Research Paper

Title: Serum magnesium levels and neurological outcomes in patients undergoing targeted temperature management after cardiac arrest

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Contribution to Emergency Nursing Practice

- The current state of scientific knowledge on serum magnesium levels indicates that its role has not been established for cardiac arrest patients undergoing targeted temperature management.
- The main finding of this research is that our multivariable analysis showed that magnesium levels did not predict neurological outcome after cardiac arrest.
- Key implications for emergency nursing practice from this research is that the magnesium

levels might not predict an unfavorable neurological outcome.

ABSTRACT

Introduction: Magnesium (Mg) plays a neuroprotective role at the physiologic level but its neuroprotective role in cardiac arrest patients undergoing targeted temperature management is not well established. We performed multiple logistic regression analysis in order to evaluate whether the Mg levels can predict neurological outcome for patients who underwent targeted temperature management after cardiac arrest.

Methods: This study had a correlational design using retrospective chart review methodology. We retrospectively investigated data on 86 patients who underwent targeted temperature management after cardiac arrest from December 2015 to November 2017. The primary outcome was to determine whether Mg levels predict unfavorable neurological outcomes for patients with return of spontaneous circulation after targeted temperature management. Cerebral Performance Categories (CPC) 3, 4 or 5 indicated unfavorable neurological outcomes. The CPC scores patients' conditions as follows: CPC 1, normal or mild disability; CPC 2, moderate disability, but independent in activities of daily life; CPC 3, severe disability and dependent in activities of daily life; CPC 4, persistent vegetative state; and CPC 5, death. We performed multiple logistic regression to evaluate the primary outcome adjusting for the time to return of spontaneous circulation, motor score of Glasgow Coma Scale, first recorded cardiac rhythm, pH, and Mg levels.

Results: Of the 86 patients, 58 had unfavorable neurological outcomes. Mean hospital stay was 19 days. Multivariable analysis indicated that the Mg levels was not associated with an

unfavorable neurological outcome. On the other hand, the time to return of spontaneous circulation >30 minutes and motor score of Glasgow Coma Scale = 1 were significantly associated with an unfavorable neurological outcome.

Discussion: The Mg levels was not associated with an unfavorable neurological outcome in the multivariable analysis. We found that the time to return of spontaneous circulation >30 minutes and a motor score of the Glasgow Coma Scale = 1 might predict an unfavorable neurological outcome. This finding may help providers in predicting an unfavorable neurological outcome after cardiac arrest. Findings from this study are limited in application to practice due to the study using only small sample size in a single facility. This scientific area requires further research.

Key words: Cardiac arrest, Magnesium, Resuscitation, Survival, Targeted temperature management

Abbreviations: CPC, cerebral performance categories; GCS, Glasgow Coma Scale; Mg, magnesium; ROSC, return of spontaneous circulation; TTM, targeted temperature management.

INTRODUCTION

Cardiac arrest is a major public health issue in the developed world. [1] More than 100,000 cases occur every year in Japan. [2] In spite of recurrent updates of guidelines for cardiopulmonary resuscitation and the spread of the “Chain-of-survival”, the survival proportions for patients in many countries have been very low after cardiac arrest. [2,3]

It is well known that targeted temperature management (TTM) is one of the key treatments

to improve survival after cardiac arrest. [4] Magnesium (Mg) plays a neuroprotective role at the physiologic level but the role of serum Mg in clinical resuscitation is unknown. Naksuk et al. found that serum Mg ≥2.4 mg/dl was a predictor of increased hospital mortality[5], and Haider et al. showed that hypermagnesemia was a predictor of mortality in critically ill patients. [6] Perucki et al. reported that high serum Mg levels correlated with unfavorable neurologic outcomes in patients who underwent TTM after cardiac arrest. [7] In the study conducted by Perucki et al., TTM had a target core temperature of 33℃ that was provided for 48 hours. [7] Resuscitation science has not formulated a protocol for TTM [4] and various protocols have been used and continue to be evaluated. However, the association between the Mg levels at administration of different TTM protocols and neurological outcomes in patients with cardiac arrest has not been evaluated.

In our hospital, patients who achieve return of spontaneous circulation (ROSC) after cardiac arrest are provided TTM and their core temperature is kept at 36°C for 24 hours. We examined the association between Mg levels at the administration of TTM and neurological outcomes in patients after cardiac arrest in our hospital. Our research question for this study was whether the Mg levels predict neurological outcomes for patients undergoing TTM after cardiac arrest.

METHODS

This study used a correlational design using retrospective chart review methodology.

The setting of the study was the Intensive Care Unit in the Department of Emergency and Critical Care Medicine, Dokkyo Medical University Saitama Medical Center, Saitama

85 Prefecture, Japan. Data was abstracted from medical records of patients who had experienced
86 cardiac arrest and achieved ROSC inside or outside the hospital, including laboratory
87 findings from blood sampling, neurological outcomes and time course. All patients who
88 achieved ROSC from December 2015 to November 2017 were provided with TTM. Core
89 temperature was maintained at 36°C using Arctic Sun® 5000 or MEDI-THERM®III (both
90 IMI, Saitama, Japan) for 24 hours from ROSC. Muscle-relaxant drugs were generally not
91 used for TTM. Based on guidelines of the Japan Resuscitation Council[8], we selected 36°C as
92 the target core temperature for TTM. The TTM in our hospital was started in intensive care
93 units and, was not provided if cardiac arrest occurred due to trauma and in cases of unstable
94 hemodynamics, severe cerebral hemorrhage, no attempt of resuscitation order, severe
95 disability, dependency in activities of daily life or pregnancy. In addition, TTM was not
96 provided when the Glasgow Coma Scale (GCS) was ≥9, verbal score of the GCS was 4 or 5,
97 and motor score of the GCS was 6.[9] Data were not used if initial blood data had not been
98 obtained. The TTM protocol in our hospital remained unchanged during the study period.
99 Blood sampling was performed in the hospital within approximately 30 minutes from
100 initial resuscitation. A clinical chemistry analyzer (JCA-BM6070, JEOL Ltd., Tokyo, Japan)
101 was used for Mg levels analysis, and a blood gas analyzer (RAPIDPoint 500 or
102 RAPIDLab1265, Siemens Healthcare, Erlangen, Germany) was used for arterial blood gas
103 analysis. All resuscitations were provided by emergency physicians and nurses according to
104 guidelines of the Japan Resuscitation Council.[8]
105 The diagnosis of cardiac arrest, defined as the cessation of cardiac mechanical activity

106 confirmed by the absence of signs of circulation [10], was made clinically by trained emergency
107 providers. Additionally, signs of circulation were confirmed by determining whether the
108 carotid artery was pulsating and by findings of electrocardiogram. Neurological outcomes
109 were evaluated using the following Cerebral Performance Categories (CPC) at discharge
110 from hospital using medical records: CPC 1, normal or mild disability; CPC 2, moderate
111 disability, but independent in activities of daily life; CPC 3, severe disability and dependent
112 in activities of daily life; CPC 4, persistent vegetative state; and CPC 5, death. [10] Patients
113 were grouped by neurological outcomes according to previous studies[11]: favorable
114 neurological outcome (CPC 1, 2) group and unfavorable neurological outcome (CPC 3, 4 or
115 5) group. The CPC is used in the international Utstein Resuscitation Registry Templates for
116 the evaluation of the prognosis after cardiac arrest.
117 The primary outcome in this study was to determine whether the Mg levels predict
118 unfavorable neurological outcomes at hospital discharge for patients with ROSC after TTM.
119 Factors between patients with favorable neurological outcomes and those with unfavorable
120 neurological outcomes were compared by the Student's *t*-test for parametric variables, Mann-
121 Whitney U-test for nonparametric variables, and Chi-square test for categorical variables.
122 Variables for the multiple logistic regression analysis were the time from recognition of
123 cardiac arrest to ROSC, which is called "the time to ROSC" in this paper, (>30 minutes vs.
124 ≤30 minutes), motor score of the GCS after ROSC (> 1 vs. =1), first recorded cardiac rhythm
125 (shockable vs. non-shockable), pH, and the Mg levels. The Mg levels in this study were used
126 as a continuous variable not as a categorical variable. When emergency medical services

personnel or medical professionals, including emergency nurses, encounter a patient with sudden cardiac arrest, they record the cardiac rhythm by the determination of whether the carotid artery is pulsating and by electrocardiographic findings. In this manuscript, we called this rhythm the first recorded cardiac rhythm. The first recorded cardiac rhythm is subdivided into “first recorded shockable cardiac rhythm” and “first recorded non-shockable cardiac rhythm”. The first recorded shockable cardiac rhythm is a cardiac rhythm that can be shocked to normal cardiac rhythm by a defibrillator or automated external defibrillator. The first recorded non-shockable cardiac rhythm is a cardiac rhythm that cannot be shocked to a normal cardiac rhythm by a defibrillator or automated external defibrillator.

This study was conducted in accordance with the act on the Protection of Personal Information and the Ethical Guidelines for Medical and Research Involving Human Subjects of Japan. [12] The requirement for individual informed consent had been waived because the procedures described in this study were performed in routine clinical practice and the study presented no additional risks to the patients. The protocol for this research was approved by the Clinical Research Institutional Review Board of Dokkyo Medical University Saitama Medical Center (Approval No. 1765). All statistical tests were two-sided, and $P < 0.05$ was considered statistically significant. All statistical analyses were performed using the SPSS statistical package version 24.0J (IBM Corp, Armonk, NY, USA).

RESULTS

Figure 1 shows selection of cases for inclusion in the analysis of the occurrence of cardiac arrests from December 2015 to November 2017. A total of 631 cardiac arrest cases were

148 registered. Cases that were not resuscitated (n = 94), those without ROSC (n = 309), and
149 those with unstable hemodynamics (n = 118), GCS ≥ 9 (n = 10), cardiac arrests caused by
150 severe cerebral hemorrhage (n = 7), trauma (n = 6), and missing data (n = 1) were excluded.
151 Finally, 86 eligible cases were analyzed: 28 with favorable neurological outcomes and 58
152 with unfavorable neurological outcomes.
153 The baseline characteristics of patients who were provided TTM after ROSC are shown in
154 Table 1. There was no significant difference in the age, sex, cause of cardiac arrest, arrests
155 witnessed, and bystander cardiopulmonary resuscitation between patients with favorable and
156 unfavorable neurological outcomes. Those with unfavorable neurological outcomes had a
157 significantly lower proportion of first recorded shockable cardiac rhythm. Additionally, those
158 with unfavorable neurological outcomes had significantly longer time to ROSC.
159 Laboratory findings at the time of initial resuscitation are shown in Table 2. Compared
160 with favorable neurological outcomes, pH, oxygen of partial pressure, base excess, total
161 protein, and platelet count were significantly lower and carbon dioxide of partial pressure,
162 lactate, potassium, and Mg were significantly higher in the group with unfavorable
163 neurological outcomes. Mean hospital stay was 19.2 days for the entire study population.
164 A regression model was constructed including key elements of patient characteristics (the
165 time to ROSC, motor score of the GCS after ROSC, first recorded cardiac rhythm, pH, and the
166 Mg levels), that were significantly different between those with favorable versus unfavorable
167 outcomes. The results of multiple logistic regression analysis of prognostic factors for
168 unfavorable neurological outcomes in patients who had ROSC after cardiac arrest are shown

in Table 3. The Mg levels was not a predictor of neurological outcome based on results from this regression model. The time to ROSC >30 minutes, and motor score of GCS = 1 were found to be predictors of unfavorable neurological outcomes in this analysis accounting for about 50% of the variance in the model.

DISCUSSION

We performed a multiple logistic regression analysis using retrospectively collected data to evaluate whether the Mg levels predict neurological outcome for patients who had ROSC after cardiac arrest. Previously reported research results showed that high serum Mg levels correlated with unfavorable neurologic outcomes in patients who were provided with TTM after cardiac arrest. [7] We hypothesized that Mg levels along with other key patient characteristics would explain a large proportion of the variance in our regression model based on this previous research. However, multiple variable analysis results in the current study showed that Mg levels does not significantly contribute to predicting favorable or unfavorable neurological outcome following ROSC based on our model.

Our study indicated that the time to ROSC >30 minutes and motor score of GCS = 1 might predict neurological outcome after cardiac arrest. These findings reinforce previously reported research results [9] and further clarifies the impact of Mg levels on neurological outcome following ROSC.

LIMITATIONS

This study has several limitations. First, as with previous correlational designs using a retrospective chart review, unmeasured possible confounding factors may have influenced the

association between Mg levels and patients' outcome. Second, information on patients' medication and comorbid conditions as well as medical history, which might have included factors that could have influenced the occurrence of the cardiac arrest, was not obtained. Third, we used combined data on patients who had experienced cardiac arrest inside and outside the hospital. Previous study has demonstrated that neurological outcomes after cardiac arrest inside and outside the hospital were very different. [13] Thus, this point could have an impact on the findings from this study. Moreover, as our sample size was small and the study setting was limited to a single facility in Japan, the results might not be easily applicable to other geographical locations.

IMPLICATIONS FOR EMERGENCY NURSES

Our findings indicated "the time to ROSC" would predict neurological outcome after cardiac arrest. Early cardiopulmonary resuscitation and shocks with the automated external defibrillator before advanced life support are essential to increase survival after cardiac arrest through shortening the time to ROSC. [14] Therefore, emergency nurses should continue to focus on basic and advanced life support for patients who experience cardiopulmonary arrest.

The emergency nurses who work in emergency departments, on rapid response teams, and intensive care units often forecast the prognosis after cardiac arrests in order to provide information to the patient's family for advanced care planning and to consult with other medical professionals on the discontinuation of resuscitation. The findings of simple blood sampling, the time to ROSC and motor score of GCS can be evaluated by emergency nurses, not only physicians. Our findings might contribute to resuscitation practices and further

clinical trials which the emergency nurses conduct.

CONCLUSIONS

By the multiple logistic regression analysis of our hospital data, the Mg levels did not predict neurological outcome after cardiac arrest in patients who underwent TTM. In addition, the time to ROSC >30 minutes and motor score of GCS = 1 predicted unfavorable neurological outcome after cardiac arrest in our regression model. Thus, basic and advanced life support for emergency nurses should be encouraged to shorten the time to ROSC. Unfortunately, the results of this study alone cannot change clinical practices. This scientific area requires further research such as prospective studies including randomized controlled trials, in order to forecast accurate prognosis after cardiac arrest and share limited medical resources.

CONFLICTS OF INTEREST

The authors report no conflicts of interest.

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FIGURE LEGEND

Figure 1. Selection of cases for inclusion in the analysis of the occurrence of all cardiac arrests

Neurological outcomes were divided into two groups: favorable neurological outcomes (cerebral performance category 1, 2) and unfavorable neurological outcomes (cerebral performance category 3, 4 or 5).

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