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Comparing perioperative magnesium sulphate, lidocaine, and their combination in preventing ventricular arrhythmia in off-pump coronary artery bypass grafting

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Abstract

Background: Techniques of coronary artery bypass grafting (CABG) have developed rapidly over the last decades. However, dysrhythmia is a common feature during off pump CABG. The aim of this work was to study effect of perioperative magnesium sulphate infusion on the incidence of cardiac arrhythmia in off-pump CABG: and comparing such effects to lidocaine alone or combined to magnesium.

Methodology: Ninety patients undergoing elective coronary artery bypass grafting surgery were randomly divided into three equal groups: magnesium group received magnesium over 12 h prior to off-pump surgery and over 30 min intraoperatively; lidocaine group were given an intravenous bolus injection of lidocaine followed by a continuous infusion; and combination group received half the doses of magnesium and lidocaine prescribed for the other two groups. The patients' perioperative hemodynamic data (heart rate and mean arterial pressure) and the occurrence of intraoperative and postoperative arrhythmia were recorded.

Results: There was statistically significant difference between study groups as regards mean intraoperative heart rate and intraoperative mean arterial pressure. In addition, the need for intraoperative beta-blockers was significantly higher in lidocaine group; there was no need for intraoperative beta-blockers for combination group. Also, the need for perioperative aortic balloon pump was significantly higher in lidocaine group (20.0%), followed by 6.7% in magnesium group, and none in combination group. The percentage of ventricular tachycardia was significantly higher in lidocaine group (16.7%), followed by magnesium group (3.3%) and none in combination group.

Conclusion: Results of the present study revealed that combination of both perioperative magnesium and lidocaine when compared to each of both drugs separately has a better effect in controlling hemodynamics (heart rate and mean arterial blood pressure intraoperatively), less ventricular tachycardia, and reduction in the need for beta blockers and aortic balloon pump perioperatively. In addition, magnesium was superior to lidocaine, although both are effective.

Keywords: Magnesium, Lidocaine, Coronary artery, Bypass graft

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Background

Coronary artery bypass grafting (CABG) is one of the most commonly performed cardiothoracic surgery in adult patients. It is usually performed with the usage of on pump cardiopulmonary bypass. But, cardiopulmonary bypass has been suggested to be related to the development of many postoperative complications. Thus, technique of operating without cardiopulmonary bypass (on a beating heart), such as off-pump coronary artery bypass (OPCAB), was established to reduce such complications (Puskas et al. 2011).

OPCAB has the advantages of being associated with preserved hematocrit levels and pulsatile flow generated by the beating heart, contributing to preservation and maintenance of microcirculatory perfusion (Papp et al. 2011). In addition, extracorporeal contact activation is absent. Furthermore, cardiac positioning during OPCAB procedures is associated with short-lasting cessation of microcirculatory flow (Atasever et al. 2011).

On the other hand, OPCAB is associated with temporary occlusion of the target artery and, with possible, hemodynamic instability and reduction in coronary blood flow (Yacoub 2001). The results of this temporary coronary artery occlusion may be insignificant, or it may lead to myocardial ischemia, severe heart failure, and, ultimately, cardiac arrest (Stillman and Soloniuk 2000).

In addition, it was reported that the decrease in the ions concentrations such as magnesium and potassium is an important factor in cases of postoperative arrhythmia. So, identifying these ionic imbalances may protect the heart from the side effects of anti-arrhythmia treatments by stabilizing membrane function. Magnesium plays a vital role in preserving cardiac rhythm (Banach et al. 2006; Heintz and Hollenberg 2005). There are several pharmacologic strategies developed to minimize postoperative arrhythmias after CABG surgery, with subsequent reduction of patient morbidity and mortality (Burgess et al. 2006). Magnesium sulfate is used perioperatively, aiming to reduce postoperative cardiac arrhythmias after CABG surgery (Taksaudom et al. 2016).

One meta-analysis investigated the magnesium role in prevention of postoperative arrhythmias showed a beneficial promising effect (Shiga et al. 2004), but another large randomized clinical trial has failed to show a significant valuable effect. Therefore, it remains unclear if magnesium infusion has a role in reduction of the postoperative cardiac arrhythmias incidence (De Oliveira et al. 2012).

Lidocaine is commonly used in local anesthesia and as an antiarrhythmic agent. It had been shown to have cardioprotective effects against myocardial ischemia and reperfusion injury by different mechanisms (e.g., cardiac sodium channels blockade, intracellular calcium loading reduction, reducing reactive oxygen species (ROS) production, and mitochondrial bioenergetics modulation) (Wang et al. 2007; Aldakkak et al. 2009).

A variety of experimental animals' investigations have shown that lidocaine has a protective effect against reperfusion injuries and myocardial ischemia (Dias et al. 2004; Kaczmarek et al. 2009).

Aim of the study

We designed this study to evaluate the effect of infusion of 5 g magnesium perioperatively (2.5 g magnesium over 12 h prior to off-pump surgery and 2.5 g magnesium over 30 min intraoperatively) in comparison with lidocaine IV bolus injection of 1.5 mg/kg; followed by IV infusion of 2 mg/kg/h and their combination on hemodynamic instability, arrhythmias, and myocardial infraction (MI).

Subjects and methods

This study was conducted in Al-Azhar University Hospitals and Damietta Cardiology and Gastroenterology Center, during the period from June 2015 to July 2016. Ninety ASA II-III patients scheduled for elective off pump CABG surgery were invited to participate in the present work. The patients had no hemodynamic instability prior to surgery, and no evidence of acute ischemia occurred within 3 months before surgery. The left ventricular ejection fraction was more than 35%. The patients had no preoperative renal insufficiency, hepatic insufficiency, pulmonary insufficiency, blood coagulation dysfunction, or concomitant valvular lesions.

They were randomly (closed envelope method) divided into three equal groups according to administration of magnesium or lidocaine. The first group (magnesium group) included 30 subjects who received 2.5 g magnesium over 12 h prior to off-pump surgery and 2.5 g magnesium over 30 min intraoperatively. The second group (lidocaine group) included 30 subjects who, after induction of anesthesia, were given an i.v. bolus injection of 1.5 mg/kg lidocaine followed by a continuous i.v. infusion of 2 mg/kg/h.

The lidocaine infusion was continued throughout the surgical procedure and then discontinued at the end of surgery. Patients of the third group (combination group) received a combination of both drugs in half the dose prescribed for the first two groups. They received 1.25 g magnesium over 12 h prior to off-pump surgery and 1.25 g magnesium over 30 min intraoperatively plus i.v. lidocaine (an i.v. bolus injection of 0.75 mg/kg after induction, and then a continuous infusion of 1 mg/kg/h).

The study protocol was approved by local ethical committee; study protocol was discussed with every patient separately and an informed consent was obtained for participation. For those eligible subjects, confidentiality was guaranteed. If any patient had been withdrawn due to any reason, we searched for another one to complete the target number of study protocol.

Operative technique

It was done as described by Besogul et al. (2009). Briefly, all patients were premedicated using intravenous midazolam (0.05–0.1 mg/kg) before admission to the operating room (OR). Standard monitoring was applied to all patients: five-lead surface electrocardiogram (ECG) with automated ST segment analysis, pulse oximetry, continuous urinary output, esophageal and rectal temperature, arterial blood pressure by cannulating radial and/or femoral artery, central venous catheter (CVC), neuromuscular monitoring, and coagulation profile monitoring. The arterial catheter was inserted under local anesthesia and the central venous catheter was inserted after induction of anesthesia. Anesthesia was induced in all patients with Midazolam (0.1 mg/kg), Fentanyl (5–8 μg/kg), Thiopental (2–3 mg/kg), and Cis-atracurium (0.2 mg/kg); maintained with inhalation of 1–2% sevoflurane and intermittent use of Fentanyl and Cis-atracurium. Routine median sternotomy was done, and then the left internal mammary artery (LIMA) was harvested. For patients with intraoperative blood pressure fluctuation, maintaining MAP > 70 mmHg to allow an adequate coronary perfusion was achieved by adjusting the depth of anesthesia, cautious fluid loading, and the use of vasopressor and/or inotropes. We used intravenous heparin (2–3 mg/kg) to achieve systemic heparinization with activated clotting time targeted at 250–300. If myocardial ischemia was suspected, nitroglycerine was used, and the surgeon revised the grafts. Heart rate was kept between 70 and 80 bpm and tachycardia was treated using esmolol as appropriate. Ventricular arrhythmias were treated with serum electrolytes' correction, amiodarone, or electrical cardioversion as appropriate. If the rhythm was AF, synchronized cardioversion was tried. The catheter of intra-aortic balloon pump (IABP) was inserted in patients with hemodynamic instability with the mean arterial pressure persistently lower than 70 mmHg irrespective of maximum dose inotropic support.

At the end of the surgery, all of patients were transferred to the intensive care unit and were weaned from the ventilator as soon as they met the following criteria: hemodynamic stability, no major bleeding, normothermia, and consciousness with adequate pain control.

Primary outcome was the occurrence of intra- and/or post-operative arrhythmia. The secondary outcome included amount of blood transfusion, postoperative myocardial infarction, duration of intubation (h), ICU stay duration (h), and duration of hospital stay (days).

Data collection

The patients' demographic and perioperative hemodynamic data including CVP, MAP, and HR were obtained. All patients were monitored and any occurrence of intra- and/or post-operative electrical rhythm other than sinus rhythm or postoperative myocardial infarction (S–T segment changes) was recorded. Duration of intubation, ICU, and hospital stay were also recorded.

Statistical analysis of data

Before conducting this study, G*Power version 3.1.9.1 software was used for sample size calculation. Twenty-eight patients per arm (total of 84 patients) are required to achieve 80% power with an error of 0.0167. The collected data was analyzed. Statistical package for social science, version 20 (SPSS, Inc., USA) was used for data analysis.

Qualitative data were expressed as relative frequency and percent distribution, while quantitative data were expressed as arithmetic mean and standard deviation (SD). Groups were compared by student (*t*) or chi square tests for quantitative and qualitative data respectively. *P* value < 0.05 was considered significant for interpretation of data.

Results

In the present work, the three groups were comparable regarding age and sex. Furthermore, there was no significant difference between the three groups as regards diabetes, smoking, and preoperative drugs (Table 1).

In the present study, there was a statistically significant difference between study groups as regards intraoperative heart rate; it was lower in magnesium group (76.23 ± 6.11) and in combination group (75.26 ± 3.13) than in lidocaine group (80.57 ± 5.03); intraoperative mean arterial pressure was 77.0 ± 7.41, 76.83 ± 5.31, and 81.70 ± 3.60 in magnesium, lidocaine, and combination groups respectively. In addition, the need for intraoperative beta-blockers was

Table 1 Patient characteristics and preoperative risk factors and drugs

Variable		Mg group	Lidocaine group	Combination group	Test	*P* value
Age		58.87 ± 2.11	59.37 ± 3.90	58.40 ± 2.91	0.75	0.47 (ns)
Sex (male/female)		18/12 (56.0:40.0%)	21/9 (70.0:30.0%)	23/7 (76.7:23.3%)	1.97	0.37 (ns)
Diabetes		8 (26.7%)	8 (26.7%)	9 (30.0%)	0.11	0.94 (ns)
Smoking		11 (36.7%)	15 (50.0%)	18 (60.0%)	3.29	0.19 (ns)
Preoperative drugs	β-blockers	0 (0.0%)	1 (3.3%)	1 (3.3%)	1.02	0.60 (ns)
	Digitalis	3 (10.0%)	1 (3.3%)	0 (0.0%)	3.66	0.16 (ns)

Data presented as mean ± SD, or number (%). *ns* not significant (*P* > 0.05) higher in lidocaine group (26.7%), decreased to 10% in magnesium group and in combination group; there was no need for intraoperative beta-blockers. Also, use of perioperative aortic balloon pump was significantly higher in lidocaine group (20.0%), followed by 6.7% in magnesium group, and none in both drugs group. Ventricular tachycardia was significantly higher in lidocaine group (16.7%), followed by magnesium group (3.3%), and none in combination group. On the other hand, there was no statistically significant difference between studied groups as regards number of vessels (it was 1.37 ± 0.49, 1.30 ± 0.46, and 1.27 ± 0.45 in Mg, lidocaine, and combination groups respectively) or ejection fraction (it was 41.87 ± 1.87, 40.96 ± 2.35, 40.67 ± 3.42 in the same order of groups).

Blood pH values and electrolytes showed a nonsignificant difference among groups. In addition, there was no statistically significant difference between the three groups as regards ST segment elevation, need for intraoperative inotropic agents, use of defibrillation, the mean number of transfused blood units, duration of intubation, duration of ICU stay, or total hospital stay duration (Table 2).

Discussion

The current study revealed that combination of both drugs provided better effects in controlling hemodynamics (heart rate and mean arterial blood pressure intraoperatively) than in the other groups. Magnesium was slightly better in controlling heart rate and mean arterial blood pressure, but significantly associated with low need for intraoperative beta blockers than lidocaine group. In addition, in combination group, no one developed ventricular tachycardia, and there was no need for the use of beta blockers or aortic balloon pump perioperatively in CABG surgery.

CABG surgeries have developed rapidly over the last decades. One of the great improvements was the introduction of off-pump CABG. It revolutionized the surgical approach by reducing the cost of surgery and decreased the morbidity association with cardiopulmonary bypass. However, dysrhythmia is a common feature during off-pump CABG due to many reasons (e.g., mechanical stimulation of the heart, myocardial ischemia, and electrolyte abnormalities including hypomagnesaemia) (Muralidhar and Narasimha 2004). Malignant ventricular dysrhythmia, especially ventricular fibrillation, may have a grave effect during off-pump CABG.

Thus, prophylactic administrant of anti-dysrhythmia agents is warranted during distal coronary anastomosis (Lee et al. 2011). However, the ideal agent used as a prophylactic drug is still under research work. There were different agents used for prophylaxis in such situation. There is evidence showing that there is high risk of magnesium depletion during CABG surgery with CPB.

This hypomagnesaemia precipitates cardiac arrhythmias and vasoconstriction of coronary arteries or mammary artery graft. This vasoconstriction in turn aggravates the arrhythmias (Treggiari-Venzi et al. 2000). Thus, magnesium

Table 2 Perioperative and outcome data

Variable	Mg group	Lidocaine group	Combination group	Test	*P* value
Number of vessels	1.37 ± 0.49	1.30 ± 0.46	1.27 ± 0.45	0.35	0.70 (ns)
Ejection fraction,%	41.87 ± 1.87	40.96 ± 2.35	40.67 ± 3.42	1.68	0.19 (ns)
Intraoperative heart rate, beat/min	76.23 ± 6.11	80.57 ± 5.03	75.26 ± 3.13	9.88	< 0.001*
Intraoperative mean arterial pressure, mmHg	77.0 ± 7.41	76.83 ± 5.31	81.70 ± 3.60	7.13	0.001*
Intraoperative pH	7.37 ± 0.07	7.36 ± 0.06	7.36 ± 0.06	0.043	0.958 (ns)
Intraoperative Na^+	136.59 ± 6.3	135.81 ± 6.3	136.56 ± 5.6	0.138	0.871 (ns)
Intraoperative K^+	3.8 ± 0.50	3.6 ± 0.63	3.7 ± 0.58	0.661	0.519 (ns)
Intraoperative Ca^{++}	8.51 ± 0.44	8.2 ± 0.61	8.2 ± 0.62	1.928	0.152 (ns)
ST elevation, number of patients	5 (16.7%)	5 (16.7%)	3 (10.0%)	0.71	0.69 (ns)
Intraoperative inotropic agents, number of patients	3 (10.0%)	4 (13.3%)	3 (10.0%)	0.22	0.89 (ns)
Intraoperative β-blockers, number of patients	3 (10.0%)	8 (26.7%)	0 (0.0%)	10.15	0.006*
Perioperative aortic balloon pump, number of patients	2 (6.7%)	6 (20.0%)	0 (0.0%)	7.68	0.021*
Perioperative ventricular tachycardia, number of patients	1 (3.3%)	5 (16.7%)	0 (0.0%)	7.50	0.024*
Intraoperative defibrillation, number of patients	0 (0.0%)	2 (6.7%)	0 (0.0%)	4.09	0.12 (ns)
Intraoperative blood transfusion units, number of patients	2.53 ± 0.51	2.54 ± 0.50	2.60 ± 0.62	0.15	0.86 (ns)
Duration of intubation (h)	16.40 ± 0.89	16.83 ± 1.59	16.13 ± 1.57	1.93	0.15 (ns)
ICU stay (h)	50.67 ± 2.69	49.47 ± 2.97	48.33 ± 2.31	2.26	0.11 (ns)
Duration of hospital stay (day)	7.30 ± 0.65	7.10 ± 0.67	7.13 ± 0.82	0.67	0.51 (ns)

Data presented as mean ± SD, or number (%). *Statistically significant at $P < 0.05$. *ns* not significant ($P > 0.05$)

supplementation can stabilize the myocardial cell membrane and provide some cardioprotective effect against ventricular arrhythmias (Kurian 2007).

Another approach to protect against ventricular dysrhythmias occurrence during CABG is the use of lidocaine (Mahli and Coskun 2012). Here, we presented our experience in the use of magnesium or lidocaine as a separate prophylactic drug and investigated the combination of both drugs.

We prospectively evaluated 90 patients who underwent elective CABG, and randomly allocated to receive perioperative magnesium (30 patients), lidocaine (30 patients), or both drugs (30 patients). Our results revealed that combination of both drugs provided the better effects in controlling hemodynamics (heart rate and mean arterial blood pressure intraoperatively). In addition, in both drugs group, there was no need for the use beta blockers and none in this group developed ventricular tachycardia.

On the other hand, magnesium was slightly better in controlling heart rate and mean blood pressure, but significantly associated with low need for intraoperative beta blockers (10.0% in magnesium group compared to 26.7% in lidocaine group), and only one patient in this group (3.3%) developed ventricular tachycardia, compared to five patients (16.7%) in lidocaine group.

One interesting finding in the present study was the reduction in the need for perioperative aortic balloon pump in magnesium group (two patients; 6.7%) when compared to lidocaine group (six patients; 20.0%) and none in group of both drugs. Results of the present study are comparable to the work of Besogul et al. (2009) who demonstrated that preoperative administration of magnesium provides optimization of hemodynamics during off-pump CABG.

To explain this effect, it was reported that magnesium is known as a natural calcium antagonist, and calcium mediates the major mechanism of ischemia-reperfusion myocardial damage (Matsusaka et al. 2002). Ravn et al. (1999) reported that intravenous magnesium resulted in 50% reduction in infarct size. In addition, animal studies suggested that magnesium supplementation before reperfusion reduces infarct size (Antman 1996). Furthermore, Guo et al. (2004) believed that high levels of magnesium decrease vessels reactivity, consequently improving coronary vessels blood flow (Ferguson et al. 2002). Caspi et al. (1995) showed that perioperative magnesium contributed to better myocardial recovery and fewer postoperative ventricular tachyarrhythmias (Virmani and Tempe 2007).

Elevation of extracellular magnesium levels reduces arteriolar tone and potentiates the dilating effects of some endogenous (adenosine, potassium, and some prostaglandins) and exogenous (isoproterenol) vasodilators. Therefore, magnesium can unload the ischemic ventricle.

In addition to its reduction effect on vascular resistance of both systemic and pulmonary, magnesium causes a concomitant slight increase in the cardiac index (Shechter et al. 2003). A growing body of evidence suggests that lidocaine has protective effects against myocardial ischemia and reperfusion injury in an animal heart either in isolated heart models (Aldakkak et al. 2009), or in vivo models (Hinokiyama et al. 2003).

To explain this cardioprotective effects, it was reported that this effects are due to reduction in ventricular arrhythmias (Canyon and Dobson 2004; Canyon and Dobson 2005), decreased myocardial dysfunction (Wang et al. 2007; Ebel et al. 2001), reduction in phosphate waste (Dias et al. 2004; Canyon and Dobson 2006), and in infarct size (Hinokiyama et al. 2003; Canyon and Dobson 2005) and apoptosis (Kaczmarek et al. 2009). Interestingly, these cardioprotective effects have also been observed in patients undergoing on-pump coronary bypass grafting surgery and during pediatric cardiac surgery (Rinne and Kaukinen 1998). In addition, the inclusion of lidocaine in cardioplegic solution was associated with an improved hemodynamic profile during surgery (Jin et al. 2008).

These results are comparable to those found in the present work. Another proposed mechanism is the blockade of sodium channels by lidocaine can reduce intracellular sodium accumulation during ischemia and reperfusion, which leads to the preservation of adenosine triphosphate and the prevention of Na^+-induced intracellular calcium overload (Wang et al. 2007).

Furthermore, lidocaine was found to reduce the generation of reactive oxygen species (ROS) during ischemia and reperfusion (Aldakkak et al. 2009). All these mechanisms of lidocaine may contribute to our finding that lidocaine reduced ventricular tachycardia, and properly controlled mean arterial pressure in patients undergoing OPCAB.

Going with results of the present study, Muralidhar and Narasimha (2004) reported that there were no significant differences regarding patient's age or ejection fraction ischemia in the magnesium group when compared to lidocaine or control group. They added that there were significantly fewer episodes of dysrhythmia and ischemia in the magnesium group. Unfortunately, we could not find any previous work that used the magnesium-lidocaine combination in off-pump coronary bypass grafting surgery.

However, we found the work of Elnakera et al. (2013) who used this combination in on-pump CABG surgery and reported that the continuous infusion of magnesium-lidocaine (ML) mixture resulted in a delay in the reappearance of spontaneous electrical activity with reduction in the incidence of spontaneous ventricular fibrillation after release of ACC and post-CPB ventricular arrhythmias compared with control group during CABG surgery.

Conclusions

Results of the present study revealed that combination of both perioperative magnesium and lidocaine when compared to each of both drugs separately has a better effect in controlling hemodynamics (heart rate and mean arterial blood pressure intraoperatively), less ventricular tachycardia, and reduction in the need for beta blockers and aortic balloon pump perioperatively. In addition, magnesium was superior to lidocaine, although both are effective.

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Availability of data and materials
The datasets analyzed during the current study are available from the corresponding author on reasonable request.

Authors' contributions
TSS, IFM, MAS: concepts, design, definition of intellectual content, literature search, clinical studies, data acquisition, data analysis, manuscript preparation, manuscript review. TSS: statistical analysis and manuscript editing. All authors read and approved the final manuscript.

Ethics approval and consent to participate
The study protocol was approved by local ethical committee, was discussed with every patient separately, and an informed consent was obtained for participation. For those eligible subjects, confidentiality was guaranteed.

Consent for publication
Not applicable.

Competing interests
The authors declare that they have no competing interests.

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