A Comparative Study to Determine the Effect of Intravenous Magnesium on Postoperative Bleeding after on Pump CABG in Patients Receiving Pre-Operative Aspirin

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Summary

Hypomagnesaemia is a common complication after cardiopulmonary bypass (CPB) and predisposes to the development of cardiac arrhythmias. Previous studies showed that intravenous magnesium reduces the incidence of postoperative cardiac arrhythmias but it also inhibits platelet function. Our aim was to compare the postoperative blood loss in patients not receiving magnesium after CPB with the group who received magnesium and to compare the requirement of blood, fresh frozen plasma (FFP) and platelets within 24 hours after surgery. This prospective randomized controlled study was conducted in 80 adult patients on oral aspirin undergoing elective CABG requiring CPB. Group A patients had not received magnesium infusion after recovery from CPB. Group B patients received magnesium infusion after recovery from CPB. Postoperative bleeding was assessed in both the groups. All the data were statistically analyzed. There was an insignificant increase in 24 hours postoperative drainage in magnesium recipient group compared to control group (p>0.05). Requirements of blood and blood products to maintain haematocrit and coagulation profile revealed insignificant (p > 0.05). Increase in requirement of PRC, FFP and platelets in magnesium recipient patients than the control group. Incidence of atrial fibrillation (Gr A 2.5%, Gr B 2.5%) and atrial extrasystoles (Gr A 2.5%, Gr B 10%) revealed comparable (p > 0.05) between the groups, but incidence of ventricular arrhythmias were significantly (p<0.05) high in the patients of Gr A (17.5%) than Gr B (5%). To conclude, magnesium may be administered to patients who continue pre-operative aspirin to undergo on-pump CABG surgery.

Key words Aspirin, Magnesium, CPB, CABG, Postoperative bleeding

Introduction

Excessive post-cardiopulmonary bypass (CPB) bleeding is a major cause of post-operative morbidity and mortality after cardiac surgery. The extracorporeal circulation leads to thrombocytopenia and platelet dysfunction which results in an increase in postoperative bleeding episodes, transfusion of blood and blood products and therefore increases the risk of transfusion related infections and immunological reactions.

Several studies have demonstrated the beneficial role of aspirin in patients of coronary artery diseases for reducing incidence of myocardial infarction. By inhibiting platelet aggregation, aspirin reduces the incidence of infarction in post infarct patients and is also recommended for primary prevention of acute coronary syndromes. It also improves graft patency rates after coronary artery bypass grafting (CABG). Studies showed that, effects of magnesium impair platelet function, a 48% prolongation of bleeding time and a 40% inhibition of ADP induced platelet aggregation were observed in healthy volunteers after administration of 8 mM magnesium sulphate. Complete inhibition of platelet aggregation at 10 mM magnesium were reported. By 8mM magnesium sulphate, serum magnesium con-
Concentration increases to 1.2 to 1.5 mM/L. Although data on the effect of magnesium on p-selectin expression and fibrinogen binding are limited. Paradoxically, the mechanisms by which aspirin confers protection against myocardial infarction and graft closure after CABG may contribute to increased bleeding complications after cardiac surgery. There are several randomized clinical trials which showed that the incidence of bleeding complications after CABG is greater in patients who take aspirin before surgery. So it has been customary to discontinue aspirin 7–10 days before surgery, which is the approximate duration of life of platelets. But recent studies have revealed that outcome is actually improved in patients who continue aspirin versus those who discontinue aspirin before cardiac surgery. Since the benefits of aspirin have been clearly demonstrated and it is not definitely associated with post-CPB bleeding, so it is reasonable to continue aspirin pre-operatively.

Hypomagnesaemia is common after cardiac surgery with an incidence of 70% after CPB due to haemodilution in the extracorporeal circulation, reduces the incidence of supraventricular and ventricular arrhythmias. Hypomagnesaemia affects the cardiovascular system in a number of ways which include coronary artery spasm, increased incidence of cardiac arrhythmias, digitalis related arrhythmias and has been associated with sudden death in patients with ischaemic heart disease. It also prolongs the duration of postoperative mechanical ventilatory support. Intravenous administration of magnesium reduces the incidence of postoperative ventricular and atrial arrhythmias and improves cardiac function after CABG. Magnesium is also effective in decreasing the number of episodes of postoperative atrial fibrillation.

A controlled trial concluded that magnesium inhibited platelet function in vitro and in vivo. Although this antithrombotic effect of magnesium may be beneficial in patients after coronary revascularization, large dose magnesium therapy should be carefully considered in patients with impaired platelet function and co-existing bleeding disorders.

Whether magnesium exerts an additive inhibitory effect on platelet function in patients receiving aspirin preoperatively has not been investigated. We studied the effect of intravenous magnesium sulphate infusion on postoperative bleeding in patients of CABG on cardiopulmonary bypass who continued to take aspirin preoperatively.

Considering the results of previous studies, the aims of this study were to compare the postoperative blood loss in patients not receiving magnesium after CPB with the group who received magnesium and to compare the requirement of blood, fresh frozen plasma (FFP) and platelet within 24 hours after surgery.

**Methods**

After approval of the Institutional Ethics Committee, this prospective, randomized, controlled, double blind study was conducted in the Department of Anaesthesiology, I.P.G.M.E&R / S.S.K.M. Hospital, Kolkata. After obtaining written, informed consent, eighty consecutive adult patients on oral aspirin undergoing elective CABG requiring CPB were prospectively randomized into two groups through a computer generated random number.

**Group-A (Control Group) (n = 40)**
Patients who did not receive magnesium infusion after recovery from CPB.

**Group-B (Magnesium Group) (n = 40)**
Patients who received magnesium infusion after recovering from CPB.

Patients with history of recent thrombolytic therapy, warfarin therapy, history of previous cardiac surgery, hepatic disease, renal disease, hypersensitivity to study drugs, emergency patients who underwent re-exploration within the study period were excluded from the study.

All patients were premedicated with diazepam 0.1 mg.kg⁻¹ orally and their usual dose of aspirin, beta blocker and calcium channel blocker in the morning.
In the operation theatre, invasive blood pressure, pulse oximetry, central venous pressure, temperature, ECG and arterial blood gases, serum electrolytes, (Na⁺, K⁺, Ca++) were routinely monitored in all patients. After proper preoxygenation, all patients were induced with fentanyl 10 mcg.kg⁻¹ iv and midazolam 0.1 to 0.4 mg.kg⁻¹ iv titrated to the effect, tracheal intubation were facilitated with pancuronium 0.1 mg.kg⁻¹ iv. Anaesthesia were maintained with oxygen in air 40%: 60% along with isoflurane, intermittent bolus of fentanyl and vecuronium along with infusion of propofol at 50 to 100mg.kg⁻¹.min⁻¹. The extracorporeal circulation circuit was primed with 1800 ml of Ringer’s lactate and 100 ml 20% human albumin. A capillary membrane oxygenator, arterial line filter, polyvinyl chloride tubings for the pump were used in all patients. Patients were anticoagulated with heparin 3 mg.kg⁻¹ iv and repeated as necessary to maintain activated clotting time (ACT)> 400 secs. Moderate systemic hypothermia, non pulsatile, filtered, arterial flow and gravity venous drainage were common features of the operation. All patients received epsilon aminocaproic acid (EACA) 100 mg.kg⁻¹ iv bolus and 10 mg.kg⁻¹.hr⁻¹ for 5 hours after administration of heparin. At the end of the operation, protamine sulphate was used to neutralize heparin in the ratio of 1.3 mg protamine per mg of heparin.

At the end of CPB, Group A (Control Group) received 100 ml normal saline iv and Group B (Magnesium Group) received 2 gm magnesium sulphate in 100 mL 0.9% NaCl solution (12.5 mL/h) just after cardiopulmonary bypass with the opening of cross clamp and continued for 72 hours postoperative period. The control group received only 100 mL 0.9% NaCl solution (12.5 mL/h) at the same time points. Infusions were guided by and directed to maintain normal tissue perfusion as indicated by normal urine output, absence of metabolic acidosis. Potassium (20mEq potassium chloride in 100 mL normal saline solution) was administered as required to maintain the concentration of potassium at 4 mmol/L. Inotropic agents were not used to raise perfusion pressure during cardiopulmonary bypass. However, pump flow was never allowed to fall to less than 2.2 L/m². In addition to potassium and calcium measurements obtained during operation and in the intensive care unit. A blood gas analysis was also performed at the latter time points and oxygen saturation obtained by pulse oximetry.

Postoperative monitoring included invasive blood pressure, pulse oximetry, central venous pressure, temperature, ECG and arterial blood gases, serum electrolytes, (Na⁺, K⁺, Ca++), urine output, volume of mediastinal drainage and other bleeding (if any).

Homologous blood was transfused when hemoglobin values dropped below 8.5 gm%. The amount of mediastinal drainage was noted for 24 hours. Perioperative transfusion therapy was guided with routine coagulation monitoring. Platelet concentrate was transfused if ACT and PT were not prolonged but patient had persistent bleeding (>150 ml/hr for >2 hrs). FFP was transfused if PT was prolonged by >50%.

Statistical analysis: Sample size was calculated from a previous study on the basis of the anticipated difference in 24hrs mean expected blood loss between the two groups. Assuming that the mean expected blood loss in 24 hrs would be 500 ml in the control group with a standard deviation of 300 ml, it was calculated that 40 patients per group would be required to detect a significant difference with 80% power and 5% probability of Type I error.

Numerical Parametric data was given as Mean ± SD. Ordinal and nominal data was expressed in cross table as number (%) of patients in each ordinal and nominal category. Numerical parametric data was compared by unpaired t-test (-independent sample t-test). Categorical data was compared by Chi-square test / Fischer’s exact test p<0.05 was considered statistically significant.
Results

Table 1 shows that, the demographic profile of the two groups were comparable, (p>0.05) with respect to age & sex and the difference was not statistically significant.

Table 2 shows that haematologic variable of the two groups was comparable and the difference was not statistically significant.

Table 3 shows that, the distribution of risk factors and associated diseases like obesity, congestive heart failure, history of smoking, diabetes mellitus and hypertension was comparable between the two groups.

Table 4 shows that, the data from the intraoperative observations revealed no statistically significant difference in the percentage of left internal mammary artery(LIMA) harvesting, number of vessels bypassed, CPB time, total dose of heparin and protamine, preoperative and postoperative haematocrit values.

Table 5 shows that, the incidence of cardiac arrhythmias after CPB were compared and revealed that, the incidence of atrial arrhythmias were comparable between the two groups. A significant increase in the incidence of ventricular arrhythmias in Group A (17.5%) was observed against Group B (5%) (p<0.05). Out of the 7 patients suffered ventricular tachycardia of Group A (Control Group), 4 patients responded to treatment with DC Cardioversion and amiodarone iv, while 3 patients suffered ventricular extrasystoles were haemodynamically insignificant treated with iv amiodarone. Only 2 patients in Group B (Magnesium Group) suffered ventricular extrasystoles which did not require any treatment.

Table 6 shows that, total collection of mediastinal drainage in 24 hours postoperative period were com-
pared and found that there was a modest increase in drainage in Magnesium Group compared to Control Group but it was statistically not significant.

Table 7 shows that, when the requirement of blood and blood products to maintain haematocrit and coagulation profile was compared between the groups and there was increased requirement of packed RBC(PrC), FFP and platelets in Group B (Magnesium Group) but was not statistically significant.

Table 6 Volume of mediastinal drainage in 24 hours postoperative period

| Volume of mediastinal drainage | Group A (n=40) | Group B (n=40) | P Value |
|-------------------------------|---------------|---------------|---------|
| Total (ml)                    | 529 ± 388     | 560 ± 465     | >0.05   |
| >1000 ml (%)                  | 5 (12.5%)     | 8 (20%)       | >0.05   |
| >1500 ml (%)                  | 1 (2.5%)      | 2 (5%)        | >0.05   |

Table 7 Transfusion requirements of allogenic blood products [mean±SD(Range)]

|                     | Group A (n=40) | Group B (n=40) | p value |
|---------------------|---------------|---------------|---------|
| Packed Red cells. (PRC) | 1.3 ± 2.0 (0-16) | 1.4 ± 1.9 (0-10) | >0.05   |
| Fresh Frozen Plasma. (FFP) | 0.4 ± 1.1 (0-8) | 0.5 ± 1.3 (0-10) | >0.05   |
| Platelets           | 0.5 ± 1.1 (0-6) | 0.5 ± 1.2 (0-6) | >0.05   |

Other relevant data revealed no significant differences in requirement of inotropes and vasodilators between the two groups during the study period. Urine output were comparable between the two groups. Patients needed re-exploration were not included in the study. Total five patients expired (three from Group A and two from Group B) and were excluded from this study.

Discussion

Aspirin exerts its antithrombotic and antiplatelet effects by irreversibly acetylating a serine residue, thus inhibiting the cyclooxygenase and hydroperoxidase reactions necessary for the production of thromboxane A₂, a potent vasoconstrictor and platelet aggregator. While perioperative aspirin use can reduce the incidence of coronary artery thrombosis, and improve graft patency after CABG, a previous study indicated that aspirin increased postoperative bleeding and transfusion requirements after cardiac surgery. But another study had not confirmed this effect on haemostasis, instead it has been revealed that outcome is actually improved in patients who continue aspirin in the perioperative period when compared to those patients who discontinue aspirin.

After CPB, hypomagnesaemia is common. Patients undergoing cardiac surgery are at risk of magnesium deficiency due to haemodilution in the extracorporeal circuit, diuretic therapy and heart failure. Haemodilution at the start of CPB causes a 17% decrease in plasma magnesium which persists until the first postoperative day. Also, assessment of magnesium status is a complex area. Only 0.3% total body magnesium is found in serum and samples are affected by magnesium of red blood cells. Measurements of ionized magnesium are prone to interference from other cations like Ca++. Thus, although monitoring of serum Mg²⁺ has a role in guiding magnesium therapy in acute situations like established cardiac arrhythmias and hypomagnesaemic convulsions; we have measured baseline serum electrolyte levels including serum magnesium but due to logistic difficulties serum magnesium level could not be measured during intraoperative and postoperative period in all patients. This is because hypomagnesaemia is common during the immediate post CPB period. We have used magnesium only in patients who had adequate urine output. All our study patients had adequate urine output and were haemodynamically stable during the study period.

Postoperative hypomagnesaemia is associated with prolonged ventilatory support and an increased incidence of cardiac arrhythmias, which may lead to prolonged PR intervals, wide QRS complexes, depressed ST segments, inverted T waves and prolonged QT intervals. The administration of magnesium after CPB reduces the incidence of supraventricular and ventricular arrhythmias and increases cardiac index and left ventricular stroke work index. Previous study
showed that, the incidence of ventricular arrhythmias in patients not received magnesium for 24hrs post CPB period was nearly three times that found in the magnesium treated group. Present study studied the incidence of arrhythmias from the immediate post CPB period and continued up to 24 hrs postoperative period in ICU. Here the incidence of atrial arrhythmias was similar between Group A (Control Group): 25% and Group B (Magnesium Group): 20%. But the incidence of ventricular arrhythmias was 35% in Group A (Control Group) compared to 10% in Group B (Magnesium Group). DC cardioversion and inj. amiodarone were instituted for the management of significant ventricular arrhythmias. Thus hypomagnesaemia may be a significant contributory factor that predispose towards the development of postoperative arrhythmias and the intra-operative administration of magnesium may reduce the incidence of serious ventricular arrhythmias following coronary revascularization.

Magnesium can lead to significant dose dependent prolongation of bleeding time, inhibition of platelet aggregation, P-selectin expression and fibrinogen binding to the platelet GP IIb/IIIa receptor in patients undergoing cardiac surgery. The results of the present study show that Group B (Magnesium Group) patients had a modest increase in the volume of mediastinal drainage noted in the 24 hours postoperative period and homologous blood requirements were also greater than Group A (Control Group) patients, but the difference was not statistically significant. Preoperative platelet function was evaluated by platelet count, prothrombin time and activated clotting time.

Blood-saving techniques are of great interest to cardiac surgeons due to the risk of allergic reactions and viral infections. Intra-operative antifibrinolytic therapy is an effective means of reducing postoperative bleeding after CPB. Epsilon aminocaproic acid (EACA) an antifibrinolytic drug, prevents fibrinolysis and platelet activation during CPB. It also prevents activation of plasminogen. EACA binds to lysine binding sites on plasminogen and fibrinogen and thereby inhibits plasminogen activator and plasmin release. When administered before CPB it inhibits fibrinolysis, decreases mediastinal bleeding and decreases transfusion requirements. In the present study both Group A (Control Group) and Group B (Magnesium Group) patients have received equivalent dosages of intravenous EACA infusion. So EACA should not have influenced the results of the study as its effect on postoperative bleeding was equal in both the groups of patients.

Thus, intravenous magnesium infusion (2 mg Magnesium Sulphate in 100 ml normal saline) may be administered to patients posted for CABG with CPB who receive perioperative aspirin therapy without any significant increase in postoperative bleeding and blood or blood product requirements. It may be concluded from the study that, magnesium may be used for its beneficial effect of preventing cardiac arrhythmias in the post-CBP period, without significant increase in risk of peri-operative haemorrhage and blood product requirements in on-pump CABG patients who continue pre-operative aspirin.

References
1. Rinder CS, Bohnert J, Rinder HM, Mitchell J, Ault K, Hillman R. Platelet activation and aggregation during cardiopulmonary bypass. Anesthesiology 1991;75:388-93.
2. Lauer Michael S. Clinical practice. Aspirin for primary prevention of coronary events. N Engl J Med 2002;346:1468-1474.
3. Verstraete M, Brown BG, Chesebro JH, Ekeström S, Harker LA, Henderson AH, et al. Evaluation of antiplatelet agents in prevention of aorto coronary bypass occlusion. Eur Heart J 1986;7:4-13.
4. Kallis P, Tooze JA, Talbot S, Cowans D, Bevan DH. Preoperative aspirin decreases platelet aggregation and increases postoperative blood loss - prospective, randomized, placebo controlled, double blind clinical trial in 100 patients with chronic stable angina. Eur J Cardiothorac Surg 1994;8:404-9.
5. Aglio LS, Stanford GG, Maddi R, et al. Hypomagnesaemia is common following cardiac surgery. J Cardiothorac Vasc Anaesth 1991;5:201-8.
6. England MR, Gordon G, Salem M, et al. Magnesium administration and dysrhythmias after cardiac surgery. JAMA 1992;268: 2395–2402.
7. Fanning WJ, Thomas CS Jr, Roach A, et al. Prophylaxis of atrial fibrillation with magnesium sulphate after CABG. Ann Thorac Surg 1991;52: 529–33.
8. André Gries, Christoph Bode, Stefanie Gross, Karlheinz Peter, Hubert Böhrer, and Eike Martin. The effect of intravenously administered magnesium on platelet function in patients after cardiac surgery. Anesth Analg 1999; 88:1213–1224.
9. Rawitscher RE, Jones JW, McCoy TA, Landsley DA. A prospective study of aspirin’s effect on red blood cell loss in cardiac surgery. J Cardiovasc Surg 1991; 32:1–7.
10. Willard JE, Lange RA, Hillis LD. The use of aspirin in ischaemic heart disease. N Engl J Med 1992; 327:175–81.
11. Boldt J, Knothe C, Zickmann B, Herold C, Dapper F and Hempelmann G. The effects of preoperative aspirin therapy on platelet function in cardiac surgery. Eur J Cardiothorac Surg 1992; 6:598–602.
12. Dacey LJ, Munoz JJ, Johnson ER, Leavitt BJ, Maloney CT, Morton JR, et al. Effect of preoperative aspirin use on mortality in CABG patients. Ann Thorac Surg 2000; 70:1986–1990.
13. Whang R,Dei TO, Aikwa J. Predictors of clinical hypomagnesaemia–hypokalaemia, hypophosphataemia, hypocalcaemia. Arch Intern Med 1984; 144:1794-6.
14. Krasner BS. Cardiac effects of magnesium with special reference to anaesthesia : a review. Canadian Anaesthetist’s Society Journal 1979;26:181 – 185.
15. Caspi J, Rudis E, Bar I, Safadi T, Saute M. Effects of magnesium on myocardial function after coronary artery bypass grafting. Ann Thorac Surg 1995; 59:942 – 7.
16. Harris JE, Crowther A, Jupp RA and Aps C. Magnesium and coronary revascularization. British Journal of Anaesthesia 1988; 60:779 – 783.
17. Aupacis, Andreas; Fergusson: Drugs to minimize perioperative blood loss in cardiac surgery: meta-analyses using perioperative blood transfusion as the outcome. Cardiovascular Anesthesia: Society of Cardiovascular Anesthesiologists. Anesthesia & Analgesia: 1997;85: 1258-1267.
18. Vander Salm TJ, Ansell JE, Okike ON. The role of epsilon aminocaproic acid in reducing bleeding after cardiac operation : A double blind, randomized study. J Thorac Cardiovasc Surg 1988;95: 538 – 552.