HYPOMAGNESAEMIA AND ROLE OF MAGNESIUM SUPPLEMENTATION DURING CARDIOPULMONARY BYPASS IN PEDIATRICS CARDIAC SURGERY

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ABSTRACT

BACKGROUND

Postoperative Junctional Ectopic Tachycardia (JET) remains one of the most common arrhythmias (8%-20%) after paediatric cardiac surgery. JET is associated with hemodynamic instability, longer mechanical ventilation time and longer stays in the Cardiac Intensive Care Unit (ICU).

AIM

The aim of this study is to evaluate the effect of prophylactic administration of magnesium on the occurrence of postoperative arrhythmias in patients undergoing intracardiac repair for Tetralogy of Fallot and to determine the incidence of hypomagnesaemia in paediatric patients undergoing cardiac surgery who require CPB.

METHODS

Forty five patients with Tetralogy of Fallot undergoing intracardiac repair were enrolled to receive saline, 25mg/kg and 50mg/kg of Magnesium as three groups intraoperatively. Postoperative ECG monitored for JET and magnesium levels measured.

RESULTS

Hypomagnesaemia was present in 28% of patients. None of the patients who were administered magnesium developed hypomagnesaemia. The incidence of JET was found to be increased (53.3%) in the placebo group as compared to 13.3% and 6.7% in the groups receiving 25 and 50mg/kg of magnesium ($p<0.001$). Eleven patients having JET 7 (64%) had hypomagnesaemia and rest of the 4(36%) occurred in patients with normal magnesium levels ($p<0.01$). The mean mechanical ventilation time and the mean length of ICU stay were both prolonged those with hypomagnesaemia. The mean mechanical ventilation time and length of ICU stay were both prolonged in the patients with JET ($p<.001$)

CONCLUSIONS

Hypomagnesemia is one of the factors responsible for JET and in turn with prolonged ICU stay and prolonged mechanical ventilation.

KEYWORDS

Cardiopulmonary bypass, Junctional ectopic tachycardia, Magnesium sulfate.

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INTRODUCTION: Postoperative arrhythmias are an important cause of morbidity and mortality after cardiac surgery for congenital heart disease. In the early postoperative period, patients with congenital heart disease are especially vulnerable to rhythm disturbances. In paediatric cardiac surgery, there is little information regarding the incidence, risk factors, management and prophylaxis for early postoperative arrhythmias. A recent

report by Roos-Hesselink and Karamermer.[1] noted an incidence between 15% and 17.7%. Postoperative Junctional Ectopic Tachycardia (JET) remains one of the most common arrhythmias (8%-20%) after paediatric cardiac surgery. JET is associated with hemodynamic instability, longer mechanical ventilation time and longer stays in the Cardiac Intensive Care Unit (ICU).[2] Although the aetiology of JET is multifactorial, some studies have associated the presence of JET with hypomagnesaemia during Cardiopulmonary Bypass (CPB).[3]

Hypomagnesaemia is defined as serum magnesium levels of less than 1.58mg/dL. Hypomagnesaemia may be due to preoperative factors like medications that increase the renal loses of magnesium, such as diuretics and digitalis. Hemodilution, blood loss and blood transfusions also contribute to the decrease in plasma magnesium levels. In addition, during surgery continuous hemofiltration, modified ultrafiltration and administration of large doses of calcium and diuretics can all cause depletion of magnesium.[4]

Magnesium is an essential cofactor for the maintenance of myocardial transmembrane potential, magnesium deficiency decreases the threshold for arrhythmias.[5,6] In adults undergoing cardiac surgery, hypomagnesaemia has been associated with the presence of arrhythmias, especially postoperative atrial fibrillation.[7,8,9,10] Furthermore, in adults the administration of magnesium sulfate (MgSO4) during cardiac surgery reduces the occurrence of postoperative atrial fibrillation.[11] In paediatric patients undergoing cardiac surgery with CPB, hypomagnesaemia is common (34%) and is associated with longer ICU stay, higher Paediatric Risk of Mortality (PRISM) score and longer mechanical ventilation time.[12] Although magnesium supplementation during CPB reduces the incidence of arrhythmias in adults, the benefits of magnesium administration in paediatric cardiac patients have neither been demonstrated nor have dosage guidelines been established.

The aim of this study is to evaluate the effect of prophylactic administration of magnesium on the occurrence of postoperative arrhythmias in patients undergoing intracardiac repair for Tetralogy of Fallot and to determine the incidence of hypomagnesaemia in paediatric patients undergoing cardiac surgery who require CPB.

MATERIAL AND METHODS: This prospective study was conducted at our Institute. After taking approval from Institutional ethics committee, all patients with tetralogy of Fallot undergoing intra-cardiac repair in the Department of Cardiothoracic and Vascular Surgery between September 2013 and December 2014 were enrolled in this study.

Patient Population: A total of 45 patients were included in this study.

Exclusion Criteria: The patients receiving any antiarrhythmic medication either prior to surgery or intraoperative were excluded from the study.

Study Design: The patients were randomly assigned to one of the following groups: Group 1 (Mg0), receiving normal saline (placebo), group 2 (Mg25), receiving 25mg/kg of MgSO4, and group 3 (Mg50), and receiving 50mg/kg of MgSO4. Maximum total dose of MgSO4 did not exceed 2g. All subjects received a single bolus of either placebo or drug into the CPB circuit at the initiation of the rewarming period. MgSO4 (500mg/mL; 4mEq/mL). The composition of the bypass circuit and perfusion protocols were according to established institutional practices. Patients receiving antiarrhythmics preoperatively or intraoperatively were excluded from the study. At the end of the surgical procedure, all the patients were transferred to the ICU. The potassium levels in all the patients were kept above 4mEq/L by repeated ABG and potassium administration. Postoperative arrhythmias were managed by the ICU intensivist. Occurrence of postoperative arrhythmia requiring intervention was the end point of the study.

The Mg level was measured at 4 time points: (1) baseline (time 1), before CPB, (2) after CPB (time 2): (3) 24 hrs. after CPB (time 3). All the measurements were performed by the same operator and using the Autoanalyser Roche Modular P 800. The reagent kit used for Autoanalyser Roche Modular P 800 is Audit, Hitachi make. The procedure involves formation of diazonium salt with magnesium and Xylidyl blue. The amount of complex formed is directly proportional to amount of magnesium in the sample and it is read spectrophotometrically in the range of 505-600nm.

The presence of hypomagnesaemia was based on Mg reference levels.[13] Normal values being 1.58mg/dL to 2.55mg/dL. A 12-lead electrocardiogram was performed on arrival in the ICU and a 2-channel, 5-lead continuous electrocardiography was done for documentation of arrhythmias during ICU stay after surgery.

RESULTS: Each group had 15 patients. The age of patients of TOF ranged from 1 to 18 years. The mean weight of enrolled patients was 18.29kgm with no statistical difference between the groups. There was no statistically significant difference between the groups in relation to age, weight, BSA, sex and preoperative sinus rhythm. (Table 1).

The baseline laboratory parameters measured were haemogram, RFT and LFT of the patients. There was no statistical difference found between the groups. There was no patient with renal azotaemia or hepatic dysfunction included in the study. Haemoglobin level and platelet counts were also comparable between the groups with no statistically significant difference.

Baseline demographic and medical history characteristics by study group					
Characteristics		Study Group			
		Group 1: Placebo	Group 2: Mg 25mg/kg	Group 3: Mg 50mg/kg	P value
Age (Year) Mean		6.33	6.93	7.07	>.05
Weight (kg) Mean		16.8	18.4	19.67	>.05
BSA (m2/kg) Mean		0.7	0.75	0.76	>.05
Gender (n)	Male	5	4	4	>.05
	Female	10	11	11	
Sinus rhythm		15	15	15	
Mean Cross Clamp time (min)		109.2	112.73	109.93	>.05
Mean Cardiopulmonary Bypass time (min)		164.93	168	167.27	>.05

Table 1: Demographic details

Surgical Parameters: Cardiopulmonary Bypass time and Cross clamp time.

The overall mean bypass time for the ICR was 166.73 min and the mean Cross Clamp time being 110 min. There has been no statistical difference between mean cardiopulmonary Bypass time and the mean Cross Clamp Time within the different groups. P value=0.992(student's t test).

Hypomagnesaemia (Baseline Mg Levels)

Hypomagnesaemia was present in (13/45) 28.9% of the total patients included in the study. There was no statistical difference among different groups in the baseline magnesium levels (p=0.469) (chi square test) (Figure 1).

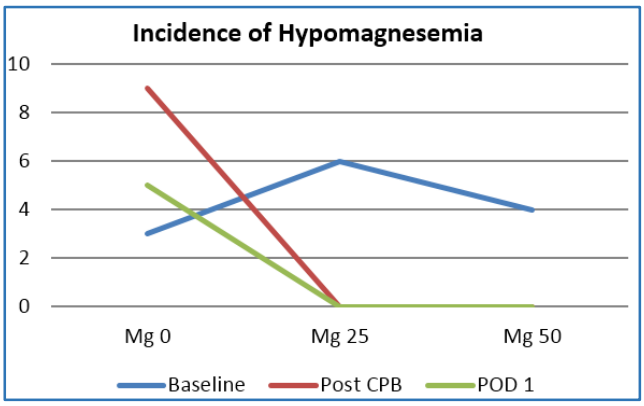

Fig. 1: Incidence of hypomagnesaemia

Post Bypass Magnesium Levels: Magnesium levels measured after Cardiopulmonary Bypass revealed no Hypomagnesaemia in groups receiving magnesium, while it was present in 66% of patients in the group where patients received no magnesium (p <0.01) (chi square test).

Post-operative day 1 magnesium levels: Magnesium levels were measured on Postoperative Day 1 of surgery with Hypomagnesaemia persisting in 5 out of 9 patients on Day 1 of surgery. Magnesium levels were normalised in patients who developed arrhythmias by administering magnesium and these patients were treated with appropriate antiarrhythmic. None of the patients who were administered magnesium developed hypomagnesaemia (Table 2).

	Baseline		Post CPB			POD1		
Mg Group	<1.58 mg/dL (n)	1.58-2.55 mg/dL (n)	<1.58 mg/dL (n)	1.58-2.55 mg/dL (n)	>2.55 mg/dL (n)	<1.58 mg/dL (n)	1.58-2.55 mg/dL (n)	> 2.55 mg/dL
Mg 0	3	12	9	6	0	5	9	1
Mg 25	6	9	0	15	0	0	15	0
Mg 50	4	11	0	11	4	0	14	1

Table 2: Table Magnesium levels in the Mg Groups

Incidence of Arrhythmias: The overall incidence of post-operative arrhythmias in TOF in our study was consistent with previous studies with incidences being JET (24.44%), Complete AV Block (4.44%), Type II AV Block (2.22%), Type I AV Block (2.22%) and Ectopic beats (15.55%). (Figure 2).

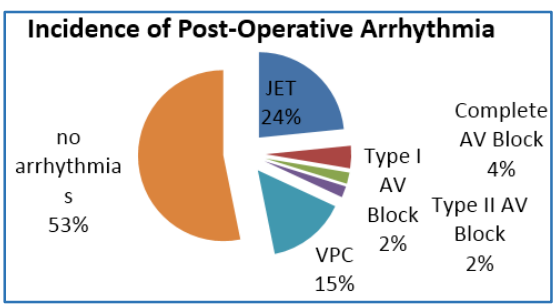

Fig. 2: Incidence of Post-operative Arrhythmia

Magnesium administration and Post-operative arrhythmias: The incidence of post-operative arrhythmias was compared in different groups receiving placebo, magnesium at 25mg/kg and 50mg/kg. The incidence of JET was found to be 53.3% in the placebo group as compared to 13.3% and 6.7% in the groups receiving 25 and 50mg/kg of magnesium. This association was found to be statistically significant with p value less than 0.001. These arrhythmias were considered end point of the study and patients were administered magnesium if patient had hypomagnesaemia. The patients who had ventricular premature complexes or ventricular ectopics with hemodynamic stability did not receive magnesium supplementation. (Figure 3).

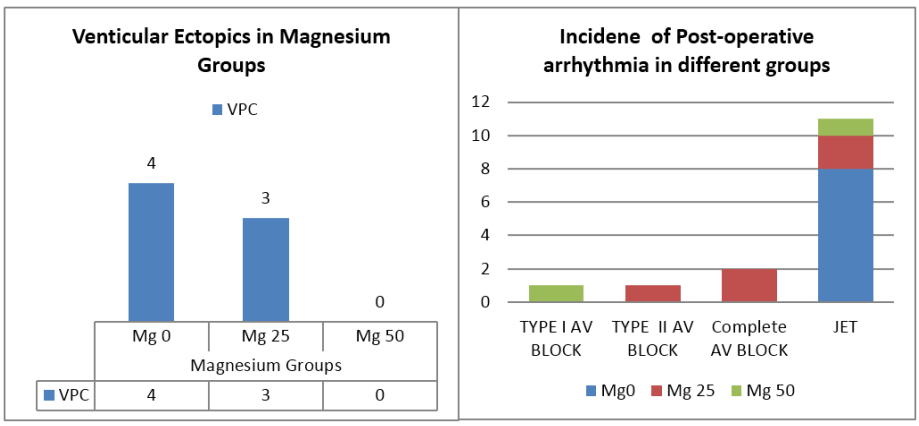

Fig. 3: Ventricular Ectopic in Magnesium Groups and Incidence of Post-operative arrhythmia in different groups

There were 7 out 45 patients who had ventricular ectopics (without any hemodynamic instability), 4 of 7 in the placebo group and rest 3 of 7 occurring in patients receiving 25mg/kg of magnesium on CPB. The association of ventricular ectopic with hypomagnesaemia was not found to be statistically significant (p value more than 0.05 by Chi square test). (Table 3).

	Type I AV Block	Type II AV Block	Type III AV Block	JET	Nil	Total
Mg0	0	0	0	8	7	15
Mg25	0	1	2	2	10	15
Mg50	1	0	0	1	13	15
Total	1	1	2	11	30	45

Table 3: Association between Magnesium Groups and Post-Operative Arrhythmias

Analysis of hypomagnesaemia and post-operative arrhythmias: JET and AV Block.

The association of post-operative arrhythmias was analysed with patients having post bypass hypomagnesaemia of the 11 patients having JET 7 (64%) had hypomagnesaemia and rest of the 4 (36%) occurred in patients with normal magnesium levels.

The association between the two was found to be statistically significant with p value less than 0.01 (Chi square test). (Figure 4).

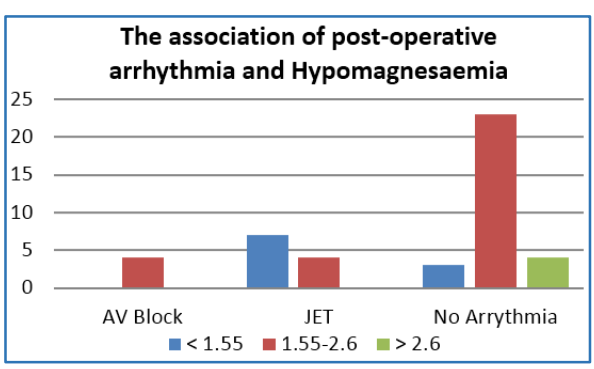

Fig. 4: The association of post-operative arrhythmia and hypomagnesaemia

Ventricular Ectopic: There were 7 patients having frequent monomorphic ventricular premature complexes, out of which 3 were associated with Hypomagnesaemia. There was no statistical significant association between hypomagnesaemia and ventricular ectopics. (P value more than 0.05) (Chi square test).

Mechanical Ventilation Time and ICU stay in different groups: The mean Mechanical Ventilation Time and the mean length of ICU stay were prolonged in the patients not receiving magnesium (placebo group) and least in the group receiving 50mg/kg of magnesium, but this was not found to be statistically significant. P value more than 0.05 (student 't' test).

ICU stay and Mechanical ventilation time in Association with Hypomagnesaemia: The mean Mechanical Ventilation Time and the mean length of ICU stay were prolonged in the patients with hypomagnesaemia as compared to patients with normal magnesium levels, but this was not found to be statistically significant. P value more than 0.05 (Chi square test).

ICU stay and Mechanical ventilation time and Post-Operative arrhythmia: The mean Mechanical Ventilation Time and the mean length of ICU stay were both prolonged in the patients with JET as compared to other patients, but this was not found to be statistically significant (Chi square test). (Figure 5).

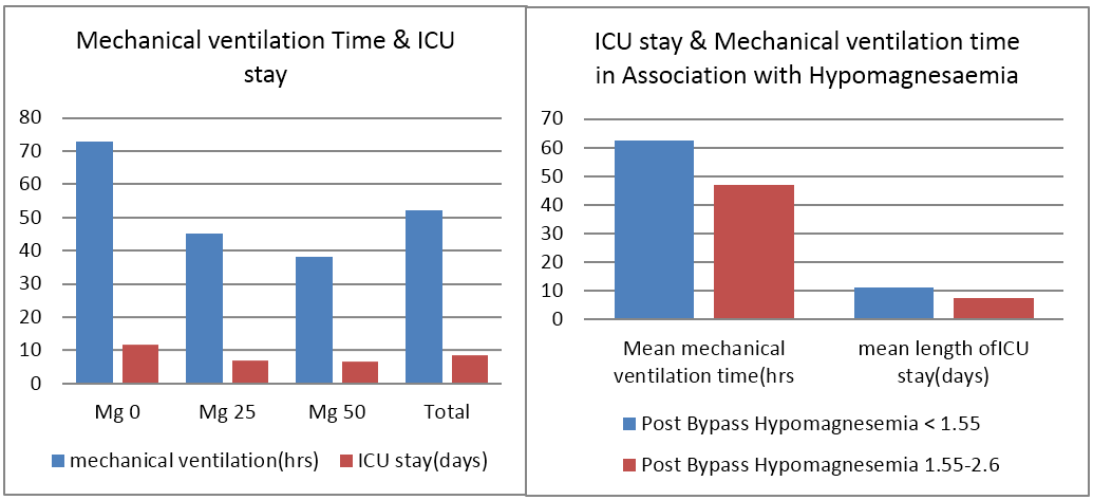

Fig. 5: Mechanical ventilation Time and ICU stay and ICU stay and Mechanical ventilation time in Association with Hypomagnesaemia

Mortality in Association with Hypomagnesaemia and Arrhythmias and Mg Groups: Mortality was higher in patients with hypomagnesaemia, patients not receiving magnesium and patients having JET. Out of 11 patients 7 patients having JET, 4 patients had mortality as compared to only 1 in other patients and this association was found to be statistically significant. (P value less than 0.05, by Chi square test) (Figure 6).

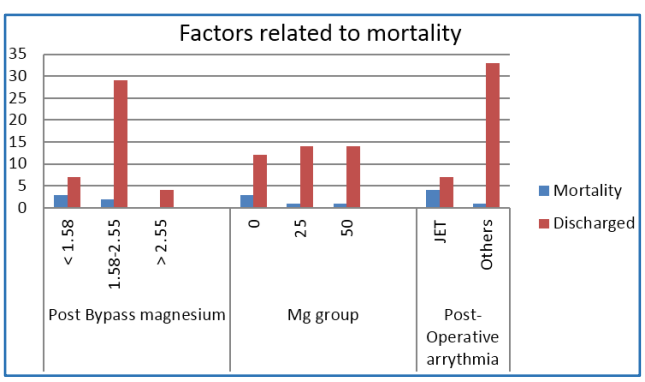

Fig. 6: Factors related to mortality

DISCUSSION: In this study, we found that in children undergoing ICR for TOF, the administration of a single dose of MgSO4 during CPB reduces the incidence of hypomagnesaemia and also decreases the incidence of JET in the immediate postoperative period. In addition, this effect of magnesium seems to be dose related. Incidence of tachyarrhythmias in the patients who received 50mg/kg of MgSO4 was 6.7%, whereas the incidence was 13.3% in patients who received 25mg/kg of MgSO4 and 53% in patients who received placebo.

Hypomagnesemia: The data analysed in the study suggests that supplementation of magnesium during Cardiopulmonary Bypass reverses hypomagnesaemia and reduces the frequency of arrhythmias in the immediate postoperative period. This finding supports the notion that hypomagnesaemia should be aggressively treated to potentially prevent JET in the immediate postoperative period. Although the specific mechanism by which the appropriate magnesium level during CPB prevents JET is not known; it is speculated that magnesium stabilizes the myocyte ionic channels leading to myocardial protection and electrical equilibrium. The critical magnesium level that protects the myocardium during CPB is unknown, but it may vary among different pathologic conditions, surgical strategies and degrees of injury.

As in study by Manrique et al., our data in the immediate post bypass period showed that the frequency of hypomagnesaemia was higher in placebo than magnesium groups. This difference may be explained by multiple factors that occur after CPB, which influence whole blood magnesium levels, such as ultrafiltration intravenous fluids, blood transfusions and drugs.[4,14,15]

Moreover, during the operation patients are exposed to hemodilution, blood loss, blood transfusions and an increase of catecholamines that cause chelation of magnesium. All of these are factors that contribute to the decrease in plasma magnesium levels. In addition during surgery, continuous hemofiltration, modified ultrafiltration and administration of large doses of calcium and diuretics can all cause depletion of magnesium. Other factors causing hypomagnesaemia include the intracellular elimination shifts induced by the extracorporeal circulation and the decrease in body temperature during surgery.[4,5,15] As expected in both groups of patients receiving magnesium the levels of Mg increased after the administration of the MgSO4. This increase was higher in the group receiving 50mg/kg of MgSO4.

The incidence of hypomagnesaemia was 60% in the placebo group in our patients. This was comparatively higher than the previous studies as done by Dittrich and associates.[16] and by Dorman and associates.[3] The lower incidence of hypomagnesaemia in these studies was attributed to higher concentration of magnesium in cardioplegia solution used as compared to our study and also to supplementation of magnesium after CPB. In the placebo group, there was also a slight elevation in the levels of Mg post bypass. This effect may be related to the hemoconcentration during the rewarming period of CPB.

There was a decrease noted in the Mg level in all the groups after CPB and further on postoperative Day 1 and Day 2. This reduction may be explained by several factors, such as the administration of diuretics, transfusion of blood products, increase in exogenous catecholamines and the modified ultrafiltration performed at the end of CPB. Although post bypass Mg levels are similar between both magnesium groups, these levels are significantly higher than those of the placebo group, indicating a beneficial effect of the administration of MgSO4 during CPB.

Post-operative Arrhythmias: The overall incidence of post-operative arrhythmias in TOF in our study was consistent with previous studies with incidences being JET (24.44%), Complete AV Block (4.44%), Type II AV Block (2.22%), Type I AV Block (2.22%) and Ectopic beats (15.55%). The incidences of post-operative arrhythmias reported in previous study by Jean et al.[17] was 35% and the arrhythmias observed were accelerated junctional rhythm and JET (17%), sinus node dysfunction with bradycardia (4%), complete atrioventricular block (4%) supraventricular tachycardia (2%) and frequent ectopic beats (8%). The increase in incidence of JET was speculated to be due to exclusion of patients receiving any antiarrhythmic intra- or pre-operatively and the difference in sample size.

Antiarrhythmic Effect of Magnesium and JET: The presence of early postoperative arrhythmias is a predictor for late complications such as ventricular dysfunction, late arrhythmias and late mortality.[2,14,16] Thus, the prevention of these arrhythmias will improve the postoperative course and outcomes. In adults after cardiac surgery, one of the most common supraventricular arrhythmias is atrial fibrillation. Several studies have demonstrated the role of hypomagnesaemia in the development of postoperative atrial fibrillation and the prophylactic effect of the supplementation with MgSO4 during or after surgery.[18] In the early postoperative period after paediatric cardiac surgery, one of the most common arrhythmias is JET. The occurrence of postoperative JET has been associated with longer ICU stay and longer mechanical ventilation time. Etiologic factors related to the development of JET are not completely clear.[2,14]

In the present study association of JET was analysed with patients having post Bypass Hypomagnesaemia. Of the 11 patients having JET, 7 (64%) had hypomagnesaemia and rest of the 4 (36%) occurred in patients with normal magnesium levels. The association between the two was found to be statistically significant with p value less than 0.01. Hypomagnesaemia has also been associated with the presence of JET in previous studies. Supplementation with MgSO4 during CPB reduces incidence of all arrhythmias in adults and children.

Dittrich et al.[16] in their randomized clinical trial in 131 patients, demonstrated the association between the supplementation with magnesium and a decrease in the incidence of postoperative arrhythmias in children and adults after surgery for congenital heart disease. They used an infusion of magnesium chloride after CPB that can cause less toxicity than MgSO4. They analysed serum Mg levels and the presence of arrhythmias at the ICU. There are some important limitations of their study, such as the assignment to study groups was not blinded in the moment of assessment of the occurrence of arrhythmias. They also used a cardioplegic solution with a high content of magnesium, which may explain the lower incidence of hypomagnesaemia at ICU admission compared with our findings. Dorman and Associates.[3] also developed a double-blind clinical trial in 28 paediatric patients after surgery for congenital heart disease. On this occasion, the group receiving 30mg/kg of MgSO4 administered in a single bolus at the end of CPB was compared with a placebo group. In this study, physicians were unblinded if patients required antiarrhythmic therapy. The study was designed for 100 patients and was stopped prematurely after finding 4 cases of JET, which were all in the placebo group. These 2 well-designed studies consistently demonstrated a decrease in the incidence of postoperative arrhythmias with the administration of magnesium. The supplementation of magnesium was performed in both cases after CPB. Hypomagnesaemia is a persistent finding all through CPB and the correction of it at that point can be critical to reach an adequate myocardial protection and consequently achieve a reduction of postoperative arrhythmias. The administration of a single dose of MgSO4 during CPB is a safer practice and can have a protective effect at the moment of heart reperfusion. Moreover, animal studies have shown that MgSO4 attenuates the degree of myocardial necrosis and plays a cardioprotective role in ischemia–reperfusion injury. The beneficial effect of the administration of MgSO4 during the reperfusion period of CPB could result from the maintenance of the stabilization of the membrane and the reduction of the vulnerability to automatic and re-entry mechanism. This supplementation of magnesium during CPB rather than after CPB might explain the lower incidence of JET in patients receiving magnesium in our study as compared to the previous studies.

Mechanical ventilation time and duration of ICU stay and mortality: In the present study we found mechanical ventilation time and length of ICU stay to be prolonged in the placebo group, patients with post CPB hypomagnesaemia and in patients with JET, but none of these associations were found to be statistically significant. In a previous study, paediatric patients with hypomagnesaemia during CPB had a longer period of mechanical ventilation, longer ICU stay.[12] We did not have the same finding in our study; however, this can be a consequence of the sample size. Moreover patients who had early mortality and associated JET spuriously shortened the mean mechanical ventilation time and length of ICU stay, which led to statistical insignificance.

There were five mortalities out of the 45 patients included in the study four of this occurring in patient who

developed JET in the immediate postoperative period. The association of mortality with JET was found to be statistically significant. This was consistent with previous studies, which have shown that the presence of early postoperative arrhythmias is a predictor for late complications such as ventricular dysfunction, late arrhythmias and late mortality.[2,18] Mortality was higher in patients with hypomagnesaemia, patients not receiving magnesium and patients having JET. There was no statistically significant association between magnesium administration and hypomagnesaemia with mortality of the patients.

LIMITATIONS OF THE STUDY: Even though baseline characteristics and surgical complexity were equal in our study groups, this population studied had small sample size and does not represent all the paediatric cardiac surgical patients with TOF who may be at risk for postoperative arrhythmias. For instance, patients requiring emergency surgery and patients who received antiarrhythmic preoperatively were not included in the study. In addition, our study was not designed to evaluate the incidence of Postoperative arrhythmias. Hence, the incidence of postoperative arrhythmias over a prolonged postoperative period was not evaluated. Another limitation of the study is the lack of available tools to measure intracellular activity of the magnesium and ionised magnesium levels. Intracellular magnesium may be a better indicator of hypomagnesaemia and arrhythmias. A study with a large number of patients will be needed to validate the results.

CONCLUSION: Hypomagnesemia is one of the factors responsible for JET and in turn with prolonged ICU stay and prolonged mechanical ventilation time. Our study suggests that supplementation of MgSO4 during CPB reduces the incidence of hypomagnesaemia and reduces the overall incidence of JET.

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