Prophylactic amiodarone reduces junctional ectopic tachycardia after tetralogy of Fallot repair

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Objective: Junctional ectopic tachycardia is common after pediatric heart surgery. After tetralogy of Fallot repair, the incidence of junctional ectopic tachycardia may be as high as 15% to 20%. We introduced prophylactic amiodarone for tetralogy repair. This study was conducted to evaluate the effectiveness of the prophylactic amiodarone.

Methods: A continuous infusion of amiodarone was started in the operating room at the time of rewarming during cardiopulmonary bypass 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). Variables studied included demographic and bypass data, surgical procedure details (transannular or nontransannular patch), preoperative and postoperative echocardiography findings, and postoperative inotropic support. Univariate and stepwise multivariate analyses were conducted to determine factors associated with the occurrence of junctional ectopic tachycardia.

Results: 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 ($P = .039$) and multivariate ($P = .027$) analyses. There were no adverse events attributable to prophylactic amiodarone use.

Conclusions: Prophylactic amiodarone is well tolerated and significantly associated with a decreased incidence of junctional ectopic tachycardia after tetralogy repair. (J Thorac Cardiovasc Surg 2012;143:152-6)

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Junctional ectopic tachycardia (JET) is common after pediatric heart surgery with an incidence reported between 2% and 22%.[1-3] JET has been reported after virtually every type of congenital heart surgery, but seems particularly common after ventricular septal defect repair, surgery for single ventricle, arterial switch operation, total anomalous pulmonary venous return repair, complete atrioventricular canal repair, and tetralogy of Fallot (TOF) repair.[4,5] The incidence of JET after TOF repair has been reported to be between 14% and 22%.[1,5-7]

This arrhythmia is usually transient, but because it may cause significant morbidity and mortality by causing low cardiac output syndrome, control of JET after pediatric heart surgery is essential. However, the mechanism of this arrhythmia after surgery is not well defined.[6,7] Empiric treatment of postoperative JET has included adequate sedation, electrolyte control, hypothermia, and minimal inotropic support.[8] In recent years, amiodarone has become the treatment of choice.[9-11]

Amiodarone has been used as prophylaxis against atrial fibrillation after adult cardiac surgery, but this approach has not been tried in children undergoing cardiac surgery. Because of a relatively high incidence of troublesome JET after TOF repair at Arkansas Children's Hospital, we introduced prophylactic amiodarone in children undergoing primary TOF repair. The purpose of this study is to review the effectiveness of this prophylaxis and to identify any adverse events associated with this novel strategy.

MATERIALS AND METHODS

Via retrospective chart review, approved by the institutional review board of the University of Arkansas for Medical Sciences, 63 consecutive patients undergoing primary TOF repair between November 2005 and November 2009 at Arkansas Children's Hospital were identified, and relevant data were abstracted from hospital records. Patients who had undergone prior palliation (n = 17, most with pulmonary atresia) were excluded, as were patients requiring right ventricle to pulmonary artery conduits, TOF with major aortopulmonary collaterals, TOF absent pulmonary valve syndrome, and TOF atrioventricular canal defect. In mid-2007, we initiated a strategy of prophylactic amiodarone continuous infusion in this patient population. The drug was started in the operating room at the time of rewarming during cardiopulmonary bypass at a rate of 2 mg/mg/d and continued for 48 hours. Among the 63 patients undergoing primary TOF repair, 20 received prophylactic amiodarone (amiodarone group) and 43 did not (control group). In 2005 and 2006, all patients were in the control group. In 2007, 18% of patients received prophylactic amiodarone; in 2008, 27% received prophylactic amiodarone; and in 2009, all patients were in

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Abbreviations and Acronyms
ICU = intensive care unit
JET = junctional ectopic tachycardia
TOF = tetralogy of Fallot

the amiodarone group. Variables studied included demographic and bypass data, surgical procedure details (transannular or nontransannular patch), preoperative and postoperative echocardiographic findings, and postoperative inotropic support details.

Surgical Technique

The standard approach to repair was transatrial and transpulmonary.[12] When the right ventricular outflow tract obstruction was not relieved by pulmonary valvotomy and right ventricular outflow tract muscle resection, the pulmonary annulus was opened and transannular patch was used, using autologous pericardium or polytetrafluoroethylene as patch material. The 0.1-mm thickness polytetrafluoroethylene sheet monocusp was placed to the transannular patch before suturing the right ventricular outflow tract. Hegar dilators 2- to 3-mm larger than the mean normal-sized pulmonary annulus were passed through the right ventricular outflow tract to calibrate. Cardiopulmonary bypass techniques included bicaval cannulation, high flow bypass (100–150 mL/kg/min), moderate hypothermia (28°C), and multidose cold-blood cardioplegia. Deep hypothermic circulatory arrest was not used in any patient.

Arrhythmia Analysis

Continuous rhythm monitoring was done in the intensive care unit (ICU). Rhythm analysis was also done by using a telemetry system on the postoperative ward. JET was defined as tachycardia originating from the His bundle with narrow QRS complexes at a rate of more than 170 beats/min. JET was initially diagnosed by the ICU staff and confirmed by electrophysiologist consultation.

Junctional Ectopic Tachycardia Treatment

If JET developed postoperatively in a patient, treatment was initiated with a bolus dose of amiodarone (5 mg/kg over 60 minutes) followed by continuous amiodarone infusion (5 mg/kg/d). If an acceptable response was not observed, the bolus was repeated up to a maximum dose of 15 mg/kg. The core temperature was reduced to 35.0°C to 36.0°C with a cooling blanket, and sedation was increased. Inotropic support was decreased as tolerated, and hypokalemia and hypomagnesemia were treated appropriately. After stabilization, treatment of amiodarone was continued and weaned over 3 to 5 days. Whenever full feeding is established, amiodarone is administered enterally.

Statistical Analysis

Categoric variables were compared with the chi-square or Fisher exact test. Continuous variables are expressed as mean and standard deviation. Mean values were compared with the Wilcoxon rank-sum test. Univariate and stepwise multivariate analyses with stepwise backward selection procedure were used to evaluate variable association with the occurrence of JET. All data were analyzed using STATA software, version 11 (StataCorp, College Station, Tex).

RESULTS

Preoperative and Operative Variables

There were no differences between groups in age, weight, and preoperative echocardiography findings (Table 1).

TABLE 1. Preoperative and operative patient data

Variables	Control group (n = 43)	Amiodarone group (n = 20)	*P* value
Age (mo)	5.1 ± 7.0	2.7 ± 1.8	.12
Weight (kg)	5.9 ± 2.3	5.3 ± 1.5	.42
PG through RVOT (mm Hg)	84 ± 22	84 ± 25	.87
Transannular patch	35 (81%)	18 (90%)	.38
Cardiopulmonary bypass time (min)	120 ± 28	133 ± 44	.33
Aortic crossclamp time (min)	76 ± 18	92 ± 28	.029

PG, Pressure gradient; *RVOT,* right ventricular outflow tract.

Aortic crossclamp times were longer in the amiodarone group (Table 2). JET was more frequently observed in the control group (Table 2). Other postoperative echocardiography and hospital course did not show any differences.

Postoperative Variables

There were no deaths in either cohort. There was no difference between the 2 groups in the degree of inotropic support required postoperatively (Table 3). Postoperative heart block developed in 1 patient in the control group (1.6%).

Variables Affecting the Incidence of Junctional Ectopic Tachycardia

The stepwise backward multiple logistic regression analysis revealed lack of prophylactic amiodarone and epinephrine use to be significant prognostic factors for the incidence of JET (Table 4).

Evaluation With Outcome of Junctional Ectopic Tachycardia

The impact of the development of JET is demonstrated in Table 5. Patients with JET were ventilated longer than JET-free peers, but they did not have longer stays in the ICU or hospital.

Amiodarone Safety

In the prophylactic amiodarone group, no hypotension or bradycardia due to drug use was identified, and no patient

TABLE 2. Postoperative profiles

Variables	Control group (n = 43)	Amiodarone group (n = 20)	*P* value
Early mortality	0/43	0/20	
JET	16/43	2/20	.026
More than moderate PI	20/42 (48%)	8/17 (47%)	.97
PG through RVOT (mm Hg)	19.2 ± 8.5	26.1 ± 19.8	.26
ICU stay (d)	7.0 ± 5.0	7.2 ± 4.9	.81
Mean hospital stay (d)	10.8 ± 7.3	12.8 ± 9.5	.58

PI, Pulmonary insufficiency; *PG,* pressure gradient; *RVOT,* right ventricular outflow tract.

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TABLE 3. Postoperative inotropic support

Variables	Control group (n = 43)	Amiodarone group (n = 20)	*P* value
Epinephrine	10/43 (23%)	5/20 (25%)	.88
Norepinephrine	6/43 (14%)	2/20 (10%)	.66
Dopamine	28/43 (65%)	13/20 (65%)	1
Milrinone	31/43 (72%)	12/20 (60%)	.34

had the prophylactic infusion terminated prematurely. Also, no proarrhythmic effect of amiodarone was detected. Lung disease or thyroid dysfunction due to amiodarone use did not develop in any patient.

DISCUSSION

Amiodarone was prophylactically applied in patients undergoing primary TOF repair with a significant associated reduction in the incidence of JET.

JET is identified as the most common tachyarrhythmia after surgery for congenital heart disease and is well recognized as a cause of low cardiac output syndrome and consequent prolonged ICU stay and hospitalization.[4] In the present study, even with aggressive amiodarone-based treatment of JET, patients in whom the arrhythmia developed had significantly longer ventilator support times. The duration of ICU and hospital stay was also longer for patients with JET, but this difference did not achieve statistical significance probably because of relatively small sample sizes. We believe it is important not to draw the conclusion that JET is a benign arrhythmia that can simply be treated when it occurs and hope that the absence of a statistically significant difference in length of ICU or hospital stay between patients with and without JET in this study would not be thus interpreted.

JET continues to be an important management consideration in children undergoing surgery for congenital heart disease and has been the subject of several contemporary reports investigating risk factors and treatments of the arrhythmia.[1-8] A recent study from Finland showed the incidence of JET after surgery for congenital heart disease is 5.0%,[4] with an incidence of approximately 1.0% for all other non-JET arrhythmias (sinus tachycardia, supraventricular tachycardia, and atrial flutter). Andreasen and colleagues[5] described risk factors for JET, including younger age at operation, longer bypass time, and higher inotropic score. Dodge-Khatami and colleagues[6] proposed a causal relationship between surgical trauma to the bundle of His and postoperative JET. In contrast, Rekawek and colleagues[13] reported that longer ischemic time is the best predictor of JET and suggested that JET is not related to surgery near the His bundle.

Many investigators have sought to discover the mechanism of postoperative JET and reported the possible cause of JET as underlying cardiac defects, type of surgery, hemodynamic instability, and electrolyte imbalances[13] because of the high incidence of postoperative JET reported in some series, even when the surgical procedure did not include the manipulation around the His bundle or right ventricular muscle resection.[2]

It is worth pointing out that virtually all surgeons strive for the gentlest surgical technique, shortest crossclamp time, shortest bypass time, and lowest inotropic use, consistent with the goals of the particular operation, so that virtually all of the putative risk factors identified for JET are not practically modifiable. With that in mind, and a high incidence of JET, despite an institutional approach of quick and gentle surgery, we initiated prophylactic amiodarone. In this series, uniform surgical technique and bypass techniques including cardioplegic solution were used. Because a single diagnosis of TOF with a uniform surgical technique was used for study cohorts, evaluation of mechanism of JET cannot be made in terms of manipulation of the area of the His bundle. There was no difference between the patient with or without JET after surgery in age, weight, and preoperative pressure gradient through the right ventricular outflow tract. These parameters are not risk factors for JET.

Repair of TOF has been identified as the surgical procedure with perhaps the highest incidence of JET after repair, with most reports describing an incidence of JET of approximately 12% to 22%.[2,4,6,7,14] In the present study, the control group had an even higher incidence of JET (37%). We are not certain of the explanation for this increased incidence, but we performed a secondary analysis in which we included patients with TOF who had undergone

TABLE 4. Prognostic factors for the incidence of junctional ectopic tachycardia

	Univariate analysis			Multivariate analysis		
Variables	Odds ratio	95% CI	*P* value	Odds ratio	95% CI	*P* value
Prophylactic amiodarone	0.19	0.04–0.9	.039	0.15	0.027–0.81	.027
Age > 6 mo	1	0.18–5.7	1			
Early and late series	0.365	0.12–1.15	.08			
Transannular patch	1.7	0.33–9.1	.52			
Epinephrine	4.32	1.3–14.9	.019	5.5	1.4–22	.014
Dopamine	1.6	0.48–5.2	.45			
Milrinone	1.9	0.54–6.9	.31			

CI, Confidence interval.

TABLE 5. Summary by outcome

Variables	No JET (n = 45)	JET (n = 18)	*P* value
Age (mo)	3.9 ± 3.8	5.3 ± 9.4	.76
Weight (kg)	5.7 ± 2.0	5.8 ± 2.5	.95
Preoperative			
PG through RVOT (mm Hg)	85 ± 23	82 ± 22	.34
Transannular patch	37/45 (82%)	16/18 (89%)	.51
CPB time (min)	124 ± 39	123 ± 16	.48
AXT time (min)	80 ± 25	84 ± 16	.28
Dopamine	28/45 (62%)	13/18 (72%)	.45
Milrinone	29/45 (64%)	14/18 (78%)	.30
Epinephrine	16/45 (7%)	8/18 (44%)	.015
Norepinephrine	4/45 (4%)	4/18 (22%)	.15
Ventilatory time (d)	1.9 ± 2.0	3.1 ± 1.8	.008
ICU stay (d)	6.8 ± 5.5	7.6 ± 3.4	.11
Hospital stay (d)	11.0 ± 8.2	12.5 ± 8.0	.13

AXT, Aortic crossclamping; *CPB,* cardiopulmonary bypass; *PG,* pressure gradient; *RVOT,* right ventricular outflow tract.

prior palliation. In the combined group of control patients plus previously palliated patients, the incidence of JET was only 20%. Because the palliated patients were older and had virtually no postrepair JET, we suggest that young age is indeed a risk factor for JET, at least in patients who do not receive prophylactic amiodarone. If some centers have markedly lower JET incidence without amiodarone prophylaxis, this prophylactic amiodarone application may not show a beneficial reduction of JET.

Amiodarone is a class III antiarrhythmic agent that prolongs phase 3 of action potential of myocardium, with both beta-blocker–like and potassium channel blocker–like actions. Amiodarone has been reported to be effective in managing JET after pediatric heart surgery.[9-11,15] In adult cardiac surgery, multiple studies demonstrated that prophylactic amiodarone decreased the incidence of postoperative atrial fibrillation,[16] using a wide variety of prophylactic regimens. Several studies showed associated benefits of reduced ventricular arrhythmia and reduction of hospital cost. Our study was not designed or powered to investigate cost, and because the incidence of ventricular arrhythmias is so low in children, we are not able to comment regarding that potential benefit.

In pediatric patients, Plumpton and colleagues[11] reported adverse effects of amiodarone for postoperative JET in 3 patients with hypotension and slow junctional rhythm. Perry and colleagues[10] showed transient hypotension during the bolus phase. In our study, hypotension or bradycardia due to prophylactic amiodarone use did not develop in any patients in the amiodarone group. This was probably because of the use of low doses of amiodarone and the fact that the drug was initiated during cardiopulmonary bypass, starting during bypass and rewarming time.

Although we are encouraged by the results of the present study, its retrospective nature is a major limitation in the strength of our conclusions. Furthermore, the sample sizes are small, and the patient population in the study was limited to a single cardiac diagnosis.

On retrospective analysis, prophylactic amiodarone given to infants undergoing primary repair of TOF was associated with a substantial reduction in the rate of postoperative JET. It is hoped that this observation will lead to further prospective evaluation of the concept of arrhythmia prophylaxis with studies of dosage, timing, duration, and extension into other populations.

Limitations to the study are inherent to the retrospective nature of data retrieval. Future randomized and blinded study will strengthen the effect of prophylactic amiodarone on postoperative JET after TOF repair. Because of the small size of each cohort, we are unable to show any difference in the postoperative courses.

CONCLUSIONS

Prophylactic amiodarone started during rewarming is well tolerated and significantly decreases the incidence of postoperative JET after TOF repair. Application of this preemptive treatment does not cause any apparent adverse events.

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