Biochem Biophys 1992; 298: 1-12.
15) Wu J, Lipsius S: Effects of extracellular Mg^{2+} on T- and L-type Ca^{2+} currents in single atrial myocytes. Am J Physiol 1990; 259: H1842-50.
16) Zuccalà G, Pahor M, Lattanzio F, et al: Detection of arrhythmogenic cellular magnesium depletion in hip surgery patients. Br J Anaesth 1997; 79: 776-81.
17) Shils ME: Experimental human magnesium depletion. Medicine (Baltimore) 1969; 48: 61-85.
18) England MR, Gordon G, Salem M, et al: Magnesium administration and dysrhythmias after cardiac surgery. A placebo-controlled, double-blind, randomized trial. JAMA 1992; 268: 2395-402.
19) Fanning WJ, Thomas CS Jr, Roach A, et al: Prophylaxis of atrial fibrillation with magnesium sulphate after coronary artery bypass grafting. Ann Thorac Surg 1991; 52: 529-33.
20) Jian W, Su L, Yiwu L: The effects of magnesium prime solution on magnesium levels and potassium loss in open heart surgery. Anesth Analg 2003; 96:1617-20.
21) Huss MG, Wasnick JD: Mgnesium and off-pump coronary artery bypass. J Cardiothorac Vasc Anesth 1999; 13: 374-5.
22) Wilkes NJ, Mallett SV, Peachey T, et al: Correction of ionized plasma magnesium during cardiopulmonary bypass reduces the risk of postoperative cardiac arrhythmia. Anesth Analg 2002; 95: 828-34.
23) Horner SM: Efficacy of intravenous magnesium in acute myocardial infarction in reducing arrhythmias and mortality: Meta-analysis of magnesium in acute myocardial infarction. Circulation 1992; 86: 774-9.
24) Fawcett WJ, Haxby EJ, Male DA: Magnesium. physiology and pharmacology. Br J Anaesth 1999; 83: 302-20.
25) Jouven X, Charles MA, Desnos M, et al: Circulating nonesterifed fatty acid level as a predictive risk factor for sudden death in the population. Circulation 2001; 104: 756-61.
26) Poole RC, Halestrap AP: Transport of lactate and other monocarboxylates across mammalian plasma membranes. Am J Physiol 1993; 264: C761-82.
27) Poole RC, Sansom CE, Halestrap AP: Studies of the membrane topology of the rat erythrocyte H+/lactate cotransporter (MCT1). Biochem J 1996; 320: 817-24.