The Impact of Perioperative Use of a Statin–Magnesium Combination on Opioid Consumption in Patients Who Underwent Cardiac Surgery: A Retrospective Study with Propensity-Score Matching

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Both statins and magnesium are associated with NMDA receptors and anti-inflammatory effect. Peripheral NMDA receptors are known to be involved in inflammation-induced pain. This study aimed to investigate the impact of perioperative use of a statin–magnesium combination on opioid consumption in patients who underwent cardiac surgery. This was a retrospective study of 542 patients who underwent cardiac surgery. The patients were divided into two groups according to statin use: the statin–magnesium group (n=375) and the magnesium-only group (n=167). Patients in the magnesium-only group received only perioperative magnesium, but no statins, to prevent atrial fibrillation following cardiac surgery. After propensity-score matching, 228 patients (n=114 in each group) were analyzed to investigate opioid consumption, visual analogue scale (VAS) pain scores over a 72-h period, and pain outcomes according to the duration of statin treatment (<1 or ≥1 yr). The consumed opioid volume was significantly smaller in statin–magnesium group than the magnesium-only group, both before (p=0.010) and after matching (p=0.017). The statin–magnesium combination did not significantly reduce the VAS pain scores compared with magnesium alone. Although the statin–magnesium combination did not significantly reduce the pain intensity compared with magnesium alone, the combination therapy was effective in reducing opioid consumption after surgery.

Key Words: *Narcotics; Pain Management; Anti-Arrhythmia Agents; Drug Interactions; Cardiac Surgical Procedures*

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INTRODUCTION

The management of pain after cardiac surgery is crucial because inadequately controlled pain may become chronic, thereby delaying rehabilitation, prolonging treatment duration, and detrimentally affecting the patient's quality of life. Effective treatment of pain in patients undergoing cardiac surgery should be multidimensional. The most frequently recommended type of analgesia is multimodal (combined pharmacotherapy), involving the simultaneous use of a few analgesic agents with different mechanisms of action, but with common properties.[1,2] Statins reduce the synthesis and increase the clearance of cholesterol, while decreasing triglyceride levels. Preclinical studies have shown that the anti-inflammatory effects of statins are associated with reductions in C-reactive protein (CRP) and proinflammatory cytokine levels.[3,4] To date, there have been very few clinical studies on the effects of statins on pain in the perioperative period.[5] A few studies have reported that perioperative statin use is not effective for reducing postoperative pain and opioid consumption.[6,7]

Magnesium, which is a cofactor of all enzymes in phosphate-transfer reactions that utilize adenosine triphosphates as substrates, is a noncompetitive *N*-methyl-D-aspartate (NMDA) receptor antagonist that blocks ion channels in a voltage-dependent manner.[8] Systemic administration of perioperative magnesium reduces postoperative pain and opioid consumption and is considered a strategy to mitigate postoperative pain in surgical patients.[1,8,9]

Both statins and magnesium are associated with NMDA

receptors and have anti-inflammatory effects. Peripheral NMDA receptors are known to be involved in inflammation-induced pain.[1,8,10] The effects of the combination of these two agents with similar properties but different mechanisms of action on pain outcomes are still unknown.

We hypothesized that because both statins and magnesium are associated with NMDA receptors and have anti-inflammatory effects, their combined therapy could reduce opioid consumption postoperatively. The aim of our study was to investigate the impact of the perioperative use of a statin–magnesium combination on opioid consumption, as the primary outcome, in patients who underwent cardiac surgery.

MATERIALS AND METHODS

1. Study design

In this retrospective cohort study, we evaluated the medical records of all consecutive patients who underwent cardiac surgery from January 1, 2013 through December 30, 2018. Ethical approval for this study (registration no. 2019-07-027-002) was provided by the relevant institutional review board in August 2019.

2. Patient selection

Patients aged >19 years, with normal sinus rhythm, who underwent elective cardiac surgery (coronary artery bypass graft [CABG] surgery, valve surgery, or CABG plus valve surgery with cardiopulmonary bypass) under general anesthesia were considered eligible for inclusion in this study. We excluded patients with incomplete medical records. Patients with previous cardiac surgery, those receiving antiarrhythmic medications (digoxin, calcium channel blocker or beta-blocker, etc.) before surgery, and those undergoing off-pump coronary artery bypass or re-do surgery were also excluded. The data for the present study were collected from the medical records of eligible patients and included information about use of statins (atorvastatin, rosuvastatin, simvastatin, and others).

The patients were divided into two groups according to statin use: the statin–magnesium group (n=375) and the magnesium-only group (n=167). Patients in the magnesium-only group received only perioperative magnesium, but no statins, to prevent atrial fibrillation following cardiac surgery. The duration of statin treatment was divided into <1 and ≥1 yr.

3. Perioperative management of cardiac surgery performed under general anesthesia

General anesthesia was induced with propofol and remifentanil and was maintained with sevoflurane. All patients underwent continuous cardiac monitoring, invasive blood pressure monitoring, and central vein pressure monitoring. Weaning from mechanical ventilation and catecholamine infusion, pulmonary artery catheter removal, and tracheal extubation in the intensive care unit were performed based on standard guidelines.

The standard of care for preventing atrial fibrillation postoperatively at our hospital was to administer magnesium sulfate and amiodarone. Magnesium was administered as a 30 mg/kg bolus followed by a 10 mg/kg/h infusion over 24 h, and amiodarone was administered as a 150 mg bolus over 30 min, followed by a 1 mg/min infusion over 6 h, and a 0.5 mg/min infusion over 24 h.

As routine care to reduce postoperative pain, each patient was administered analgesics using a patient-controlled analgesia (PCA) pump containing fentanyl (4000 μg), ketorolac (360 mg), and ramosetron (0.9 mg) in a total volume of 500 mL saline. This device was set to deliver a background infusion of 2 mL/h and bolus doses of 1 mL with a 10-min lockout period. Postoperative pain intensity was documented using a 100-mm linear visual analogue scale (VAS). The VAS scores for pain at rest and during movement were measured at intervals of 24, 48, and 72 h after surgery.

4. Primary outcome and secondary outcomes

The primary outcome was opioid consumption based on the volume of PCA containing fentanyl (in milliliters) consumed over 72 h after surgery. The secondary outcomes included VAS pain scores over 72 h, mechanical ventilation therapy, intensive care unit stay, pain outcomes according to the duration of statin treatment (<1 or ≥1 year), and incidence of postoperative atrial fibrillation.

5. Statistical analysis

Data are presented as mean±standard deviation or number (percentage) of patients. Continuous variables were analyzed using the independent t-test after performing the Shapiro–Wilk test for normality, whereas categorical variables were analyzed using the chi-square test or Fisher's exact test. Variables that differed between the two groups were subjected to propensity-score matching, which resulted in balanced variables between the statin-magnesium group and magnesium only groups at p>0.1 and a standardized mean difference (MD) <0.1. Variables that could affect postoperative pain outcome were selected for propensity-score matching, and standardized MD of ordinal variables such as age and body mass index were calculated as nominal variables. No further adjustment was made after confirming a balance between the two groups as a criterion of p>0.1 and SMD <0.1. The association of statin-treatment duration with PCA volume and VAS pain intensity was analyzed using the Pearson's correlation test. Variables that differed between the two groups and that might affect the postoperative pain outcome were selected for PS matching. Statistical analysis was performed using SPSS version 18.0 (SPSS Inc., Chicago, IL, USA). p<0.05 was considered statistically significant.

RESULTS

Six hundred patients underwent cardiac surgery at this hospital from January 1, 2013 through December 30, 2018.

Of these, 58 patients were excluded because of incomplete medical records, previous cardiac surgery, antiarrhythmic medication before surgery, and re-operation because of bleeding. Thus, 542 patients were included in this study. Propensity-score matching for baseline and clinical characteristics identified 228 paired patients in the two groups (n=114 per group).

The proportions of patients with diabetes mellitus, hypertension, smoking, peripheral arterial occlusive disease, and preoperative cerebrovascular accident were significantly higher in the magnesium-only group than in the statin–magnesium group before matching; however, these differences between the groups were not statistically significant after matching. The statin–magnesium combination treatment significantly increased the creatinine level at 1-day postoperatively after matching. The combination therapy also reduced the peak CRP level and the CRP level from the first to the third day postoperatively, before and after matching. Age, sex, body mass index, type of commonly prescribed statins, type and duration of cardiac surgery, mechanical ventilation, intensive care unit stay, creatinine

level before surgery, and preoperative CRP levels were not significantly different between the two groups both before and after matching. Creatinine at 1 day after surgery was not significant between two groups before matching but creatinine was significantly increased in statin–magnesium group compared with magnesium only group (p=0.017) (Table 1).

The statin–magnesium group consumed significantly lower volumes of PCA containing fentanyl (in milliliters) over a 72-h period postoperatively than did the magnesium-only group, both before matching (p=0.010) and after matching (p=0.017). The VAS pain scores during movement in the first 24 h postoperatively were significantly lower in the statin–magnesium group than in the magnesium-only group, before matching. However, the VAS pain scores at 24, 48, and 72 h were not significantly different between the groups after matching (Table 2).

Patients with statin treatment ≥ 1 yr consumed significantly lower PCA volumes than did those with statin treatment <1 year, both before (p=0.047) and after matching (p=0.047). The VAS pain scores over a 72-h period in

TABLE 1. Patients' demographic data

Variables	Before matching			After matching		
	Magnesium-only (n=375)	Statin–magnesium (n=167)	p-value	Magnesium-only (n=114)	Statin–magnesium (n=114)	p-value
Age (years)	59.8±5.8	59.7±5.8	>0.05	59.8±6.0	59.4±5.9	>0.05
Sex (male/female)	125/250	53/114	>0.05	43/71	31/83	>0.05
Body mass index (kg/m^2)	26.1±1.4	26.1±1.5	>0.05	26.1±1.4	26.0±1.5	>0.05
Diabetes mellitus	66 (17.6)	44 (26.3)	0.019	19 (16.7)	29 (25.4)	>0.05
Hypertension	139 (37.1)	80 (47.9)	0.018	50 (43.9)	51 (44.7)	>0.05
Smoking	107 (28.5)	65 (38.9)	0.016	36 (31.6)	39 (34.2)	>0.05
Peripheral arterial occlusive disease	63 (16.8)	47 (28.1)	0.002	22 (19.3)	29 (25.4)	>0.05
Preoperative cerebrovascular accident	25 (6.7)	23 (13.8)	0.007	13 (11.4)	19 (16.7)	>0.05
Commonly prescribed statins						
Atorvastatin		63 (37.7)			40 (35.1)	
Rosuvastatin		48 (28.7)			33 (28.9)	
Fluvastatin		26 (15.6)			20 (17.5)	
Others		30 (18.0)			21 (18.4)	
Duration of statin treatment						
<1 year		76 (45.5)			51 (44.7)	
≥ 1 year		91 (54.5)			63 (55.3)	
Type of cardiac surgery						
Coronary bypass graft surgery	131 (34.9)	57 (34.1)	>0.05	40 (35.1)	39 (34.2)	>0.05
Valve surgery	122 (32.5)	55 (32.9)	>0.05	37 (32.5)	38 (33.3)	>0.05
Coronary bypass graft surgery+valve surgery	122 (32.5)	55 (32.9)	>0.05	37 (32.5)	37 (32.5)	>0.05
Duration of cardiac surgery	335.5±22.8	333.4±26.3	>0.05	334.7±22.2	332.6±25.2	>0.05
Mechanical ventilation (h)	16.9±2.9	17.0±2.7	>0.05	16.8±2.8	17.0±2.7	>0.05
Intensive care unit stay (h)	62.3±7.5	62.9±7.4	>0.05	61.8±7.5	62.8±7.4	>0.05
Creatinine before surgery (mg/dL)	0.69±0.12	0.70±0.13	>0.05	0.69±0.12	0.71±0.13	>0.05
Creatinine at 1 day after surgery (mg/dL)	1.26±0.26	1.28±0.21	>0.05	1.27±0.21	1.29±0.21	0.017
Preoperative CRP (mg/L)	4.2±1.9	4.2±1.8	>0.05	4.28±1.9	4.22±1.8	>0.05
CRP at 1 day after surgery (mg/L)	96.9±15.1	92.2±13.2	0.001	96.4±14.0	92.4±13.0	0.026
CRP at 3 day after surgery (mg/L)	155.2±20.1	149.0±20.0	0.001	153.4±19.7	146.5±19.1	0.008

Values are expressed as mean±standard deviation or numbers (%).
CRP: C-reactive protein.

TABLE 2. Pain intensity and opioid consumption in patients who underwent cardiac surgery

Variables	Before matching			After matching		
	Magnesium-only (n=375)	Statin–magnesium (n=167)	p-value	Magnesium-only (n=114)	Statin–magnesium (n=114)	p-value
Volume of PCA containing fentanyl over 72 h postoperatively (mL)	341.3±31.3	334.1±29.1	0.010	341.8±30.8	332.3±28.4	0.017
VAS score at rest in the first 24 h postoperatively	43.0±11.0	41.1±11.3	>0.05	43.0±11.3	40.7±11.3	>0.05
VAS score with movement in the first 24 h postoperatively	62.6±10.9	60.4±11.4	0.035	62.5±11.3	60.2±11.2	>0.05
VAS score at rest in the first 48 h postoperatively	33.6±11.9	33.4±12.0	>0.05	33.6±12.0	33.3±12.0	>0.05
VAS score with movement in the first 48 h postoperatively	51.7±10.0	50.2±11.5	>0.05	51.7±10.4	49.7±11.3	>0.05
VAS score at rest in the first 72 h postoperatively	26.3±7.9	26.0±7.8	>0.05	26.7±7.9	25.9±7.5	>0.05
VAS score with movement in the first 72 h postoperatively	39.3±10.5	38.3±10.0	>0.05	39.6±10.8	38.1±9.8	>0.05

Values are expressed as mean±standard deviation.
PCA: patient-controlled analgesia, VAS: visual analogue scale.

TABLE 3. Pain intensity and opioid consumption according to the duration of statin treatment in patients who underwent cardiac surgery

Variables	Before matching			After matching		
	Duration <1 year	Duration ≥1 year	p-value	Duration <1 year	Duration ≥1 year	p-value
Volume of PCA containing fentanyl over 72 h postoperatively (mL)	338.9±30.9	329.9±27.0	0.047	337.5±31.4	327.0±24.1	0.047
VAS score at rest in the first 24 h postoperatively	43.1±11.9	39.3±10.5	0.031	42.8±11.9	38.6±10.3	0.046
VAS score with movement in the first 24 h postoperatively	62.5±11.8	58.7±10.7	0.031	62.1±11.6	58.2±10.5	>0.05
VAS score at rest in the first 48 h postoperatively	35.6±12.2	31.4±11.5	0.025	35.4±12.0	31.2±11.7	>0.05
VAS score with movement in the first 48 h postoperatively	52.5±11.9	48.2±10.8	0.017	52.1±11.8	49.4±10.4	>0.05
VAS score at rest in the first 72 h postoperatively	27.4±8.5	24.8±6.9	0.029	27.2±8.2	24.6±6.6	>0.05
VAS score with movement in the first 72 h postoperatively	39.7±10.5	37.1±9.4	0.090	39.3±10.3	36.8±9.1	>0.05

Values are expressed as mean±standard deviation.
PCA: patient-controlled analgesia, VAS: visual analogue scale.

patients with statin treatment ≥1 year were significantly lower (p<0.05) than those in patients with statin treatment <1 year, before matching. However, the duration of statin treatment had a weaker effect on reducing the VAS pain scores over the 72-h period after matching (Table 3). There was a statistically significantly negative, although weak, association of statin-treatment duration with opioid consumption over 72 h postoperatively (r=−0.154, p=0.047), VAS score at rest (r=−0.167, p=0.031), and VAS score with movement (r=−0.167, p=0.031) in the first 24 h postoperatively. Additionally, the VAS score at rest (r=−0.173, p=0.025) and VAS score with movement (r=−0.185, p=0.017) in the first 48 h postoperatively, and the VAS score at rest (r=−0.169, p=0.029) and VAS score with movement in the first 72 h postoperatively (r=−0.132, p=0.09), were statistically significantly negatively, but weakly, correlated (Table 4).

The incidence of postoperative atrial fibrillation was not significant, regardless of the subtype of cardiac surgery before matching. After matching, the incidence of postoperative atrial fibrillation in the statin–magnesium group was significantly reduced compared with that in the magne-

TABLE 4. Association of statin-treatment duration with pain intensity and opioid consumption

	Statin-treatment duration	
	Correlation coefficient	p-value
Volume of PCA containing fentanyl over 72 h postoperatively (mL)	−0.154	0.047
VAS score at rest in the first 24 h postoperatively	−0.167	0.031
VAS score with movement in the first 24 h postoperatively	−0.167	0.031
VAS score at rest in the first 48 h postoperatively	−0.173	0.025
VAS score with movement in the first 48 h postoperatively	−0.185	0.017
VAS score at rest in the first 72 h postoperatively	−0.169	0.029
VAS score with movement in the first 72 h postoperatively	−0.132	0.09

PCA: patient-controlled analgesia, VAS: visual analogue scale.

TABLE 5. Postoperative atrial fibrillation in patients according to type of cardiac surgery

Variables	Before matching			After matching		
	Magnesium-only (n=375)	Statin–magnesium (n=167)	p-value	Magnesium-only (n=114)	Statin–magnesium (n=114)	p-value
Postoperative atrial fibrillation	64 (17.1)	23 (13.8)	>0.05	28 (24.6)	14 (12.3)	0.017
Coronary bypass graft surgery	27 (20.6)	6 (10.5)	>0.05	12 (30)	2 (5.1)	0.004
Valve surgery	18 (14.8)	9 (16.4)	>0.05	8 (21.6)	7 (18.4)	0.729
Coronary bypass graft surgery+valve surgery	19 (15.6)	8 (14.5)	>0.05	8 (21.6)	5 (13.5)	0.359

Values are expressed as numbers (%).

sium-only group, but was reduced only in patients who underwent CABG surgery (Table 5).

DISCUSSION

The present study showed that the statin–magnesium group consumed significantly lower volumes of PCA containing fentanyl over a 72-h period postoperatively than did the magnesium-only group, both before and after propensity-score matching. Before matching, the VAS pain scores with movement in the first 24 h postoperatively in patients who received the statin–magnesium combination was significantly lower than those in patients who received magnesium alone. After matching, the VAS pain scores at 24, 48, and 72 h were not significantly different between the two groups. The finding that the VAS pains scores at these time-points did not differ significantly between the groups might be attributable to the increased use of opioids by the magnesium-only group to reduce pain levels.

Preclinical and clinical studies have shown conflicting results regarding the effect of statins on pain outcomes.[3,4,6,7] Animal studies have also suggested the beneficial effects of statins on pain,[3,4] whereas clinical studies have indicated that statin treatment is not effective with respect to pain outcomes.[6,7] At our hospital, magnesium has been administered as a standard of care for preventing postoperative atrial fibrillation. Some studies recommended magnesium administration as a strategy to mitigate postoperative pain in surgical patients.[8,9] In the present study, the statin–magnesium combination significantly reduced pain compared with magnesium alone. Although statins and magnesium each have their own specific properties, both are associated with NMDA receptors and have an anti-inflammatory effect.[1,8,10] Due to these common properties, the statin–magnesium combination shows a synergic effect compared with magnesium alone and may affect opioid consumption. Available clinical studies have reported the relationship between perioperative statin use and postoperative pain and opioid consumption.[6,7] However, this study addresses the synergistic effect of a perioperative statin–magnesium combination on opioid consumption and pain intensity.

Since the results of studies on the effect of prolonged use of statins on pain and nociception are contradictory, the use of statins as analgesic adjuvants is not yet supported by evidence.[6,7] In the present study, statin treatment ≥ 1 yr resulted in significantly greater reduction in opioid consumption than did statin treatment <1 yr. However, correlation analysis showed a weakly negative relationship between the duration of statin treatment and opioid consumption or pain intensity. This result indicates that the effect of statin-treatment duration on opioid consumption and pain intensity remains controversial in terms of clinical implications.

Some studies have reported that there is an excess risk of acute kidney injury (AKI) within 2 years after statin initiation in high-potency statin users compared to lower-potency statin users, but only among patients without chronic kidney disease at baseline.[11,12] However, other studies did not find a significant association between statin treatment and the risk of AKI or an excess risk of AKI with high-potency versus moderate-/low-potency regimens.[13,14] The creatinine level after surgery in the present study did not differ significantly between the two groups, but the statin-magnesium group was higher than magnesium group after propensity-score matching. The most frequently reported risk factors for AKI after cardiac surgery include advanced age, female sex, New York Heart Association function class IV, reduced left ventricular ejection fraction or congestive heart failure, diabetes mellitus, poor glycemic control, peripheral vascular disease and chronic obstructive pulmonary disease, type of surgery, duration of CPB, blood transfusion, and hemolysis.[15]

According to the type of cardiac surgery in the present study, the incidence of postoperative atrial fibrillation in the statin–magnesium group was significantly lower in patients who underwent coronary artery bypass surgery than in those who underwent valve surgery or combined surgery. Some studies have reported that the beneficial effect of statins on postoperative atrial fibrillation was found only in patients who underwent CABG, but not in those who underwent valve surgery. Valvular diseases are mostly related to the aging process, due to calcification of the valves, but not to inflammatory responses or lipid deposition.[16]

This study had some limitations. First, this retrospective study had a small sample size, which limits the generalization of the results.[17] Studies with very large sample sizes may be needed to identify rare or controversial outcomes.

Second, retrospective studies are known to have an inherent risk of bias if some key points are not addressed. Although we attempted to reduce this risk through propensity-score matching, some unmeasured or confounding factors may have influenced the results of the present study. Third, the observed effect of the statin–magnesium combination on opioid consumption and pain intensity in the present study might be difficult to apply to the effect of statin use only on pain outcomes. Finally, data on perioperative factors that could potentially affect the outcomes, such as total dose of opioids and anxiolytics, method of sedation, and postoperative nausea and vomiting, were not available for analysis.

In conclusion, the results of the present study demonstrate that the perioperative use of the statin–magnesium combination seems to reduce opioid consumption significantly postoperatively, which might be due to the synergistic reaction between statin and magnesium; however, it was unable to reduce pain intensity.

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CONFLICT OF INTEREST STATEMENT

None declared.

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