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ORIGINAL ARTICLE

Safety and Efficacy of Prophylactic Amiodarone in Preventing Early Junctional Ectopic Tachycardia (JET) in Children After Cardiac Surgery and Determination of Its Risk Factor

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Abstract Postoperative arrhythmia is a common complication after open heart surgery in children. JET is the most common and dangerous arrhythmia. We aimed to assess safety and efficacy of prophylactic amiodarone in preventing JET in children underwent cardiac surgery and to assess risk factors for JET among our patients. In total, 117 children who underwent cardiac surgery for CHD at Tanta University Hospital from October 2011 to April 2015 were divided in two groups; amiodarone group (65 patients) was given prophylactic amiodarone intraoperatively and placebo group (52 patients). Amiodarone is started as loading dose of 5 mg/kg IV in the operating room after induction of anesthesia and continued for 3 days as continuous infusion 10–15 μg/kg/min. Primary outcome and secondary outcomes of amiodarone administration were reported. We studied pre-, intra- and postoperative factors to determine risk factors for occurrence of JET among these children. Prophylactic amiodarone was found to significantly decrease incidence of postoperative JET from 28.9 % in placebo group to 9.2 % in amiodarone group, and symptomatic JET from 11.5 % in placebo group to 3.1 % in amiodarone group, and shorten postoperative intensive care unit and hospital stay without significant side effects. Risk factors for occurrence of JET were younger age, lower body weight, longer cardiopulmonary bypass, aortic cross-clamp time, hypokalemia, hypomagnesemia, acidosis and high dose of inotropes. JET was more associated with surgical repair of right ventricular outlet obstruction as in case of tetralogy of Fallot and pulmonary stenosis. Most of JET 15/21 (71.4 %) occurred in the first day postoperatively, and 6/21 occurred in the second day (28.6 %). Prophylactic amiodarone is safe and effective in preventing early JET in children after open heart surgery.

Keywords Amiodarone · Postoperative arrhythmia · Children · Risk factors · JET

Introduction

Postoperative arrhythmias are common complication of cardiac surgery in pediatrics [7]. JET is the most common hemodynamically significant arrhythmias after cardiac surgery in children with an incidence of 2–22 %. The peak incidence of early postoperative JET is usually in the first 48 h postoperatively [27].

JET is associated with an increased risk of postoperative hemodynamic deterioration, increased length of intensive care unit (ICU) and hospital stays, healthcare costs and mortality, so preventive measures to decrease the incidence of this arrhythmia are recommended [23].

Risk factors for development of early postoperative JET in children and neonates differ greatly in many studies; some demonstrated that young age, low body weight, long cardiopulmonary bypass (CPB) time, aortic cross-clamp (ACC) time, high postoperative inotropes, electrolyte imbalance, circulatory arrest and type of surgery were powerful risk factors for the occurrence of JET [3, 5, 12, 19].

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Although the mechanism of this arrhythmia is not fully understood, it can be related to direct trauma or infiltrative hemorrhage to the bundle of His by resection or excision of muscle bundles in right ventricular outflow tract obstruction as in case of repair of TOF or PS or edema from sutures and traction close to the conduction system as in VSD repair. This leads to enhanced automaticity within the bundle of His or delayed after repolarization. However, it can occur after cardiac surgery away from His bundle, suggesting involvement of another mechanism in its pathogenesis [12].

Treatment of postoperative JET usually includes digoxin, magnesium, intravenous procainamide, flecainide, hypothermia and propranolol with varying degrees of success [1, 8]. Now, the first line of treatment of JET is intravenous amiodarone and hypothermia [22].

However, amiodarone has been proved to be effective and safe in preventing postoperative AF in adult after open heart surgery in many studies [2, 4, 11], and its use in pediatrics for preventing postoperative arrhythmias is still underused.

To the best of our knowledge, only one study has been performed to detect prophylactic effect of amiodarone in preventing JET in children after TOF repair, but it was limited by its retrospective nature of data retrieval, small number of patients and limitation to a single cardiac lesion (TOF repair) [13].

The objective of this study was to assess the safety and efficacy of prophylactic amiodarone in preventing early postoperative JET in children undergoing cardiac surgery and to identify risk factors for JET among these children.

Patients and Methods

This prospective study was conducted in cardiothoracic department, Tanta University Hospital, a tertiary referral hospital in Delta area in Egypt, during the period from October 2011 to April 2015, on 117 children who underwent cardiac surgery for CHD correction. The study has been approved by the local ethics committee of the Faculty of Medicine, Tanta University Hospital, and informed consents were taken from the parents.

We excluded patients who had arrhythmias or history of arrhythmias before surgery. For amiodarone use, we excluded patients with known history of amiodarone hypersensitivity, those with marked sinus bradycardia while awake, patients with CHF, patients with persistent hypotension, patients with AV block, patients with prolonged corrected QT interval, patients with peripheral neuropathy, patients with clinical hypo- or hyperthyroidism, and cases with liver disease.

Patients were classified into two groups:

Amiodarone group (65 cases)
Placebo group (52 cases)

Five milligrams/kilogram of amiodarone or placebo (5 % aqueous dextrose solution) administered intravenously over 30 min at the time of anesthesia induction followed by continuous infusion of 10–15 μg/kg/min IV diluted in dextrose 5 % over 24 h for the first three postoperative days.

JET was defined as a narrow QRS complex tachycardia at a rate of more than 170 beats/minutes with AV dissociation with a ventricular rate greater than the atrial rate [5]. Early onset postoperative JET was defined as presence of JET during the first 48 h postoperatively. Continuous ECG monitoring was used continuously in the intensive care unit (ICU). Standard 12-lead ECGs were registered in all patients preoperatively and at the time of ICU admission. When JET was detected on the ECG monitor, this was also documented with a standard ECG.

In our study, high doses of inotropic agents administered in the ICU were considered when dose was greater than 0.5 mcg/kg/min for epinephrine and norepinephrine, and 10 mcg/kg/min for dopamine and dobutamine.

$$\begin{aligned}\text{Inotropic score} = {} & (\text{dopamine} \times 1) + (\text{dobutamine} \times 1) \\ & + (\text{adrenaline} \times 100) \\ & + (\text{noradrenaline} \times 100) \\ & + (\text{milrinone} \times 10).\end{aligned}$$

Dosage of the previous drugs were in mcg/kg/min.

The primary outcomes were to assess incidence of the occurrence of JET and symptomatic JET that need treatment by attending physician during the first 5 days postoperatively, while the secondary outcomes were to assess the effectiveness, safety and advantage of prophylactic amiodarone administration on the incidence of hospital and ICU lengths of stay and mortality. The drawbacks of amiodarone usage as bradycardia and hypotension were reported.

When postoperative diagnosis of JET is achieved, a treatment protocol was initiated including general measures such as correcting fever, electrolyte abnormalities, anemia, hypovolemia, pain control, decrease inotropic support when possible, maintenance dose of digoxin, and amiodarone.

Statistical Analysis

Statistical analysis was performed with SPSS statistical program (SPSS 11 Inc., Chicago, IL). For quantitative data, the range, mean and standard deviation were calculated. For comparison between means of two groups, student's

t test was used. A *P* value of <0.05 was considered statistically significant.

Results

One hundred and seventeen (117) infants and children who underwent cardiac surgery for CHD were included. The 2 groups (amiodarone and placebo groups) were homogenous as regards pre- and postoperative data (Table 1).

JET was detected postoperatively in 21 patients out of 117 (17.9 %). The incidence of postoperative JET was 9.2 % (6 out of 65) in amiodarone group, while it was 28.9 % (15 out of 52) in placebo group. Two patients were symptomatic in amiodarone group (two out of six), while six patients were symptomatic in placebo group (6 out of 15) and they needed treatment. There was significant difference in the incidence of JET (*P* value <0.05) and in the incidence of symptomatic JET (*P* value <0.05) between the two groups (Table 2).

Bradycardia occurred in six patients (5.1 %), and hypotension occurred in four patients (3.4 %) after amiodarone or placebo administration, and there was no significant difference as regards the incidence of bradycardia (*P* value 0.88) and the incidence of hypotension (*P* value 0.776) between the two groups (Table 3).

There was significant difference between two groups as regards length of ICU admission (*P* value 0.031) and high significant difference between two groups as regards the length of hospital stay (*P* value 0.0005), while there was no significant difference regarding mortality rate between the two groups (*P* value 0.482) (Table 3).

Risk factors statistically associated with JET after analysis were age (*P* value <0.001), weight (*P* value <0.001), serum potassium (*P* value <0.001) and magnesium (*P* value <0.001), duration of cardiopulmonary bypass (*P* value 0.01), aortic cross-clamp time (*P* value 0.002), high inotropic support (*P* value 0.028) and acidosis (*P* value <0.001) (Table 4).Type of surgery was an important risk factor for the occurrence of postoperative JET. JET was more frequent after TOF repair (35.7 %), PS repair (28.6 %), AVSD (18.8 %) and VSD closure (17.4 %) (Table 5).

Most of JET 15/21 (71.4 %) occurred in the first day postoperatively, and 6/21 occurred in the second day (28.6 %) (Fig. 1).

Discussion

Our results revealed that prophylactic amiodarone decreased the incidence of JET in pediatric patients undergoing open heart surgery for correction of CHD from 28.9 % in placebo group to 9.2 % which was consistent with Imamura et al. [13] who found that prophylactic amiodarone decreased the incidence of postoperative JET from 37.2 % in control group to 10 % in amiodarone group.

We preferred to start amiodarone therapy intraoperatively and not before to decrease the overall dose of amiodarone in order to decrease its potential side effects. This was supported by Buckley et al. [4] who found that there were no significant differences in patients in whom

Table 1 Distribution of pre- and postoperative data in both groups

Pre- and postoperative data	Amiodarone group ($n = 65$)		Placebo group ($n = 52$)		*P* value
Age (months)	15.7 ± 6.6		16.6 ± 7.3		0.485
Sex (male/female)	1.32 (37:28)		1.26 (29:23)		0.950
Weight (kg)	(11.5 ± 2.2)		(10.9 ± 1.9)		0.122
Type of surgery					
VSD	19	29.2 %	15	28.8 %	
ASD	13	20 %	12	23.1 %	
VSD + ASD	12	18.5 %	9	17.3 %	
AVSD	9	13.8 %	7	13.5 %	0.999
Fallot tetralogy	8	12.3 %	6	11.5 %	
Critical PS	4	6.2 %	3	5.8 %	
Cyanosis	12 (18.5 %)		9 (17.3 %)		0.935
Body temperature	36.9 ± 0.22		36.9 ± 0.19		0.814
Aortic cross-clamp time (min)	55.4 ± 23.1		53.1 ± 26.1		0.614
Total cardiopulmonary bypass time (min)	105.1 ± 30.3		100.4 ± 31.1		0.412
Inotropes score before arrhythmia	11.07 ± 5.04		13.39 ± 4.73		0.024*

* Significant or $P < 0.05$

VSD ventricular septal defect, *ASD* atrial septal defect, *AVSD* atrioventricular septal defect, *PS* pulmonary stenosis

Table 2 Primary outcomes in both groups

Primary outcomes	Amiodarone group ($n = 65$)		Placebo group ($n = 52$)		P value
JET	6	9.2 %	15	28.9 %	0.012*
Symptomatic JET	2	3.1 %	6	11.5 %	0.026*

* Significant or $P < 0.05$

Table 3 Secondary outcomes in both groups

Secondary outcomes	Amiodarone group ($n = 65$)		Placebo group ($n = 52$)		P value
Bradycardia	4	6.2 %	2	3.8 %	0.88
Hypotension	2	3.1 %	2	3.8 %	0.776
Length of ICU admission (day)	2.8 ± 2.1		3.7 ± 2.9		0.031*
Length of hospital stay (day)	7.8 ± 2.6		9.3 ± 3.1		0.005*
Hospital mortality	2	3.1 %	4	7.7 %	0.482

* Significant or $P < 0.05$

Table 4 Characteristics and risk factors in patients with JET

Risk factors	JET ($n = 21$)	Non-JET patients ($n = 96$)	P value
1. Age (months)	(10.7 ± 1.8)	(18 ± 3.2)	<0.001*
2. Gender (male/female)	(13:9)	(53:42)	0.965
3. Body weight (kg)	8 ± 1.3	11.5 ± 1.2	<0.001*
4. Electrolyte			
Serum potassium	2.3 ± 0.31	4.1 ± 0.52	<0.001*
Serum calcium	8.75 ± 0.26	8.92 ± 0.47	0.112
Serum magnesium	1.31 ± 0.1	2.50 ± 0.37	<0.001*
5. Duration of cardiopulmonary bypass (minutes)	107.7 ± 54.5	85.3 ± 54.3	0.0001*
6. Duration of aortic cross-clamp (minutes)	71.5 ± 32.2	48.1 ± 30.6	0.002*
7. Inotropic support			
High dose	13 (61.9 %)	30 (31.3 %)	0.028*
8. Body temperature	36.5 ± 1.3	36.2 ± 1.2	0.308
9. Cyanosis	7 (33.3 %)	14 (14.6 %)	0.086
10. Postoperative acidosis	7 (33.3 %)	3 (3.1 %)	0.0001*

Table 5 JET related to type of surgical correction

Type of surgery	Number of patients with JET ($n = 21$)	Number of patients undergoing this surgical intervention ($n' = 117$)	% (n/n')
VSD closure	6	34	17.4
ASD closure	3	25	12
ASD + VSD closure	2	21	9.5
TOF repair	5	14	35.7
AVSD repair	3	16	18.8
Pulmonary stenosis	2	7	28.6

amiodarone prophylaxis was initiated preoperatively from those initiated intra- or postoperatively.

We found that amiodarone prophylaxis significantly shortened postoperative ICU and hospital stay and consequently the cost of surgery but did not affect the incidence of mortality. This was achieved without significant side effects as bradycardia and hypotension (only six cases with amiodarone, and it was not significant and not

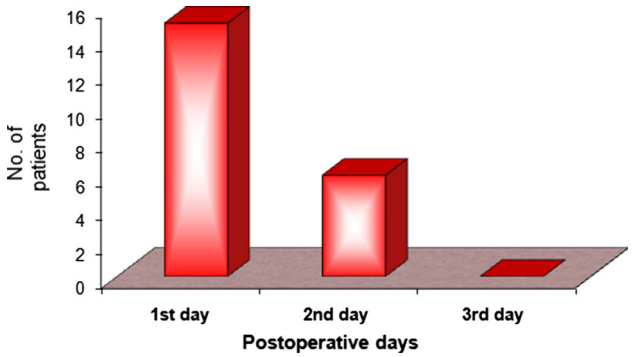

Fig. 1 Postoperative timing of JET as most of JET 15/21 (71.4 %) occurred in the first day postoperatively and 6 patients had JET in the second day (28.6 %); no patients had JET after the second day postoperatively

necessitating the stoppage of amiodarone) which is inconsistent with Imamura et al. [13] who found no postoperative bradycardia and hypotension at all after prophylactic intravenous amiodarone. This may be explained by smaller number of their patients and the usage of lower doses of intravenous amiodarone and for shorter duration in their research. Our results reflected the high efficacy of prophylactic amiodarone and favorable outcomes in preventing JET in children after open heart surgery.

Amiodarone is a class III antiarrhythmic drug that prolongs repolarization and refractory period of atrial, nodal and ventricular tissue, with both beta-blocker-like and potassium channel blocker-like actions. Its effect in JET may be related to its inhibition of abnormal automaticity, and the increase in the refractory period of the AV node and His–Purkinje system. So, amiodarone has been reported to be one of the most effective drugs in managing JET after pediatric heart surgery [16, 20, 22, 25].

JET occurs in 17.9 % of all patients similar to that found in Chelo et al. [5] who found JET in 15.7 % of patients, but it was lower than that found by Imamura et al. [13] who detected postoperative JET in 28.6 % of patients (18 out of 63). This can be explained by performance of our research on varieties of CHD surgical correction, while they did their research on children with TOF correction only and it is unknown from many studies that the incidence of postoperative JET with TOF correction is much higher [15, 28].

Early onset arrhythmia was defined as presence of arrhythmia during the first 48 h postoperatively. In our study, most of early onset JET (15/21) occurs in the first day postoperatively that accounts for 71.4 % of cases, and six cases developed JET in the second day (28.6 %). Same results were reported by other studies [15]. This could be due to early postoperative unstable hemodynamics, electrolyte disturbances, acidosis, and swelling of myocardium that are common in this period besides the release of inflammatory mediators that alter membrane potential of myocyte [14].

It is worth pointing out that the exact cause of JET is not known, but several associations and risk factors for JET have been studied and identified in many studies [6, 9]. SO, knowing these association and risk factors will definitely help in preventive management strategies. This is why we investigated risk factors associated with occurrence of JET in our study.

In our study, the average age and weight of patients with JET were significantly lower than those with no JET arrhythmias. This is similar to the results of other investigators [1, 5, 15, 23]. This can be explained by increased incidence and effect of electrolyte and acid base imbalance in these patients. Moreover, manipulation and traction during surgery are relatively greater in a small heart. Moreover, the myocardium of the young child has a reduced storage capacity for calcium [6].

In our study, it was not surprising to found that long CPB and aortic cross-clamp time were associated with higher incidence of JET. Many investigators reported them as the most significant risk factors for postoperative JET [9, 15, 21]. This can be due to change in micro- and macro-equilibrium.

Our result showed that occurrence of JET was related to type of surgery, such as tetralogy of Fallot, ventricular septal defect and right ventricular outflow repair. This could be due to increased risk of direct trauma to conduction system. This was in accordance with findings of previous investigators [8, 15, 26]. However, JET appeared also after surgical procedure away from AV node, e.g., ASD (12 %), suggesting involvement of another mechanism in its pathogenesis, e.g., myocardial ischemia and reperfusion injury after CPB.

In the present study, postoperative acidosis was a risk factor for development of JET that matched result of other studies [15]. This can be explained by the effect of acidosis on electrolyte imbalance that increases the myocardium automaticity and irritability.

In our study, we found that high doses of postoperative inotropes and hypokalemia were associated with higher incidence of JET. Hypokalemia and high-dose inotropes affect the stability of cellular membrane, leading to increase myocardial irritability and automaticity. These findings went with the results of other investigators [7, 10, 15, 17, 24].

Our study showed that lower postoperative Mg level was significantly associated with increased incidence of JET. This is supported by the result of other investigators [3, 18]. This is because hypomagnesaemia causes an intracellular potassium deficiency and increased intracellular calcium concentration, leading to increased myocardial excitability. In addition, magnesium plays a cardioprotective role in ischemia–reperfusion injury by decreasing the endogenous catecholamine release from the

adrenal medulla [6]. This is why Mg supplementation during cardiopulmonary bypass is now recommended to decrease incidence of postoperative JET [18].

In conclusion, prophylactic amiodarone is safe and effective in preventing early JET in children after corrective heart surgery for CHD. Risk factors for JET were young age, low weight, type of surgery, prolonged CPB and ACC time, hypomagnesemia, hypokalemia, acidosis and high dose of inotropes, and these risk factors should be corrected, as possible, to decrease incidence of postoperative JET.

Compliance with Ethical Standards

Conflict of interest The authors declare that they have no conflict of interest.

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