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EFFECTIVENESS OF ORAL AMIODARONE IN PREVENTION OF PERIOPERATIVE JUNCTIONAL ECTOPIC TACHYCARDIA IN PATIENTS OF TETRALOGY OF FALLOT UNDERGOING INTRACARDIAC REPAIR

Surgery

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ABSTRACT

OBJECTIVES: Evaluation of the effectiveness of oral amiodarone in prevention of perioperative junctional ectopic tachycardia in patients of Tetralogy of Fallot undergoing intracardiac repair.

MATERIALS AND METHODS: 50 patients of Tetralogy of Fallot were divided into two groups of 25. One group received preoperative amiodarone before intracardiac repair whereas the other did not. Intraoperative and post-operative outcomes were examined.

CONCLUSIONS: Preoperative oral amiodarone is not effective in preventing perioperative junctional ectopic tachycardia in patients of Tetralogy of Fallot undergoing intracardiac repair.

KEYWORDS

Tetralogy Of Fallot, Junctional Ectopic Tachycardia, Amiodarone

INTRODUCTION

Tetralogy of Fallot (TOF) is most commonly seen in 3 of every 10,000 live births, and accounts for 7–10% of all forms of congenital cardiac malformations [1,2]. It is characterised by the following anatomic features- right ventricular outflow tract (RVOT) obstruction, ventricular septal defect (VSD), aortic override and right ventricular hypertrophy[3]. Postoperative complications after surgery for TOF include bleeding, low cardiac output, arrhythmias, prolonged ventilation, renal dysfunction and pulmonary dysfunction.

Postoperative arrhythmias after open heart surgery for congenital heart disease contribute significantly to both morbidity and mortality. [4] Junctional ectopic tachycardia (JET) is a malignant form of arrhythmia of unknown aetiology, and a growing source of concern. It is most frequently observed after complete repair of tetralogy of Fallot (TOF) and surgeries in the vicinity of the atrioventricular (AV) node and the bundle of His.

JET is found to be the most common hemodynamically significant tachycardia which is seen within 24 hours after surgery in the postoperative setting [5,6,7]Hemodynamic instability results from loss of atrioventricular synchrony and extreme tachycardia[7] causing decrease in stroke volume and cardiac output. Volume infusion and increase in inotropic support are required to maintain adequate BP. This increase in inotropic support causes a vicious cycle of increasing heart rate and further decrease in stroke volume and cardiac output which may lead to mortality.

The exact mechanism of JET is unknown, however it is believed to be caused due to mechanical trauma to the proximal conduction tissue produced by suture placement or indirect stretch injury causing oedema produced during resection of muscle bundles, correction of right ventricular outflow tract and correction of VSD [8] Paradoxically, JET also occurs in patients in whom surgery does not involve areas around the atrioventricular node. Furthermore cardiopulmonary bypass (CPB) with ischemia reperfusion and the related cellular biochemical effects as well as medical interventions such as electrolyte shifts and catecholamine administration may affect the stability of the cellular membrane and result in an increased myocardial irritability and automaticity.[9,10] Young age of the patient, duration of CPB, aortic cross clamp time (ACC), electrolyte imbalance, use of inotropic agent and type of surgery are some of the most common risk factors associated with JET [11,12]

Diagnostic criteria for JET includes:

(1) Narrow QRS tachycardia seen in the absence of surgically induced right bundle branch block,
(2) Heart rate between 170 - 230 beats/min
(3) AV dissociation with hemodynamic instability, and
(4) Ventricular rate faster than the atrial rate.

Management of JET includes lowering the core body temperature, correcting serum potassium, magnesium and giving IV amiodarone. In 24 to 48 hours some patients return to sinus rhythm and some patients succumb to the results of low cardiac output in absence of other residual surgical problems.

Amiodarone is class III antiarrhythmic drug which shows structural similarities to thyroxine. It acts by sodium and potassium channel blockade, mild antisympathetic action and some calcium channel blockade. Its effect is not immediate.

DOSING

The standard dosing regimen is intravenous 300 mg over 20 min–2 hours (use central vein where possible)followed by 900 mg over next 24 hours (maximum 1200 mg in 24 hours) followed by oral maintenance dose (oral loading dose of 200–400 mg three times a day) for 10–14 days. A maintenance of 200–400 mg/day is given thereafter. This will prolong the QT interval on the ECG and is typically a feature of the therapeutic effect of amiodarone.

Most of the amiodarone and its primary metabolite is found in the deep compartment, consisting of lymph nodes, liver, lung, [13]. The peripheral compartment composed of muscle and brain which contributes to a smaller volume of distribution and therefore a lower solubility coefficient. Previous studies in this regard have shown that the short initial half life of Amiodarone is followed by a much longer elimination period as it tends to redistributes from deep compartments [14]. The longer the administration of amiodarone, the greater the amount of parent drug and its metabolite that gets accumulated in the deep compartment. The accumulation of drug in the deep compartments accounts for the delay in the onset of antiarrhythmic activity when loading doses in smaller amount is used. Therefore a higher dose is generally required to attain a myocardial and plasma concentration to bring out the therapeutic effects [15].

AIMS AND OBJECTIVES

The aim of the study was to evaluate the effectiveness of oral amiodarone in prevention of perioperative junctional ectopic tachycardia in patients of Tetralogy of Fallot undergoing intracardiac repair.

MATERIALS AND METHODS

This prospective study was conducted in the Department of Cardiothoracic and Vascular Surgery, Advanced Cardiac Centre, Post-Graduate Institute of Medical Education and Research, Chandigarh between October 2014 to June 2016.

HYPOTHESIS:

Amiodarone given preoperatively prevents the incidence of JET following intracardiac repair for TOF.

INCLUSION AND EXCLUSION CRITERIA
All patients including both males and females with Tetralogy of Fallot who consented for intracardiac repair in the Department of Cardiothoracic and Vascular Surgery. Patients not consenting to the study were excluded.

SAMPLE SIZE -
50 patients
GROUP A (AMIODARONE GROUP)–
25 patients.
GROUP B (NON AMIODARONE GROUP)–
25 patients.

Alternate patients were selected for the grouping.
GROUP A PROTOCOL:
Amiodarone administration and monitoring: Oral amiodarone was given in dose of 2mg/kg of body weight 7 days before surgery. The patient's heart rate, blood pressure and were monitored every 6 hourly and ECG was also done daily to see QT prolongation and bradycardia.
GROUP B PROTOCOL:
Patients were prepared for intracardiac repair of TOF. The patient's heart rate, blood pressure and were monitored every 6 hourly and ECG was also done daily.

PREOPERATIVE VARIABLES
Detailed history and cardiovascular examination, hematologic & biochemical investigations, 2D echocardiography and cardiac catheterization study of all cases were recorded.

PERIOPERATIVE VARIABLES
Heart rate, blood pressure, CVP, SpO_2 and arrhythmias such as complete heart block, atrial fibrillation, junctional ectopic tachycardia, sinus tachycardia and haemodynamics were recorded during intracardiac repair and in postoperative stay of ICU.

POST OPERATIVE FOLLOW UP
All patients were followed up at 1 week, one month and 3 months after intracardiac repair. Any complications were noted.

ANAESTHESIA AND OPERATIVE PROCEDURE
Patient was anaesthetized as per Institute protocol. Arterial pressure line in radial/femoral artery and central venous access to right internal jugular vein or femoral vein were secured. Induction was done by administering intravenous morphine/fentanyl with propofol and muscle relaxation with vecuronium. Endotracheal intubation and ventilation maintained by mechanical ventilator. On cardio pulmonary bypass (CPB), anaesthesia was maintained with morphine and vecuronium. The perfusion pressures were maintained and controlled with phenylephrine and nitro glycerine and if required with sodium nitroprusside.

MYOCARDIAL PROTECTION
Core cooling to 28-32°C was done and heart was arrested with antegrade del Nido cardioplegia (20 ml/kg) initially and subsequently (10 ml/kg) was given through antegrade route after every 40-60 minutes.

INTRACARDIAC REPAIR
The heart was approached through median sternotomy, thymus dissected/resected leaving the cervical portion and pericardial patch was harvested and was immersed in 0.6% glutaraldehyde for 10 minutes. MAPACS (if present) were embolised preoperatively / clipped or ligated via posterolateral thoracotomy/ sternotomy just before ICR. Systemic heparinization (3-4 mg/kg) was done. Aortic and bicaval cannulation was done and CPB was established, surgically created shunt was ligated and divided, and the ductus (if present) was ligated prior to establishment of CPB. Heart was arrested and protected by Del Nido cardioplegia. The patient was cooled to 32°C. LV vent was placed through Fossa Ovalis or RSPV. Resection of septal and parietal bands were done through RA/PA/Right ventriculotomy as per the cases required. VSD was closed by interrupted or continuous suture technique depending on surgeon's choice. Wherever required transannular pericardial patch augmentation of RVOT /MPA was done with pericardial patch. Patient rewarmed to 36 °C and weaned from bypass. Intraoperative TEE was done for all patients to check for the adequacy of repair and cardiac function. Venous and aortic decannulation was done. Haemostasis achieved, sternum and skin closed, patient then shifted to ICU. In immediate postoperative period in ICU continuous recording of ECG, CVP, urine output, drainage, SpO2, arrhythmias and incidence of JET were done.

OBSERVATION AND RESULTS
A total of 53 patients were enrolled for the study. Demographic and patient variables were comparable in both groups (Table 1) except for the mean blood pressure and saturation which was significantly lower (p=0.04 and 0.03 respectively) in the Amiodarone group. 3 patients who amiodarone preoperatively developed bradycardia (hear rate <60/min) and drug was discontinued.

The cross clamp time was comparable (Table 2) in both groups (184±6.48 vs.174±7.73, p=0.9). The cardiopulmonary bypass time was not significantly different for both groups (Table 2) (200±8.16 vs.192±13.1 minutes, p=0.24).

In the peri operative course, patients who received amiodarone preoperatively had significantly lesser heart rates (p=0.04) and mean blood pressures(p=0.02) (Table 2) Postoperatively, 3 patients in the amiodarone group and 5 patients in the non-amiodarone group developed junctional ectopic tachycardia. However, there was no statistical significance in the incidence of junctional ectopic tachycardia in both groups (p=0.47) with a total prevalence of 16% in the study population. There was no statistical significant association of JET between the amiodarone and non-amiodarone group (p=0.47)(Table 2). Amiodarone infusion was started for all the patients who developed JET and was further managed by inducing hypothermia and serum potassium correction. Overall 5 mortalities were seen in 50 patients, out of which 2 were seen in patients who had postoperative JET and 3 in patients who did not have postoperative JET. The cause of death in these 2 patients with JET was low cardiac output and respiratory failure due to extensive tuberculosis related fibro cavitary disease of the lung. 3 patients who did not suffer from JET died of low cardiac output related complications.

TABLE 1

Preop-Variable	Group A (Amiodarone group)	Group B (Non Amiodarone group)	p-value
Age (years)	9.16±8.22	11.346±8.54	0.36
BSA (m2)	0.817±.425	0.902±.438	0.48
SpO2 (%)	76.60± 11.34	82.50±8.74	0.04
Mean HR (bpm)	101.92± 18.61	98.31±12.67	0.42
Mean MBP (mm Hg)	70.82± 15.32	79.51±13.40	0.03
Bradycardia (Heart rate< 50)	3	0	

TABLE 2

Perioperative Variable	Group A (Amiodarone group)	Group B (Non Amiodarone group)	p-value
Junctional Ectopic Tachycardia	N=3/25 (12%)	N=5/25 (20%)	0.47
SpO2 (%)	98.88± 1.79	98.346±2.67	0.66
Mean HR (bpm)	113.84± 3.60	110.154±8.09	0.04
Mean MBP (mm Hg)	106.64± 21.35	120.82±21.98	0.02
Trans annular patch	12	14	0.5
Cross clamp time (min)	184±6.48	174±7.73	0.9
CPB time (min)	200±8.16	192±13.1	0.24
Temperature (degree Celsius)	39.46±0.20	39.58±0.13	0.22

DISCUSSION
The incidence of JET following congenital cardiac surgery range from 8-10%. It occurs with all types of congenital cardiac surgery, however in patients with TOF it causes significant morbidity because of pressure overload changes in RV.

In our study the incidence of JET was 16%. JET is of multifactorial in nature of which young age, long cross clamp time, long CPB time, high temperature, low serum potassium, stretching and traction injury to the conduction, excessive RVOT resection, transannular patch, requirement of high inotropic support, trans atrial approach have been considered. All these factors can't be modified in a considerable way.

In addition to control of serum potassium correction, body temperature control, IV Amiodarone is the main pharmaceutical treatment of JET. In our 8 patients (16%), who developed JET they responded to iv amiodarone , all of them responded to sinus rhythm. JET was not the etiological factor of mortality in these patients. The causes of mortality were respiratory failure, RV dysfunction in spite of maintaining normal sinus rhythm.

We did not find any correlation between the incidence of JET and demographic profiles, cross clamp time, CPB time, RVOT patch any residual cardiac lesion.

Prophylactic use of oral amiodarone is not entirely safe. 3 patients out of 50 developed bradycardia within 3-5 days of starting amiodarone, therefore oral amiodarone was withdrawn.

There was no significant difference in the incidence of JET in 2 groups of patients (25 each) of which in one group oral amiodarone was given in a dose of 2mg/kg 7 days preoperatively and other group acted as control. Inamura et al [16] introduced prophylactic amiodarone for Tetralogy repair and then conducted a study to evaluate the effectiveness of the prophylactic amiodarone at a rate of 2 mg/kg/d and continued for 48 hours. Between November 2005 and November 2009, 63 consecutive patients underwent primary repair of tetralogy, of whom 20 had prophylactic amiodarone (amiodarone group) and 43 did not (control group). The incidence of junctional ectopic tachycardia was 37% in the control group and 10% in the amiodarone group. The groups were similar in age, weight, bypass time, rate of transannular patch usage, and preoperative and postoperative gradient through the right ventricular outflow tract. Prophylactic amiodarone was significantly negatively associated with junctional ectopic tachycardia by both univariate (p= 0.039) and multivariate (p = 0.027) analyses. There were no adverse events attributable to prophylactic amiodarone use which was well tolerated and significantly associated with a decreased incidence. Our results however does not support the finding of Inamura [16] who observed significant difference in the incidence of JET 10% vs 37% in whom amiodarone was given for 48 hours preoperatively.

LIMITATIONS OF THE STUDY

Even though baseline characteristics and surgical complexity were equal in our study groups, this population sample size has been small and does not represent all the paediatric cardiac surgical patients who may be at risk for postoperative arrhythmias. Another limitation of the study is bioavailability of oral Amiodarone & low therapeutic index of the drug was not evaluated. Perhaps higher doses of the drug along with continuous monitoring of HR, BP & ECG might have been beneficial, therefore a study with a large number of patients with higher doses of oral Amiodarone (bioavailability 30%) and monitoring of plasma level of drug (due to lower therapeutic index) may be beneficial.

CONCLUSION AND SUMMARY

Preoperative oral amiodarone for preventing peri operative junctional ectopic tachycardia is not entirely safe, it does cause bradycardia. It needs to be given with intensive monitoring. However, intravenous amiodarone in the post-operative period is effective in the management of the same dysrhythmia.

ABBREVIATIONS

TOF- Tetralogy of Fallot
RVOT- Right ventricle outflow tract
VSD- Ventricular septal defect
RV- Right ventricle
JET- Junctional Ectopic Tachycardia
CHD- Congenital heart disease
AV- Atrio ventricle
CPB- Cardiopulmonary bypass
PS- Pulmonary stenosis
PA- Pulmonary artery
RV-PA- Right ventricle pulmonary artery
ECG- Electrocardiogram
CVP- Central venous pressure
SpO2- Oxygen saturation
ABP- Arterial blood pressure
HR- Heart rate
JVP- Jugular venous pressure
KCL- Potassium chloride
MgSO4- Magnesium sulphate
MAPCAS- Multiple aorto pulmonary collateral arteries
ICR- Intracardiac repair
LV- Left ventricle
RA- Right atrium
MPA- Main pulmonary artery
LPA- Left pulmonary artery
RPA- Right pulmonary artery
TEE- Transoesophageal echocardiography
ICU - Intensive care unit
SD- Standard deviation
DOE- Dyspnoea on exertion
LRTI- Lower respiratory tract infection
BSA- Body surface area
PCV- Packed cell volume
CXR- Chest X ray
LVEF- Left ventricle ejection fraction
RVEF- Right ventricle ejection fraction
RVEDV- Right ventricle end diastolic volume
RVESV- Right ventricle end systolic volume
BP- Blood pressure
K+- potassium
Wt.- Weight
mg/kg - milligram per kilogram
mg/day - milligram per day
ml/kg - millitre per kilogram

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