فعالية استخدام البروبرانولول قبل الجراحة في الوقاية من تسرع القلب الوصلي المنتبذ بعد الإصلاح الجراحي الكامل لرباعي فاللو

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الملخص

خلفية البحث وهدفه: يعتبر تسرع القلب الوصلي المنتبذ من اللانظميات الشائعة والتي تؤدي إلى تدهور هيموديناميكي بعد الإصلاح الجراحي الكامل لرباعي فاللو. على الرغم من استعمال البروبرانولول في هؤلاء المرضى للوقاية وتدبير نوب الزرقة، فإن تأثيراته المضادة لاضطرابات النظم لم تدرس بشكل واسع في فترة بعد الاصلاح الجراحي. لقد قمنا بإجراء هذه الدراسة لدراسة التأثيرات الوقائية الممكنة للبروبرانولول في منع حدوث تسرع القلب الوصلي المنتبذ بعد الإصلاح الجراحي لرباعي فاللو.

مواد البحث وطرائقه: تم إجراء هذه الدراسة المستقبلية في وحدة عناية جراحة القلب عند الأطفال في مشفى الأطفال الجامعي وشملت 124 مريض من المرضى الذين أجري لهم إصلاح جراحي كامل لرباعي فاللو. تم تقسيم المرضى في مجموعتين: مجموعة البروبرانولول وتضم المرضى الذين تلقوا علاج بالبروبرانولول قبل الجراحة (71 مريض) ومجموعة المراقبة وتضم المرضى الذين لم يتلقوا علاج بالبروبرانولول قبل الجراحة (53 مريض)

النتائج : كان معدل حدوث نوب الزرقة أعلى في مجموعة البروبرانولول مقارنة مع مجموعة المقارنة وكانت قيمة p=0.005، وكان معدل الوقوع الإجمالي لتسرع القلب الوصلي المنتبذ في دراستنا 16.9%، حيث كان معدل حدوثه في مجموعة البروبرانولول 8.5% مقارنة مع 28.3% في مجموعة المقارنة وقيمة p=0.004. الحاجة للمقويات القلبية بجرعات عالية كانت أقل في مجموعة البروبرانولول وقيمة p=0.028. كان معدل الوفيات أعلى عند مرضى تسرع القلب الوصلي المنتبذ (10 وفيات في مرضى التسرع الوصلي المنتبذ 47.6% مقابل 10 وفيات عند بقية المرضى 9.7%) وكان هذا الفارق هام إحصائياً p=0.0001 .

الاستنتاج : إن الاستخدام الوقائي للبروبرانولول ترافق مع انخفاض معدل حدوث تسرع القلب الوصلي المنتبذ بعد الإصلاح الجراحي الكامل لرباعي فاللو عند الأطفال.

كلمات المفتاحية: تسرع قلب وصلي منتبذ، رباعي فاللو، بروبرانولول، أطفال

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Efficacy of Preoperative Propranolol in Preventing Junctional Ectopic Tachycardia after Complete Repair of Tetralogy of Fallot

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Abstract

Background and Objective: Junctional ectopic tachycardia (JET) is a common arrhythmia causing hemodynamic impairment following tetralogy of Fallot (TOF) complete repair. Although propranolol is used in these patients to prevent and control hypercyanotic spells, its antiarrhythmic effects are not widely studied in the postoperative period. We undertook this study to examine possible preventive effects of propranolol on postoperative JET after complete surgical repair of TOF.

Materials and Methods: This is a prospective study conducted in the pediatric cardiac intensive care unit (PCICU) at University Children's Hospital, and was carried out on 124 patients who had complete repair of tetralogy of Fallot. Patients were classified into two groups: the propranolol group (*71*patients) who received propranolol preoperatively, and the control group (*53* patients) who did not receive propranolol preoperatively.

Results: Incidence of cyanotic spells was higher in the propranolol group compared to the control group (p value=0.005). The overall incidence of JET in our study was 16.9%, where the incidence of postoperative JET was 8.5% in the propranolol group and 28.3% in the control group (*P* value=0.004). High inotropic requirements were lower in the propranolol group (p value=0.028). The mortality rate was higher in JET patients (10 deaths in JET patients 47.6% vs. 10 deaths in the other patients 9.7%) which was a statistically significant difference (*P* value=0.0001).

Conclusions: Prophylactic use of propranolol is associated with a significantly decreased incidence of postoperative junctional ectopic tachycardia in children after complete surgical repair of TOF.

Keywords: Junctional ectopic tachycardia, Tetralogy of Fallot, Propranolol, children.

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Introduction:

Postoperative junctional ectopic tachycardia (JET) is the most common tachyarrhythmia after congenital cardiac surgery and is usually seen during early postoperative care with incidence rates ranging from 2%–11.2% of children undergoing cardiac surgery [1]. Although the exact mechanism of JET is still unclear, it can be related to direct trauma, ischemic, or stretch injury to the AV conduction tissues during excision of muscle bundles in right ventricular outflow tract obstruction and closing VSD as in case of complete repair of TOF and other surgical repairs of congenital heart defects [2,3]. The risk factors associated with an increased incidence of early postoperative JET in children and neonates include young age, low body weight, long cardiopulmonary bypass (CPB) time, aortic cross-clamp (ACC) time, high postoperative inotropes, and electrolyte imbalance [4]. Junctional ectopic tachycardia is defined as a narrow QRS tachycardia with a rate of _170/min, often with an atrioventricular (AV) dissociation resulting in the ventricular rate exceeding the atrial rate or with 1:1 retrograde ventriculoatrial conduction [5]. Junctional ectopic tachycardia (JET) after pediatric heart surgery is a malignant arrhythmia that not only rapidly and drastically deteriorates patient hemodynamics but is often resistant to conventional medications, resulting in high morbidity and mortality [6]. Treatment of postoperative JET usually includes Minimizing inotropes if possible, mild hypothermia, correcting electrolytes disturbance, optimizing analgesia and sedation, atrial cardiac pacing, and antiarrhythmic drugs [7,8]. The first line of pharmacologic treatment of JET is intravenous amiodarone and should be given when the patient is hemodynamically unstable [9]. several studies assessed the effect of some pharmacologic agents like dexmedetomidine, amiodarone, and propranolol on preoperative prophylaxis for JET [10,11].

Propranolol is a frequent beta-blocker medication used in patients with TOF for prophylaxis and management of hypercyanotic spells. The effectiveness of propranolol is apparently due to its efficacy in reducing the spasm of the right ventricular infundibulum. However, there is little information regarding the relationship between preoperative use of propranolol and the incidence of postoperative JET. The objectives of this study are to identify the incidence and mortality rates of JET and to assess the efficacy of using prophylactic preoperative propranolol in preventing early postoperative JET in children undergoing total repair of tetralogy of Fallot.

Materials and Methods:

This is a prospective study conducted in the pediatric cardiac intensive care unit (PCICU) at University Children's Hospital and was carried out on 124 patients who had complete repair of Tetralogy of Fallot at Cardiothoracic Unit of children hospital between November 2018 and August 2020.

Approval was obtained from the institutional ethics committee of the hospital. Informed consent was obtained from the parents of the participating children.

Inclusion criteria were children aged less than 13 years who underwent complete repair of tetralogy of Fallot. Exclusion criteria were a history of preoperative arrhythmias. Patients with incomplete data regarding the preoperative dose of propranolol and who underwent surgery with warm blood cardioplegia were also excluded.

Patients were classified into two groups: the propranolol group (*71*patients) who received propranolol preoperatively, and the control group (*53* patients) who did not receive propranolol preoperatively. In the propranolol group, the dose of propranolol was reported as 1 mg/kg/day, and the last dose was administered on the day of surgery. In addition, all children of the propranolol group were taking the propranolol for different periods before surgery, and we didn’t give propranolol as a single dose before surgery for any children in this study.

Surgery during these two years was performed by the same surgeons with similar techniques and under standard CPB conditions with cold blood

cardioplegia. In all cases, VSD closure was performed by either a transatrial –transpulmonary or a transventricular approach. A commissurotomy or valvulotomy with Hegar dilation was performed in patients with valvular-PS. Complete infundibular muscle resection was performed and 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 a transannular patch was used, using autologous pericardium or polytetrafluoroethylene as patch material.

Hospital medical records were reviewed to abstract the relevant clinical variables from the index hospitalization, including demographics. The preoperative history included oxygen saturation on admission, the incidence of cyanotic spells and the history of administrating prophylactic propranolol before surgery or not. Parents of patients who appeared to meet the inclusion criteria were approached in the cardiac intensive care unit (in the immediate postoperative period), and informed consent was obtained. At the same time, the past medical history had been verified through parents.

Data collection was done in the operative room (OR) and the pediatric cardiac intensive care unit (PCICU) with the help of Drager – Infinity Delta Kappa, which provides a facility to record the events. Perioperative data collection started at the time of surgery and occurred daily. From the operative procedure, we collected the following times: cardiopulmonary bypass (CPB) and aortic cross-clamp (ACC). Postoperative intensive care data included the occurrence of JET, use inotropic support, and incidence of deaths. In our study, high doses of inotropic agents administered in the ICU were considered when the dose was greater than 0.5mcg/kg/min for epinephrine and norepinephrine, and 10 mcg/kg/min for dopamine and dobutamine. Continuous ECG monitoring was used continuously in the intensive care unit (ICU) with Drager monitors. 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. 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. Some patients with postoperative bundle branch block had JET with wide complex tachycardia.

When the 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, and amiodarone. Amiodarone was started 5mg/kg as a bolus dose over 1 hour followed by continuous amiodarone infusion 5 μcg /kg/min till sinus rhythm was established or the heart rate slowed to an acceptable rate with stable hemodynamic. If an acceptable response was not observed, the bolus was repeated up to a maximum dose of 15 mg/kg. After stabilization, the treatment of amiodarone was continued and weaned over 3 to 5 days.

The primary outcomes were to assess the effectiveness and advantage of using prophylactic preoperative propranolol on the incidence of JET during the postoperatively period in the ICU, while the secondary outcomes were to assess the incidence of JET and its mortality rates.

Statistical Analysis:

Descriptive statistics were calculated as frequency counts and percentages for categorical variables and median with interquartile range (IQR) for continuous variables. Two-sample t-test or Mann-Whitney test was used to compare continuous variables and chi-squared test to compare categorical variables between the propranolol group and the control group. $P<0.05$ was considered statistically significant. All analyses were performed using SPSS 26 software (IBM SPSS Statistics for Windows, Version 26.0. Armonk, NY: IBM Corp).

Results:

During this study, one hundred and twenty-four (124) infants and children who underwent

complete repair of tetralogy of Fallot were included in this study. Patient demographic characteristics were comparable between two groups of patients and recorded in Table 1. The median age at operation was 2 years (IQR: 1.22-3.65 years) without any statistically significant difference between the two groups (p value=0.7). Incidence of cyanotic spells was higher in the propranolol group compared to the control group which was statistically significant (p value=0.005).

Operative data were summarized in Table 2. There was no significant difference between the propranolol and the control group regarding aortic cross-clamp time (p value=0.26), the lowest temperature on CPB (p value=0.68), and transannular patch performance (p-value =0.26). Cardiopulmonary bypass time was longer in the propranolol group than in the control group but the difference was not statistically significant (p value=0.36).

Table (1): Preoperative patient demographics data

Variable	Propranolol group n=71	Control group n=53	Total n=124	P
Male sex	43 (60.6%)	37 (69.8%)	80 (64.5%)	0.19
Age (years) (median, IQR)	2, 1.3-3.5	2.2, 1.2-4.75	2, 1.22-3.65	0.7
Weight (kg) (median, IQR)	10, 8.5-14	11, 8.5-16.5	11, 8.5-15	0.81
BSA (m2) (median, IQR)	0.47, 0.42-0.61	0.49, 0.40-0.66	0.49, 0.42-0.61	0.72
SPO2% (median, IQR)	85, 80-90	82, 76-90	84, 78-90	0.27
Preoperative cyanotic spells	52 (73.2%)	26 (49.1%)	78 (62.9%)	0.005
BSA: Body Surface Area, IQR: Interqurtile range				

Table (2): Operative data

Variables	Propranolol group n=71	Control group n=53	Total N=124	P
CPB time (minutes) (Median ,IQR)	100, 83-130	88, 75.5-125	97, 80-129	0.36
ACC time (minutes) (Median ,IQR)	73, 61-98	69, 59-91.5	72, 59-95	0.26
Lowest temperature on CPB (°C) (Median ,IQR)	31, 28-33	30, 28-32	31, 28-32	0.68
TAP	13 (18.3%)	13 (24.5%)	26 (21%)	0.26
CPB: Cardiopulmonary bypass; ACC: Aortic Cross Clamp time; PA: Pulmonary atresia; JET: Junctional ectopic tachycardia; TAP: Transannular Patch				

Postoperative data were reported in Table 3. The overall incidence of JET in our study was 16.9%. It was documented in 21 patients out of 124 patients after surgery. The incidence of postoperative JET was 8.5% in the propranolol group vs 28.3% in the control group, which was a statistically significant difference (*P* value=0.004). High Inotropic Requirements were lower in the propranolol group vs the control group, and this difference between the two groups was statistically significant (p value=0.028). Three patients out of the propranolol group developed complete heart block after surgery without a significant difference between the two groups (p value=0.18).

There were 20 deaths in this study (overall mortality rate was 16.1%). The mortality rate was

higher in JET patients (10 deaths in JET patients 47.6% vs. 10 deaths in the other patients 9.7%) which was a statistically significant difference (*P* value=0.0001). Nevertheless, there was no significant difference concerning the mortality rate between patients in the propranolol group compared to the control group (p value=0.31). Furthermore, Mechanical ventilation time (in hours), and duration of intensive care unit stay (in days) was slightly lower in the propranolol group compared to the control group (P-value was 0.89, 0.19 respectively).

Table (3): postoperative data

Variable	Propranolol group n=71	Control group N=53	Total n=124	P
JET	6 (8.5%)	15 (28.3%)	21 (16.9%)	0.004
Mortality	10 (14.1%)	10 (18.1%)	20 (16.1%)	0.31
Complete heart block	3 (4.2%)	0 (0%)	3 (2.4%)	0.18
High Inotropic Requirements	18 (25.4%)	23 (43.4%)	41 (33.1%)	0.028
Mechanical Ventilation Time (hours) (Median ,IQR)	20, 7-46	20, 6-76	20, 6-48	0.89
Intensive Care Unit Stay(days) (Median ,IQR)	3, 2-4	3, 2-5.5	3, 2-4	0.19
Bleeding	5 (7%)	5 (9.4%)	10 (8.1%)	0.43
JET: Junctional Ectopic Tachycardia, IQR: Interqurtile range				

DISCUSSION:

JET is one of the most serious and life-threatening postoperative arrhythmias that is difficult to manage and can cause serious hemodynamic deterioration that is poorly tolerated after pediatric cardiac surgery. Prophylaxis of arrhythmia after pediatric cardiac surgery became the focus of many trials recently[8,10,12,13]. In our study, the incidence of JET was 16.9 % of all patients, which was lower than what found by Imamura et al, who detected postoperative JET in 28.6 % of patients (18 out of 63) [10], and lower than what found by Mahmoud et al, where the incidence of JET was 29% (32 patients out of 109)[9]. This difference in JET incidence could be attributed to the diagnostic criteria used and the wide variability in patients' characteristics especially age[14]. The major finding of our study was that prophylactic propranolol decreased the incidence of postoperative JET in pediatric patients undergoing TOF repair from 28.3% in the control group to 8.5% in the propranolol group, which was in agreement with the results of the previous studies[9,15,16]**.** Propranolol is a nonselective beta-adrenergic receptor blocking agent that is also used in the management of JET. It relieves the spasm of the infundibular muscle of RVOT. This property of propranolol helps in the prevention and treatment of TET spells. Nevertheless, the mechanism of the antiarrhythmic effect of propranolol has not been established. However, it may inhibit pacemaker potentials and decreases the frequency of spontaneous depolarization [17]. Pharmacokinetic studies of propranolol may explain the preventive mechanism of preoperative use of propranolol on the postoperative incidence of JET observed in our study. Preoperative propranolol pharmacokinetic

studies reported a biological half-life between 3.2 h and 5.2h[18].

However, the pharmacokinetics of propranolol may be altered by hypothermic cardiopulmonary bypass, where the plasma levels of propranolol decreased with the onset of CPB and then there was a sustained increase in plasma levels after CPB. This increased plasma level post CPB can have a protective effect on the incidence of JET. Hence, it can be conceived that the preoperative use of propranolol has a preventive role on

postoperative JET[18]. The effect of heparin administration on plasma protein binding is also of importance. Heparin administration results in lipoprotein lipase and hepatic lipase release, which in turn hydrolyze plasma triglycerides into non-esterified fatty acids which can lead to displacement of plasma protein-bound drugs such as propranolol and raises their concentrations[19]. Lung isolation from the circulation during CPB can cause sequestration of several drugs including propranolol, which may return back to circulation after re-establishment of the pulmonary circulation[20]. From the pharmacokinetic data of propranolol, we can assume that in the propranolol group due to the effect of hypothermic cardiopulmonary bypass, heparin administration, and lung sequestration might result in therapeutic serum level of propranolol in the postoperative period. This therapeutic level of propranolol might have been responsible for decreased incidence of postoperative JET. The overall mortality rate was 16.1%, which is very high compared to other studies (0-3%)[9,15,16]. This wide difference probably reflects statistical imprecision due to small sample sizes and to the difference in populations, study settings, and follow-up duration. Nevertheless, these results require further evaluation to determine the mortality risk factors and find ways to improve prophylactic measures in our center.

The incidence of JET was associated with a more than fivefold increase in mortality (47.6% vs. 9.7%) with a statistically significant difference (*P* value=0.0001). However, this result contradicts the previous study results, in which no statistically significant difference in mortality between the JET and non-Jet patients was found[9,15,16]. Furthermore, there were no significant differences between the two groups as regards the length of ICU admission and Mechanical ventilation time (P values were 0.19, 0.89 respectively), which were inconsistent with the results of earlier studies [9,16]. Another important observation from our study is that the propranolol group required lower doses of inotropes than the control group, which was statistically significant. This finding contradicts the previous reports [9,16].

Study Limitations:

This was a nonrandomized observational study. We cannot completely isolate the effect of inotropic support and cardiopulmonary bypass time on JET because sicker patients generally require longer cardiopulmonary bypass time and higher inotropic support in the postoperative period.

Atrial pacing wires are not routinely placed at our institution after surgery for congenital heart disease if no rhythm issue is apparent at the time of completion of surgical repair. Hence, the impact of pacing to optimize AV synchrony using temporary pacing wires in patients with JET could not be evaluated.

This study involves a relatively small number of patients. Also, we should have studied the duration of JET along with incidence rather than just incidence. Finally, we have not taken into consideration the duration and dosage of the preoperative use of propranolol in this study which is important.

Conclusion:

Junctional ectopic tachycardia is a frequent serious complication after Tetralogy of Fallot repair, which associated with a high mortality rate in our study. However, our findings suggest that the preoperative use of propranolol may have a potential benefit of preventing postoperative JET after complete surgical repair of TOF. A prospective randomized study may help to elucidate the exact relationship between the preoperative use of propranolol and the incidence of postoperative JET.

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