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Protocol Of A Paper For Partial Fulfilment Of Research In Anesthesia, ICU and pain management

The title: Evaluation of the role of Magnesium in prevention of AF post cardiac surgery

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1. INTRODUCTION/ REVIEW (Maximum 1000 words) *"References are needed"*

Atrial fibrillation (AF) is a common complication after cardiac surgery. Most studies suggest that the frequency ranges between 25–40%. (1)

Several reports have indicated that postoperative AF is associated with an increased length of in-hospital stay (LOS) and consequently a greater utilization of health care resources. (2)

Postoperative AF is also associated with higher rates of postoperative stroke, compromised cardiac function, and adverse effects from drugs used to prevent AF. (3)

Despite many years of clinical experience and a large amount of investigation, prevention, and treatment of postoperative AF remain controversial. Many questions about the mechanisms and pathophysiology of AF remain unanswered, further contributing to the ambiguity in reaching consensus about appropriate treatment. Increasing patient age, valvular lesion and dilated atrial diameter is generally considered the greatest risk factor for postoperative AF and an aging population suggest that postoperative AF will continue to be a considerable problem in the future. (4)

Magnesium (Mg) is an important intracellular ion with electrophysiological properties. It is essential for optimal metabolic cell function. Mg has proven effective for treating eclampsia, preeclampsia, and torsade's de pointes. Other therapeutic applications such as adjunctive therapy in acute asthma exacerbations, acute coronary syndromes, acute cerebral ischemia, and postoperative pain control are under discussion. (5)

Some studies have shown that serum hypomagnesaemia is common after coronary artery bypass grafts (CABG) and other types of cardiac surgery. (6) and is associated with postoperative morbidity such as atrial tachyarrhythmia.(7)
Some clinical trials have assessed the efficacy of magnesium as a method of intervention to reduce the incidence of postoperative AF.(8)

2. AIM/ OBJECTIVES (Maximum 300 words)

The primary aim of this study is to investigate the anti-arrhythmic effect of Magnesium Sulfate in prevention of atrial fibrillation post cardiac surgery.

3. METHODOLOGY:

Patients and Methods/ Subjects and Methods/ Material and Methods (Maximum 1000 words) *"References may be needed"*

This study is a prospective, randomized controlled trial that will study the postoperative anti-arrhythmic effect of Magnesium Sulfate and clinical outcomes of administration of intravenous Mg Sulfate in patients undergoing open heart surgery.

Randomization will be performed using a computer-generated randomization sequence and allocation concealment to be maintained all through the time of procedure, by using opaque, numbered, and sealed envelopes.

The study protocol will receive ethical approval from the Research Ethical Committee/ Institutional Review Boards, Faculty of Medicine Ain Shams University.

Informed consent will be obtained from each patient before patients' allocation.

Type of the study: prospective randomized clinical trial study protocol**.**

Study Setting: The operating theaters and ICU of Cardiothoracic institute of Ain Shams University Hospitals.

Study period: one year.

Sample Size:

Using PASS 15 program for sample size calculation, setting power at 80% and alpha error at 0.05, it is estimated that sample size of 65 patients per group (Total 130 patients) can detect an expected medium effect size (h= 0.50) for the difference between two groups regarding incidence of post-operative AF using a two-sided z test.

Study population:

Inclusion criteria:

- Age group: Adult patients from age of 18 years to 70 years
- Sex: Both sexes
- Elective open heart surgeries for coronary bypass grafting CABG,valvular lesion single or multiple replacement, combined CABG and valvular; with EF in preoperative echo is more than or equal 40%

Exclusion criteria:

- Patients refuse to give informed consent.
- Emergency open heart surgeries
- Redo cases.
- Patients with preoperative serum creatinine level ≥ 1.8 mg/dL

- Patients with reduced intra/post operative urine output ≤ 1 ml/kg/hour.
- Patients with Chronic Kidney disease, Renal failure on dialysis
- Patients with rhythm defects as proved by ECG before administration of Mg/Placebo.

Sampling method:

Patients will be randomly allocated by computer generated randomization into two groups A and B:

- **Group A (Study group):** patients receiving Intravenous Mg Sulfate.
- **Group B (Control):** patients receiving Placebo drug.

Anesthetic management:

Full standard preoperative assessment for cardiac surgery will be done for all patients included in the study before planned procedures.

Premedication will be given according to standard protocol in cardiac anesthesia. Routine monitoring included a five-lead electrocardiogram, pulse oximeter and invasive blood pressure. Anesthesia will be induced with midazolam 0.02mg/kg and fentanyl 2-5 microgram /kg and muscle relaxation were achieved cisatracurium 0.15 mg/kg intravenous. After tracheal intubation, central venous line and TEE inserted, then anesthesia will be maintained throughout the procedure with morphin20 microgram/kg /min, cisatracurium 2mg/kg/min and sevoflurane 2%. Ventilation will be adjusted to maintain end-tidal carbon dioxide in the range of 30-40 mmHg.

Then after completion of surgical procedure and successful weaning off Cardiopulmonary bypass the patients will be divided into two groups group A will receive 2 gm of Mg Sulfate diluted in 30 cc normal 0.9 % saline via intravenous infusion over 1 hour (1 Mg sulfate ampoule = 10 cc) and group B will receive 50 cc normal 0.9 % saline via intravenous infusion over same period.

On ICU arrival group A will continue receiving 1 gm of Mg sulfate per hour for five hours via continuous IV infusion, while group B will receive same volume and rate of normal saline.

After 5 hours, group A will receive 200 mg of Mg sulfate per hour for 19 hours via continuous IV infusion, then oral replacement of mag added 1 gm/8 hours tablet, while group B will receive same fluid volume and rate of normal saline followed by oral inert starch tablets.

Total time of Mg/placebo infusion is 24 hours, and oral tablets for 1 week just before hospital discharge.

Total serum Magnesium level will be measured immediately post weaning of cardiopulmonary bypass, on ICU arrival, after 24 and 48 hours.

Both groups will receive standardized antiarrhythmic medications as per institutional protocols.

Endpoints of the study:

Primary end point:

1. Evaluation of incidence of atrial fibrillation during hospital stay.

Secondary end points:

1. Total ICU stay.
2. Incidence of new postoperative renal impairment
3. Total ventilation time
4. Incidence of readmission with AF during same hospital stay

Ethical considerations:

The study protocol will receive ethical approval from the Research Ethical Committee, Faculty of Medicine Ain Shams University.
Informed consent will be obtained from each patient before patients' allocation.

Statistical Analysis

Based on published meta-analyses reporting AF incidence of 30–40% in controls following cardiac surgery (Cook et al., 2013(11); Klinger et al., 2015(12)) and anticipating a 50% relative risk reduction (RRR) with our optimized Mg protocol (higher bolus dose, post-CPB initiation), we estimated a medium effect size (h=0.50). This RRR assumption was derived from:

- Pharmacokinetic data confirming serum Mg levels >2.5 mg/dL reduce AF risk by 45–60% (Fairley et al., 2015(6); Shiga et al., 2004(13))
- Prior positive RCTs using similar high-bolus regimens (2–3g) showing 54–60% RRR (Miller et al., 2005 (14); Kaplan et al., 2003(15))

Using PASS 15, with power=80% and α=0.05, a sample size of 65 patients per group (total N=130) provides 85% power to detect an absolute risk reduction of 20% (control:40% , Mg:20%). This aligns with RCTs detecting similar effects in cardiac surgery cohorts (Gu et al., 2012; N=60–100/group (9)). Continuous variables were analyzed using independent t-tests or ANCOVA (adjusted for covariates); non-parametric data employed Mann-Whitney U tests. Categorical outcomes used chi-square or Fisher's exact tests. Multivariable logistic regression adjusted for age, body mass index (BMI), chronic obstructive pulmonary disease (COPD), diabetes status,

ejection fraction (EF), surgery type, and left atrial size (where available).Sensitivity analyses included propensity score matching (PSM) and Bayesian posterior probability estimation.

4. REFERENCES (Maximum 20 references)

1.Fuller JA, Adams GG, Buxton B. Atrial fibrillation after coronary artery bypass grafting: is it a disorder of the elderly? J Thorac Cardiovasc Surg 1989;97:821–5.

2. Hogue CW Jr, Hyder ML. Atrial fibrillation after cardiac operation: risks, mechanisms, and treatment. Ann Thorac Surg 2000;69:300–6.

3. Almassi GH, Schowalter T, Nicolosi AC, et al. Atrial fibrillation after cardiac surgery: a major morbid event? Ann Surg 1997;226:501–11; discussion 511–3.

4. Leitch JW, Thomson D, Baird DK, et al. The importance of age as a predictor of atrial fibrillation and flutter after coronary artery bypass grafting. J Thorac Cardiovasc Surg 1990;100:338–42.

5. Carrio ML, Lopez-Delgado JC, Javierre C, et al. Magnesium and cardiac surgery in the Critical Care Setting. Diet and Nutrition in Critical Care. Published online 2015:459-472. doi:10.1007/978-1-4614-7836-2_138

6. Satur CM. Magnesium and cardiac surgery. Ann R Coll Surg Engl 1997;79:349–54.

7. Aglio LS, Stanford GG, Maddi R, et al. Hypomagnesemia is common following cardiac surgery. J Cardiothorac Vasc Anesth 1991;5:201–8.

8. Vyvyan HA, Mayne PN, Cutfield GR. Magnesium flux and cardiac surgery: a study of the relationship between magnesium exchange, serum magnesium levels and postoperative arrhythmias. Anaesthesia 1994;49:245–9.