



The Effect of Proton-Pump Inhibitors the on Development of Arrhythmia and Hypomagnesemia After Off-Pump Coronary Artery Bypass Surgery

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Abstract

Background: Long-term use of proton-pump inhibitors (PPI) can result in hypomagnesemia and arrhythmia. This study aimed to compare the effect of PPI and histamine 2-receptor antagonists (H₂RA) on the incidence of hypomagnesemia and arrhythmia in patients following off-pump coronary artery bypass surgery (CABG).

Method: In this randomized-controlled clinical trial 290 patients admitted to the ICU after off-pump CABG were randomly divided into two groups of H₂RA (n=145) and PPI (n=145). For patients in the H₂RA group, 50 mg intravenous ranitidine was prescribed every 8 hours after the nothing by mouth (NPO) period, followed by 40 mg famotidine tablets after starting the oral regimen (PO). The PPI group received 40 mg pantozol IV injections every 12 hours during the NPO period and 40 mg pantozol tablets once daily after becoming PO. The patients were investigated for the development of hypomagnesemia and associated arrhythmia.

Results: In total 271 patients with a mean age of 59.3 ± 10 years completed the study (female/male=32.8%). Hypomagnesemia occurred in 60.1% of the patients, 76 (56.7%) in the H₂RA group and 87 (63.5%) in the PPI group (P=0.245), whereas arrhythmia had a prevalence of 12 (9.6%) and 15 (11.1%) cases, respectively (P=0.690). The mean time of occurrence of hypomagnesemia and arrhythmia was 1.75 ± 1.08 and 3.0 ± 0.9 days after the operation in the H₂RA group (P=0.111) and 1.47 ± 0.7 and 2.9 ± 1.5 days in the PPI group (P=0.897), respectively.

Conclusion: Our study revealed that the short-term use of PPIs does not result in higher rates of hypomagnesemia and associated arrhythmia in comparison to H₂RA consumption after off-pump CABG.

Keywords: Proton-pump inhibitors (PPI), Hypomagnesemia, Arrhythmia, Off-pump CABG, Histamine 2-receptor antagonist (H₂RA)

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Introduction

Critically ill patients hospitalized in intensive care units (ICUs) have a higher risk of stress ulcers and subsequently, gastrointestinal (GI) bleeding, which can result in higher mortality rates (1). To reduce stress-related mucosal injury while maintaining tissue perfusion and initiating early oral nutrition, various drugs aimed at reducing gastric acid secretion and sustaining the gastric pH above 4 can be used when the likelihood of injury is at its maximum (2).

The use of proton-pump inhibitors (PPIs) is one of the most common treatments for all gastric-acid-related diseases, such as gastroesophageal reflux and peptic ulcer, mainly due to their higher efficacy in comparison to histamine 2-receptor antagonists (H₂RA).

However, proton pump inhibitors are associated with hypomagnesemia. Among them, omeprazole is associated with the least and pantoprazole with the highest rate of hypomagnesemia.

Hypomagnesemia is often seen with long-term, especially over one year, use of PPIs. However, it has also been reported in adults who have used the drug for under 3 months, resulting in drug termination and magnesium supplement initiation (3).

Nevertheless, hypomagnesemia secondary to PPI consumption is both dose- and time-dependent and is one of the most common electrolyte disorders that occur in hospitalized patients, especially in the ICU. Although mild hypomagnesemia can be symptom-free, its severe forms can be accompanied by serious complications (4-9).



Hypomagnesemia has been reported in as high as 70% and 22.5%–35% following on-pump (10) and off-pump coronary artery bypass surgery (CABG) (11-13), respectively, and can result in increased occurrence of arrhythmias such as atrial fibrillation along with increased mortality and length of ICU stay (1,2). In contrast, Mohammadzadeh et al studied the effect of magnesium on arrhythmia after CABG and found no association between the serum magnesium level and arrhythmia up to 3 days after surgery (14).

The main purpose of this study was to compare PPIs and H₂RA regarding hypomagnesemia induction and the associated arrhythmia after off-pump CABG. The secondary aim was to compare the onset, GI bleeding rate, and ICU and hospital length of stay between the two groups.

Materials and Methods

This randomized controlled clinical trial was performed at the postcardiac surgery ICU of Imam Reza hospital, Mashhad, Iran. The convenience sampling method was used.

Patients with the following criteria were included in the study: candidates for off-pump elective CABG, preoperative total serum magnesium ≥ 1.7 mg/dL, no known history of kidney disease, no heart attack or prolonged *cardiopulmonary resuscitation* before surgery, no sign of severe malnutrition ($>10\%$ body weight loss in the last month), no history of allergy to the prescribed drugs, ejection fraction (EF) $\geq 35\%$, no pre-operative arrhythmia, no history of antiarrhythmic drug consumption, no electrolyte imbalance, no risk factors for arrhythmia, no history of gastric discomfort or receiving pantoprazole or H₂-blockers before the operation.

The patients were excluded in case of mistaken use of magnesium sulfate, electrolyte imbalance (hypo or hyperkalemia and hypo or hypercalcemia), and acute kidney injury after surgery.

The study protocol was fully described to each patient, and informed consent was obtained before study entry. Patients in the pantoprazole group received intravenous pantoprazole 40 mg (Omid Darou Salamat Company, Iran) every 12 hours while NPO and pantoprazole tablet 40 mg once daily (Tehran Chemie Pharmaceutical Company, Iran) afterward (for a total of 6 days). For the H₂RA group, intravenous ranitidine 50 mg (Caspian Tamin Pharmaceutical Company, Iran) was given every 8 hours during the NPO period, and famotidine tablets (40 mg) (Pursina Pharmaceutical Company, Iran) once daily afterward (for a total of 6 days).

The total serum magnesium level was measured before surgery and then daily for 6 days by the calorimetric method and by kit (Pars Azmoon Company). In the case of hypomagnesemia (Mg < 1.7 mg/dL) intravenous magnesium 2 g was initially administered and repeated

each 8–12 hours until correction, and the PPI group regimen was replaced by H₂RAs.

During the study, the serum potassium and calcium levels were maintained in the normal range of 3.5–5.5 meq/L and 8.5–10.5 mg/dL, respectively, and in case of electrolyte imbalance or renal failure, the patient was excluded from the study.

The patients were explored for frequency and time of onset of hypomagnesemia and arrhythmia as well as hospital and ICU length of stay.

The sample size was calculated as 135 for each group based on the study by El-Charabaty et al (15). Considering a 10% possible dropout, the sample size was increased to 145 for each group.

A histogram was used to determine the normality of data distribution. Quantitative data with normal distribution was analyzed using the t test, while non-normally distributed data was analyzed using the Mann-Whitney U test. The relationship between qualitative variables was studied with chi-square and Fisher's exact tests. Statistical analyses were done with SPSS version 16, and the significance level was set at $P < 0.05$.

Results

For this study, 290 individuals were enrolled, among whom 19 (8 from the pantoprazole and 1 from the H₂RA group) were excluded due to inadvertent administration of magnesium before hypomagnesemia and mistaken administration of a single dose of stress ulcer prophylactic drug; therefore, 271 cases completed the study, 137 in the PPI and 134 in the H₂RA group.

Hypomagnesemia occurred in 163 (60.1%) patients (78.6% female and 51.1% male) ($P < 0.001$) 57.7% on the 1st postoperative day, 31.1% on the 2nd day, and 7.4% on the 3rd day. The two groups were similar regarding age, sex, body mass index, duration of surgery, pre- and post-operative serum albumin level, Euro II score (standard and logistic), serum magnesium levels pre-operation and at the onset of hypomagnesemia, and time of development of hypomagnesemia after surgery (Tables 1 and 2).

Arrhythmia was diagnosed in 27 (10.4%) patients, 17 (63%) cases with supraventricular and 10 (37%) cases with ventricular origin; yet no significant association was found between arrhythmia and hypomagnesemia ($P = 0.245$). Of the arrhythmias, 81.5% occurred during

Table 1. Comparison of qualitative variables between the two groups of patients undergoing off-pump CABG

Variable		H ₂ RA	Pantoprazole	P value
Gender	Male	33.6%	32.1%	0.797
	Female	66.4%	67.9%	
Hypomagnesemia		56.7%	63.5%	0.254
Arrhythmia (yes-no)		9.6%	11.1%	0.690
Mortality		1.5%	2.2%	1

Table 2. Comparison of quantitative variables with normal and non-normal distribution between the two groups of patients undergoing off-pump CABG

Variable	H ₂ RA	Pantoprazole	P value
Age (y)	60.1±9.6	58.6±10.5	0.224
Body mass index (kg/m ²)	26.4±4.3	4.8±27.1	0.224
Surgery duration (min)	253.5±49.4	257.3±57.3	0.559
Serum albumin before surgery (mg/dL)	3.8±0.6	3.8±0.7	0.634
Serum albumin after surgery (mg/dL)	2.8±0.8	2.9±0.8	0.704
Arrhythmia incidence time after surgery (days)	2.9±1.5	3.0±0.9	0.897
Serum magnesium at hypomagnesemia onset (mg/dL)	1.4	1.5	0.358
Hypomagnesemia onset time after surgery (days)	1	1	0.111
Serum magnesium before surgery (mg/dL)	2.2	2.1	0.517
Hospitalization duration (days)	6	6	0.783
ICU stay duration (days)	2	2	0.249
Standard Euro II Score	1	1	0.401
Logistic Euro II Score	1.15	1.15	0.453

the 2nd to 4th post-op days. The two groups were similar in terms of prevalence and onset of arrhythmia, and ICU and hospital length of stay (Tables 1 and 2). GI bleeding was reported in none of the patients, and the all-cause mortality rate did not differ between the two groups (Table 1).

Discussion

This study showed that the short-term administration of PPIs does not significantly affect hypomagnesemia and its related arrhythmia after off-pump CABG in comparison to H₂RAs ($P=0.245$ and $P=0.690$, respectively).

Post-CABG arrhythmias are among the most common complications of cardiac surgeries and can lead to other complications. The effect of serum magnesium level, hypomagnesemia treatment, and the prophylactic administration of magnesium in the occurrence and prevention of such arrhythmias has long been a controversial issue and a matter of debate.

The serum magnesium level undergoes many changes after coronary artery surgery as the rate of hypomagnesemia following CPB surgery has been reported to be as high as 70% (10). The prevalence of hypomagnesemia in patients undergoing off-pump CABG has been reported as 22–35% (11,12). However, in the present study, hypomagnesemia occurred in 60.1% of the cases after off-pump CABG. The difference observed between this study and that of Peyvandi Yazdi et al, who reported this figure as 46.7%, could be due to the different kinds of surgeries (elective abdominal surgery) used in these studies (16). The difference between these results and those of Maslow et al (11) may be due to differences in the prevalence of hypomagnesemia before surgery and its definition. It seems that the highest prevalence of hypomagnesemia is solely due to CABG surgery and might be attributed to decreased intracellular magnesium, blood dilution during surgery, chelating of ionized magnesium

with heparin following myocardial hypoxia, and the use of allogeneic blood (17).

In our study, although we did not use cardiopulmonary bypass, hypomagnesemia was still observed in a large percentage of patients on the first post-op day, which is different from the results of Najafi et al, who reported 1st-day hypomagnesemia in only 1.4% of the patients. This difference could be due to the difference in the prevalence of pre-operative hypomagnesemia, magnesium administration after surgery, and the different definitions of hypomagnesemia in the two studies (18).

Iqbal et al in 2010 reported the prevalence of arrhythmia in patients undergoing off-pump CABG as 22%, 72.7% of whom developed atrial fibrillation (AF) (13); although the prevalence of arrhythmia was twice that of our study, AF had a similar percentage to ours (63%). Arrhythmia was reported in 31% of the cases by Najafi et al and 32.8% by Mohammadzadeh et al, with 23.5% and 60% AF, respectively (14,18). The difference can be due to performing off-pump CABG in our study while the mentioned studies performed off-pump and on-pump CABG.

Mohammadzadeh et al. studied the effect of magnesium on post-CABG arrhythmia; they found no relationship between serum magnesium level and arrhythmia during the initial 3 post-op days, which is consistent with our findings (14).

Kieboom et al showed that hypomagnesemia is only seen with long-term consumption of PPIs (3). Hoorn et al reported that the duration of PPI consumption is a major factor in the occurrence of complications such as hypomagnesemia in such patients, and those who have been under treatment for over one year can have significant clinical symptoms (19). In another study, Kim et al demonstrated that hypomagnesemia is directly related to the duration of PPI consumption and should be considered in patients requiring chemotherapy or long-

term PPI administration (20). Khosravi Khorashad et al compared serum magnesium levels before and after PPI therapy in patients under treatment for less than 3 and over 6 months; no hypomagnesemia was reported (21).

The ICU and hospital length of stay in our study were similar to those of Kieboom et al, Hoorn et al, Kim et al, and Khosravi Khorashad et al. (3,19-21)

In the current study, no difference was observed in the incidence of arrhythmia between the PPI and H₂RA groups, which is consistent with the results of Chen et al, who reported that PPI consumption does not increase the risk of cardiac arrhythmia in ICU-hospitalized patients (9).

In the present study, no direct association was found between ICU and hospital mortality and hypomagnesemia ($P=0.294$ and $P=1$, respectively). Moreover, no difference in the mentioned variables was seen between the H₂RA and PPI groups. The findings of Honarmand and Safavi showed that ICU and hospital length of stay, necessity of mechanical ventilation and its duration, and mortality rate were significantly higher in patients with hypomagnesemia compared to those with normal magnesium levels, which is inconsistent with our findings (9,22,24). However, correlating mortality with hypomagnesemia requires the exclusion of other confounding variables which can be done by multi-regression analysis, which was not performed in this study.

We did not measure serum ionized magnesium levels, which is a limitation of this study. Moreover, only patients having undergone off-pump CABG were studied, so the results cannot be generalized to all cardiac surgeries, especially those in which CPB is used.

Conclusion

Our study showed that hypomagnesemia has a relatively high prevalence in patients undergoing off-pump CABG, but its incidence in the short term is not related to the type of drug prescribed for stress ulcer prevention (PPI or H₂RA).

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Authors' Contribution

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Competing Interests

The authors declare that there is no conflict of interest.

Ethical Approval

The study was also approved by the Research Ethics Committee of Mashhad University of Medical Sciences (MUMS) and registered in the IRCT (IRCT201511088384N5).

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