THERAPEUTIC HYPOTHERMIA AND TEMPERATURE MANAGEMENT
Volume 4, Number 4, 2014

DOI: 10.1089/ther.2014.0012

Magnesium Depletion in Patients Treated with Therapeutic Hypothermia After Cardiac Arrest

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Magnesium (Mg^{2+}) depletion can have detrimental effects in postcardiac arrest patients through multiple potential mechanisms. Therapeutic hypothermia (TH) produces a Mg^{2+} diuresis, but the effects of postcardiac arrest TH on serum Mg^{2+} levels in patients with postcardiac arrest syndrome (PCAS) are yet to be systematically quantified. We conducted a retrospective chart review of 119 consecutive comatose PCAS patients treated with TH between 2005 and 2010 and compared them to 33 matched historic controls (HCs) seen at the same institution between 2002 and 2005 who were not treated with TH. We abstracted data from the first 96 hours postarrest, including date, time, and value of serum Mg^{2+} levels and date, time, and amount of Mg^{2+} repletion, along with outcomes at discharge. The median Mg^{2+} level of TH patients was 2.0 mg/dL [interquartile range (IQR), 1.9–2.2 mg/dL] (0.82 mmol/L [IQR, 0.78–0.90 mmol/L]) versus 2.2 mg/dL [IQR, 1.9–2.4 mg/dL] (0.90 mmol/L [IQR, 0.82–0.99 mmol/L]) ($p = 0.2$) in HCs. In addition, 42.9% (520/1214) of Mg^{2+} levels in TH patients versus 31.9% (43/135) ($p = 0.014$) in HC patients were below 2.0 mg/dL [0.82 mmol/L]. The average number of times the Mg^{2+} level was checked in TH patients was 10.2 (range 1–18) versus 4.1 (range 1–10) in HCs. The TH patients were more likely to receive supplemental Mg^{2+} than HCs (81.5% [97/119] vs. 27.3% [9/33] [$p < 0.01$]). The mean supplemental Mg^{2+} dose was 1.9 g for TH patients versus 0.5 g for HC patients. Mortality in patients treated with TH was 53.1% (60/113) versus 78.6% (22/28) ($p = 0.014$) in HCs. Low serum Mg^{2+} levels with subsequent Mg^{2+} supplementation were more common in comatose patients with PCAS treated with TH compared to normothermic HC patients. The effect of untreated hypomagnesemia on postcardiac arrest outcomes remains to be determined.

Introduction

Magnesium (Mg^{2+}) is a divalent cation that has a multitude of physiologic effects. Its actions at the cellular level are primarily due to the effects of Mg^{2+} on calcium channels, hormone receptor binding sites, and through adenylate cyclase using second messenger systems (Altura, 1994; Fawcett *et al.*, 1999). Magnesium is a cofactor in more than 300 enzymatic reactions throughout the body (Fawcett *et al.*, 1999). Magnesium also has well-established effects on the myocardium and is critical in maintaining normal cardiac conduction (Iseri, 1990). In the brain, Mg^{2+} is a natural antagonist at the N-methyl-D-aspartate (NMDA) receptor channel, and therefore, a potential modulator of neuronal irritability and excitotoxicity (Kuner and Schoepfer, 1996). Low serum Mg^{2+} levels have been associated with cardiac dysrhythmias (Fawcett *et al.*, 1999), increases in proinflammatory cytokines (Weglicki *et al.*, 1992), free radical injury, shivering in brain-injured patients (Badjatia *et al.*, 2008; Polderman, 2009), and ultimately, cellular death (HACA, 2002).

Therapeutic hypothermia (TH) has been demonstrated to improve neurologic outcomes in comatose patients with postcardiac arrest syndrome (PCAS) and has become a standard postresuscitation care in many institutions (HACA, 2002; Young, 2009; Hollenberg *et al.*, 2013). In addition, it has been postulated that Mg^{2+} may have neuroprotective effects during the postcardiac arrest period and low serum

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Poster presentation at 2nd International Therapeutic Hypothermia Conference, Lund, Sweden, September 2009.

Mg^{2+} levels may exacerbate neuronal injury, although this has not been studied in a controlled randomized manner (Reis *et al.*, 2008). Despite the clear benefits of TH on neurologic outcomes, significant adverse effects have been associated with the use of TH. Electrolyte abnormalities, including hypokalemia, hypophosphatemia, and hypomagnesemia, have been noted in ~20% of patients undergoing TH (Nielsen *et al.*, 2009).

Although hypomagnesemia has not been definitively linked with adverse outcomes in the setting of postcardiac arrest TH, data are currently limited (Polderman, 2004; Nielsen *et al.*, 2011; Tømte *et al.*, 2011). At the same time, hypomagnesemia has been associated with adverse effects and increased mortality in medical patients with critical illness (Rubeiz *et al.*, 1993; Soliman *et al.*, 2003; Tømte *et al.*, 2011). The effect of postcardiac arrest TH on Mg^{2+} levels has not been specifically investigated. The objective of this study was to determine if TH after cardiac arrest had a significant effect on serum Mg^{2+} levels and whether clinicians responded to low Mg^{2+} levels in TH patients by checking levels or repleting Mg^{2+} more frequently.

Materials and Methods

Study design

This study is a retrospective chart review of comatose patients with PCAS treated with TH between 2005 and 2010 compared to a cohort of comatose historical controls (HCs) who had a cardiac arrest between 2000 and 2005 and received standard postarrest care without TH.

Study setting and population

The study was approved by the Institutional Review Board at the Hospital of the University of Pennsylvania and conducted at an urban teaching hospital with ~58,000 emergency department visits and 100 cardiac arrests annually during the time the study was conducted. Patients were included if they were ≥18 years of age, suffered a cardiac arrest, and had return of spontaneous circulation (ROSC), but were subsequently comatose and treated with TH. Coma was defined as a Glasgow Coma Scale (GCS) <6 (specifically not following commands). HC patients would have been eligible for TH had the protocol existed at the time of their arrest but instead were treated with standard postresuscitation care, as TH was not the standard of care at that time.

TH protocol

TH was induced with chilled saline and continued with a surface cooling system with a target temperature of 33°C. Ice packs were utilized if there was difficulty achieving or maintaining the target temperature with initial measures. TH was then maintained for 24 hours. Active rewarming was performed over at least 8 hours by increasing the temperature set point by 0.25–0.33°C/hour. In addition, patients received early hemodynamic optimization and standard intensive care unit measures. Institutional protocol recommends checking Mg^{2+} levels every 6 hours during all phases of TH. As part of the TH protocol, there is a computerized order set that prompts the clinician to order 2 g Mg^{2+} IV if the serum Mg^{2+} level is <1.8 g/dL.

Data collection

Data were obtained for both the TH and HC groups during the first 96 hours postarrest or until the time of death, whichever occurred first. Each patient's medical record was reviewed and data were extracted and entered into a Microsoft Excel 2007 database (Microsoft Corp, Redmond, WA). Specific information collected included the date, time, and value of serum Mg^{2+} levels, reported in mg/dL and mmol/L, using the following conversion formula: Mg^{2+} level (mg/dL)× 0.4114 = Mg^{2+} level (mmol/L). In addition, we collected the date, time, and amount of Mg^{2+} repletion. The primary outcomes were serum Mg^{2+} levels and the total amount of Mg^{2+} supplementation that occurred during the study period. Secondary outcomes included neurologic outcome at hospital discharge, reported as cerebral performance category (dichotomized into good and poor outcomes) and survival to hospital discharge.

Statistical analysis

All data were analyzed using standard statistical software (Stata v.12.1, College Station, TX). Continuous data were analyzed by means with ranges and standard deviations for parametric data and medians with ranges for nonparametric data. Comparisons were made using the Student's *t*-test and Mann–Whitney *U* tests. P-values of <0.05 were considered statistically significant. Categorical data were compared using Fischer's exact test.

Results

Baseline characteristics and outcomes

One hundred nineteen consecutive comatose PCAS patients were treated with TH and compared to 33 HCs (Table 1). The mean age of TH patients versus HC patients was 59.8 ± 15.3 versus 54.9 ± 16.2 years ($p = 0.14$). Fifty-seven percent of TH patients were male compared with 52% for HCs ($p = 0.62$). African-Americans comprised 46% of the TH group versus 64% in the HCs. Ventricular fibrillation (VF) or pulseless ventricular tachycardia (VT) was the initial rhythm in 36% of TH patients and 39% of HCs ($p = 0.72$) Mortality in patients treated with TH was 54% (62/116) versus 79% (22/28) in HCs ($p = 0.02$) (see Table 1 for complete demographics and outcomes).

Magnesium levels

During the first 96 hours postarrest, patients in the TH group had Mg^{2+} levels checked more frequently compared to HC patients. The average number of times the Mg^{2+} level checked in TH patients was 10.2 ± 3.4 versus 4.1 ± 2.6 times in HCs ($p < 0.01$). TH patients had lower median serum Mg^{2+} levels (2.0 mg/dL; interquartile range (IQR), 1.9–2.2 mg/dL) (0.82 mmol/L [IQR, 0.78–0.90 mmol/L]) than HC patients (2.2 mg/dL, IQR, 1.9–2.4 mg/dL; $p = 0.2$) (0.90 mmol/L [IQR, 0.82–0.99 mmol/L]). A higher percentage of Mg^{2+} levels were below 2.0 mg/dL (0.2 mmol/L) in TH patients than in HC patients (42.9% [520/1214] vs. 31.9% [43/135]; $p = 0.014$). Patients treated with TH were more likely to be given supplemental Mg^{2+} than HC patients (81.5% [97/119] vs. 27.3% [9/33]; $p < 0.01$). The mean Mg^{2+} dose administered to TH patients was 1.9 ± 1.3 versus 0.5 ± 0.9 g ($p < 0.01$) for HC

Table 1. Comparison of Demographics and Outcomes Between Therapeutic Hypothermia Patients and Historic Controls

Parameter	*Therapeutic hypothermia (n = 119)*	*Historic controls (n = 33)*	p-*Value*
Mean age (years) (SD)	59.8 ± 15.3	54.9 ± 16.2	NS
Male sex (%)	68/119 (57%)	14/27 (52%)	NS
African-American (%)	55/119 (46%)	17/28 (61%)	NS
Caucasian (%)	55/119 (46%)	9/28 (32%)	NS
Initial rhythm, VF, or pVT (%)	43/119 (36%)	11/28 (39%)	NS
Initial GCS recorded after ROSC (range 3–15)	4	5	NS
Mortality (%)	62/116 (54%)	22/28 (79%)	0.02
Good neurological outcome at hospital discharge (CPC 1 or 2)	42/53 (79%)	6/6 (100%)	NS

CPC, cerebral performance category; GCS, Glasgow Coma Scale; NS, nonsignificant; pVT, pulseless ventricular tachycardia; ROSC, return of spontaneous circulation; SD, standard deviation; VF, ventricular fibrillation.

patients. Postarrest TH patients given Mg^{2+} supplementation received an average total Mg^{2+} dose of 3.8 ± 3.2 versus 0.7 ± 1.5 g ($p < 0.01$) for HC patients (Table 2; Fig. 1).

Adverse effects in TH patients

Thirty-eight percent (45/119) of patients had major adverse effects of TH therapy (defined as postarrest fever, skin breakdown, shivering, and dysrhythmias). The most common side effect noted was postarrest fever ($n = 26$), followed by skin breakdown ($n = 12$), shivering ($n = 8$), and dysrhythmias ($n = 5$). Patients with adverse effects had significantly lower mean Mg^{2+} levels than those without adverse effects (1.98 ± 0.18 mg/dL [0.81 mmol/L] vs. 2.07 ± 0.28 mg/dL [0.85 mmol/L]; $p = 0.015$). They also had more Mg^{2+} repletion (2.33 ± 1.21 vs. 1.27 ± 1.23 g; $p < 0.001$).

Discussion

This preliminary investigation suggests that comatose PCAS patients undergoing treatment with TH are more likely to have lower serum Mg^{2+} levels and receive more Mg^{2+} repletion than patients who do not receive TH. These findings could be the result of TH-associated hypomagnesemia or that providers at our institution became more vigilant about monitoring serum Mg^{2+} levels and repleting Mg^{2+} compared to the pre-TH era, particularly with an electronic TH order protocol in place. Ultimately, it is likely that a combination of these factors is at play. Clinicians checked Mg^{2+} levels more frequently in a higher percentage of TH patients and responded to low or low normal levels by repleting Mg^{2+} more aggressively in this population. Despite this increased vigilance, mean serum Mg^{2+} levels were lower in TH patients than in HC patients.

Magnesium wasting is a well-described phenomenon during TH and results from increased fluid diuresis and temperature-sensitive changes in Mg^{2+} ion resorption channels in the ascending loop of Henle and the distal tubule of the kidney (Salem *et al.*, 1995; Weisinger and Bellorin-Font, 1998), which ultimately promote Mg^{2+} excretion. It has also been demonstrated that induction of hypothermia causes the shift of electrolytes from the extracellular to the intracellular compartments (Longstreth *et al.*, 2002). Interestingly, a study by Tømte *et al.* (2011) found a greater degree of intracellular shifting in patients who underwent induction of TH with core-cooling measures compared to surface cooling; however, the underlying mechanism of this phenomenon is yet to be elucidated. It is unclear what percentage of changes in Mg^{2+} levels is due to intracellular shift and what percentage due to temperature-dependent Mg^{2+} wasting. In traumatic brain injury (TBI) patients with increased ICP treated with TH, Polderman *et al.* (2001) demonstrated statistically significantly increased urine excretion of Mg^{2+} during cooling, which reverted to baseline levels after rewarming (3.7 ± 1.7 mmol in 6 hours before cooling; 9.5 ± 4.7 mmol/6 hours during cooling; 3.1 ± 1.2 mmol in 6 hours after cooling; $p < 0.01$). The authors reached very similar conclusions as we did: magnesium ''depletion occurred (in the cooling group) despite the fact that moderate and, in some cases, substantial doses of (magnesium) repletion were given to many patients (Polderman *et al.*, 2001).''

Table 2. Comparison of Magnesium Results Between Therapeutic Hypothermia Patients and Historic Controls

Parameter	*Therapeutic hypothermia (n = 119)*	*Historic controls (n = 33)*	p-*Value*
Patients who had Mg^{2+} checked (%)	119 (100%)	33 (100%)	1.00
Mean Mg^{2+} level, mg/dL (IQR) [mmol/L (IQR)]	2.0 (1.9–2.2) [0.82 (0.78–0.90)]	2.2 (1.9–2.4) [0.90 (0.82–0.99)]	0.2
Mean No. of serum Mg^{2+} checks (range)	10.2 (1–18)	4.1 (1–10)	< 0.01
No. of Mg^{2+} values below 2 mg/dL [0.82 mmol/L] (%)	66 (47.5%)	8 (21.6%)	0.005
No. of patients given Mg^{2+} repletion (%)	97 (81.5%)	9 (27.3%)	< 0.01

IQR, interquartile range.

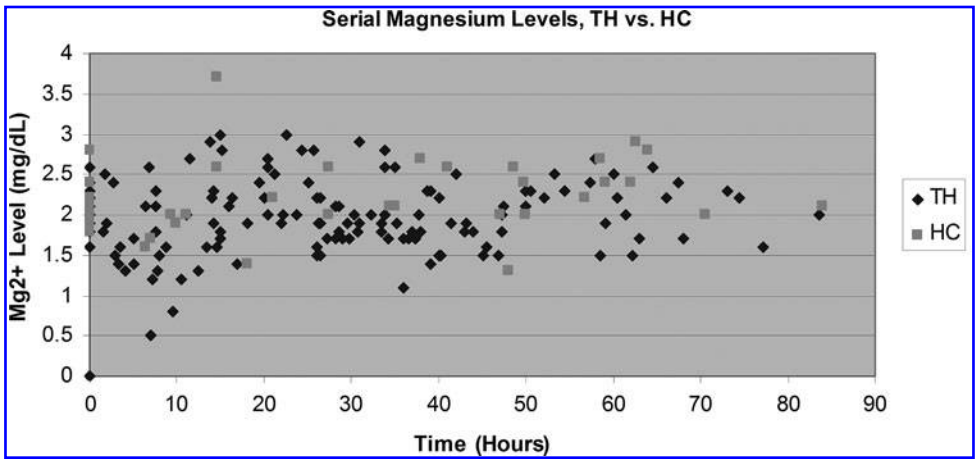

FIG. 1. Magnesium values over time for TH and HC patients. HC, historic controls; TH, therapeutic hypothermia.

PCAS is a dynamic critical illness that affects multiple organ systems, with particular impact on the brain and heart. It triggers a wide range of pathophysiologic processes, including amplified production of inflammatory markers, free radical generation, mitochondrial and endothelial dysfunction, and cellular apoptosis (HACA, 2002; Young, 2009; Hollenberg *et al.*, 2013). Because Mg^{2+} plays a critical role in all of these processes, the effects of hypomagnesemia and the importance of subsequent Mg^{2+} repletion in PCAS patients may have significant clinical implications (Weglicki *et al.*, 1992; Weisinger and Bellorin-Font, 1998; Fawcett *et al.*, 1999; Iseri, 1990). Patients with PCAS are predisposed to cardiac dysrhythmias, such as VT and VF, as well as neuronal dysfunction, all of which may be exacerbated by hypomagnesemia (Soliman *et al.*, 2003; Polderman, 2004; Polderman, 2009; Nielsen *et al.*, 2011).

The extent to which hypomagnesemia affects clinical outcomes in patients undergoing TH postcardiac arrest remains unclear. We found significantly lower Mg^{2+} levels in patients with adverse effects of TH versus those without adverse effects of TH. A study by Nielsen *et al.* (2011) did not find an association between hypomagnesemia and increased mortality in PCAS patients treated with TH. In an attempt to further explore this question, Longstreth *et al.* conducted a randomized controlled trial of infusion of Mg^{2+}, diazepam, or both, immediately after ROSC to comatose survivors of cardiac arrest. After controlling for potential confounders, there was no difference in outcomes between the treatment arms (Longstreth *et al.*, 2002). The Duke Internal Medicine Housestaff performed a randomized trial of magnesium infusion during cardiac arrest for patients with in-hospital cardiac arrest at Duke Hospital. Seventy-six patients randomized to receive a bolus of 2 g of Mg^{2+} during arrest followed by 8 g of Mg^{2+} over the next 24 hours were compared to 80 patients who received placebo. The investigators found no differences between the groups in the percentages who achieved ROSC, survival to hospital discharge, or good neurological outcomes (Thel *et al.*, 1997). However, these approaches of intra-arrest, immediate post-ROSC, or prophylactic infusion of Mg^{2+} are significantly different from the measurement and maintenance of normal Mg^{2+} levels over the 96-hour postarrest period. Ultimately, the true clinical impact of TH-induced hypomagnesemia as well as the optimal management strategy is yet to be determined.

Our results suggest that hypomagnesemia occurs in a significant percentage of PCAS patients undergoing TH and this finding may have relevance when designing and implementing the optimal management strategy and institutional TH protocols. This is particularly important because of the critically ill nature of the patients involved. Institutional TH protocols should be designed not only to prompt providers to frequently monitor Mg^{2+} levels but also to provide adequate Mg^{2+} repletion. Based on prior data, patients who undergo TH with core-cooling measures may be at higher risk for hypomagnesemia and may require more vigilant monitoring and intervention (Tømte *et al.*, 2011). It is also important to keep in mind that hypomagnesemia may persist despite aggressive repletion. For example, as noted previously, Polderman *et al.* (2001) documented a similar Mg^{2+} diuresis in patients with TBI treated with TH, where the urine output increased and serum Mg^{2+} levels decreased despite significant Mg^{2+} repletion. In a subsequent review of the mechanism of action, physiological effects, and complications associated with TH, Polderman suggested that Mg^{2+} levels ''should be kept in the high normal range during and after hypothermia treatment (Polderman, 2009). Extrapolation of these findings to patients treated with postcardiac arrest TH is difficult because a significant percentage of the TH-TBI patients were also treated with mannitol, a potent osmotic agent, which was not used in our patient population.

Our study raises important questions regarding Mg^{2+} monitoring and repletion in the postarrest state, which represents an opportunity for future research. Should Mg^{2+} levels be corrected only when they fall below the lower reference range of normal or should prophylactic supplementation be instituted? Should Mg^{2+} levels be aggressively maintained in a normal range to treat and prevent shivering and other side effects of cooling? Or should Mg^{2+} be infused until supratherapeutic levels are achieved to optimize organ protection? These questions remain unanswered. It is also unclear to what extent TH-induced hypomagnesemia affects clinical outcomes. Finally, systematic studies should be performed to evaluate whether a synergistic neuroprotective effect of Mg^{2+} supplementation and TH exists. Because of the critically ill nature of PCAS patients undergoing TH and the lack of data regarding the outcomes associated with associated hypomagnesemia, we recommend that clinicians treating these patients should monitor serum Mg^{2+} levels on

a frequent set schedule and aggressively replete Mg^{2+} to maintain levels in the midrange of normal. In addition, efforts should be made to educate physicians and other healthcare providers who manage TH patients regarding the potential for hypomagnesemia.

Limitations

Our study is limited by its small sample size and retrospective design. Furthermore, the number of patients in the HC group is approximately half of that in the hypothermia group. We speculate that this occurred for a number of reasons. (1) Inherent limitations in historic chart reviews, including insufficient documentation of neurologic status to determine coma postarrest; (2) changes in the Philadelphia Emergency Medical Services leading to increased numbers of arrests brought to our hospitals; and (3) referrals to our center as we established ourselves as a cardiac arrest center. In addition, Mg^{2+} levels were checked less frequently in historical control patients and there was no specific protocol for repletion in those patients. Provider knowledge of TH-induced hypomagnesemia was not evaluated. We did not explore the adverse events related to hypomagnesemia, and this study was not designed to assess a clinical benefit from maintaining a normal Mg^{2+} level when treating PCAS patients with TH.

Conclusions

Targeted temperature management is now considered the standard of care to optimize neurological recovery in comatose PCAS patients. Our results suggest that TH induces a significant Mg^{2+} diuresis and intracellular shifting, requiring frequent monitoring of serum Mg^{2+} levels and adequate Mg^{2+} repletion, with a goal of keeping serum levels within the normal range. Given its possible neuroprotective effect, standardized intervals for checking and repleting Mg^{2+} may improve the care of comatose PCAS patients undergoing treatment with TH. Additional studies should be performed to investigate the clinical effects of TH-induced hypomagnesemia and whether there is a relationship between Mg^{2+} levels and TH on outcomes in comatose survivors of cardiac arrest.

Disclosure Statement

No competing financial interests exist.

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