ORIGINAL ARTICLE

Predictors of acute neurological complication following tetralogy of Fallot operation in Serdang Hospital, Malaysia

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ABSTRACT

Background: The long waiting time for Tetralogy of Fallot (TOF) operation may potentially increase the risk of hypoxic insult. Therefore, the objective of this study is to determine the frequency of acute neurological complications following primary TOF repair and to identify the peri-operative risk factors and predictors for the neurological sequelae.

Methods: A retrospective review of the medical and surgical notes of 68 patients who underwent TOF repair in Hospital Serdang, from January 2013 to December 2017 was done. Univariate and multivariate analyses of demographics and perioperative clinical data were performed to determine the risk for the development of acute neurological complications (ANC) among these patients.

Results: ANC was reported in 13 cases (19.1%) with delirium being the most common manifestation (10/68, 14.7%), followed by seizures in 4 (5.9%) and abnormal movements in two patients (2.9%). Univariate analyses showed that the presence of right ventricular (RV) dysfunction, prolonged duration of inotropic support (≥7 days), prolonged duration of mechanical ventilation (≥7 days), longer length of ICU stays (≥7 days), and longer length of hospital stay (≥14 days), were significantly associated with the presence of ANCs (p<0.05). However, multivariate analyses did not show any significant association between these variables and the development of ANC (p>0.05). The predictors for the development of postoperative delirium were pre-operative oxygen saturation less than 75% (Odds Ratio, OR=16.90, 95% Confidence Interval, 95%CI:1.36, 209.71) and duration of ventilation of more than 7 days (OR=13.20, 95%CI: 1.20, 144.98).

Conclusion: ANC following TOF repair were significantly higher in patients with RV dysfunction, in those who required a longer duration of inotropic support, mechanical ventilation, ICU and hospital stay. Low pre-operative oxygen saturation and prolonged mechanical ventilation requirement were predictors for delirium which was the commonest neurological complications observed in this study. Hence, routine screening for delirium using an objective assessment tool should be performed on these high-risk patients to enable accurate diagnosis and early intervention to improve the overall outcome of TOF surgery in this country.

KEYWORDS:
Paediatrics, TOF repair, delirium, neurological complications, post-operative

INTRODUCTION

Tetralogy of Fallot (TOF) is the most common cyanotic congenital heart disease with an incidence of 3 per 10,000 live births.[1] Most of the TOF cases will require surgical repair in the early childhood period itself. With the advancement in anaesthesia and cardiopulmonary bypass (CPB) technology as well as better myocardial protection strategy in the past few decades, the surgical approach to cyanotic as well as acyanotic infants with TOF has evolved to the stage that primary corrective repair can be performed safely in all age groups with a very low surgical mortality rates of 0% to 2%.[2] However, along with this improvement in the mortality rates following cardiac surgery, the development of postoperative neurological sequelae is now increasingly being recognised and described.[3] The mechanisms and aetiologies involved in neurological injuries following cardiac surgery are multifactorial, which include cerebral ischemia during CPB, systemic inflammatory response toward surgery, perioperative insults, and iatrogenic factors related to postoperative paediatric cardiac intensive care unit (PCICU) management.[4,5] Brain injury manifestation depends on the extent of the insult, which ranged from stroke, seizure, or coma to transient neurocognitive impairment with or without long term cognitive deterioration.[4] Delirium is an acute brain dysfunction that was reported to affect as high as 49% of the children who had undergone cardiac bypass surgery.[5] Studies that report on the neurologic sequelae in children following cardiac surgery are scarce because careful, prospective neurologic and neuropsychological evaluations are rarely performed in these group of patients. In Malaysia, patients with TOF often have delays in their operation being performed where patients may develop frequent hypercyanotic spell or had lower preoperative oxygen saturation as the severity of the right ventricular outflow tract (RVOT) obstruction usually worsens with time. This may potentially increase their risk of developing hypoxic insult.

Therefore, the objective of this study was to determine the frequency of acute neurological complications (ANC) following TOF repair and to identify the perioperative risk factors and the predictors for these neurological sequelae.

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MATERIALS AND METHODS

Patients and Data Collection

This study involved a retrospective review of the clinical records of all patients who underwent TOF repair from January 2013 to December 2017, at Hospital Serdang, Selangor, Malaysia. This established cardiac referral centre has been providing complex congenital heart surgeries service under the Ministry of Health of Malaysia since mid-2012. The paediatric cardiac service is run by a paediatric cardiothoracic surgeon, six paediatric cardiologists, a paediatric intensivist, a team of cardiac anaesthetists with the maximum capacity of 10 paediatric intensive care unit (PICU) beds, equipped with extracorporeal membrane oxygenation (ECMO) facilities.

A total of 68 patients were identified over the five years period from the Hospital Serdang database after excluding cases of TOF with pulmonary atresia, TOF with the absent pulmonary valve syndrome and patient age of more than 18 years. Institutional review board and ethics committee approval for the study was obtained prior to the commencement of the study.

The data were collected on a structured pro forma and included demographic information (age, gender, gestation), clinical parameters (oxygen saturation, haematocrit and haemoglobin levels), intraoperative data including the duration of CPB and aortic cross-clamp (ACC) and postoperative data such as highest lactate concentration, lowest pH level, cardiac complications, duration of inotropic support, vasoactive-inotropic score (VIS) which was calculated as described by Davidson et al.,[6] duration of mechanical ventilation, length of intensive care unit (ICU) and hospital stay as well as mortality rates. The diagnosis of RV dysfunction was based on clinical assessment (low cardiac output, high central venous pressure, and hepatomegaly) with echocardiographic qualitative evidence of impaired RV contractility. VIS that was calculated was based on the highest dosage for each inotrope used during the immediate post-operative period. Data on the development of ANC was based on a description from the medical notes as this study was retrospective in nature. Impairment in at least one executive function from the following categories, which included cognition, perception, thought, language, emotion, and psychomotor disturbances was needed to establish the diagnosis of delirium.[7] The presence of an altered mental state and the carer's/parent assessment of the patient's personality or behaviour and developmental regression/stasis were also considered as part of the diagnostic criteria. Abnormal movements were defined as any unwanted excess movement, which included chorea, athetosis, dystonia, and tremors.[8]

Statistical Analysis

Data were entered and analysed using Statistical Package for the Social Sciences (SPSS) version 25.0. For descriptive statistics, categorical data were presented as frequencies (%), and its association with the presence of acute neurological complications (ANC) was analysed using Chi-Square or Fisher Exact test. Continuous data with a Gaussian distribution was presented as mean (standard deviation) while data with non-Gaussian distribution were presented as median (interquartile range). Independent t-test was used to analyse continuous data while the Mann Whitney U test was used for continuous variables if it was not normally distributed. Univariate regression analysis was initially performed using selected demographic and perioperative data. Variables that had a p-value <0.05 were then entered into the multivariate regression analysis to determine the odds ratios (ORs) and 95% confidence intervals (CI) of the predictors of postoperative neurological complications following TOF repair. The significance level was set at $p<0.05$. The dependent variable was the presence of neurological complications.

RESULTS

Demographic and Clinical Characteristics

Of the 68 patients who had undergone TOF repair, 41 were males (60.3%) and 27 females (39.7%) with a median age of TOF repair at 26.5 months (interquartile range, IQR of 13 months). 11 patients (16.2%) were born preterm (before 37 weeks of gestation). Prior to corrective TOF repair, a total of eight patients (12%) had undergone palliative procedures due to severe hypoxaemia (RVOT stenting in four and Blalock-Taussig shunt in another four). Seven patients (10.3%) in our study group had Down syndrome, while 13 patients (19.1%) had developmental delay. Echocardiographic findings of the patients demonstrated a median Mc Goon index of 1.8 (IQR of 0.4). The mean level of preoperative oxygen saturation was 83.7 % (standard deviation, SD±7.3%) Preoperative haemoglobin status revealed a mean haemoglobin level of 17.1 g/dl (SD±3.5g/dl) and a median haematocrit level of 50.7% (IQR of 16.1%). The median duration of CBP surgery was 176 minutes (IQR of 32 minutes) and the mean aortic cross-clamp time was 121.8 minutes (SD±24.1 minutes). Postoperatively, the highest lactate concentration recorded in our patients showed a mean level of 3.7mmol/L (SD±1.5), and the lowest pH monitoring recorded a median of 7.32 (IQR of 0.08). Majority of the patients (43, 63.2%) developed the low cardiac output syndrome (LCOS) in the immediate postoperative period. RV dysfunction and junctional ectopic tachycardia (JET) occurred in 35 (51.5%) and 22 (32.4%) of the cases, respectively. Extracorporeal membrane oxygenation (ECMO) support was used in seven cases with severe LCOS. Inotropic score (IS) and VIS were recorded at a median score of 20 and 40, respectively. The demographic and perioperative clinical data are presented in Table I comparing patients who developed ANC to those who did not.

Frequency of acute neurological complications

Thirteen patients (19.1%) developed ANC following TOF repair. The frequency and type of ANC are presented in Table II. A total of 13 patients were affected either by a single ANC or combination of two ANCs. Postoperative encephalopathy (delirium) was the most frequent ANC, observed in 10 cases (14.7%) followed by seizure in four (5.9%) and abnormal movements in two patients (2.9%). All the seizures observed in our study were generalised seizures, three of these patients requiring anti-epileptic drugs (AED) with two of them receiving single AED. The only patient who received multiple AEDs, namely diazepam, and phenytoin, was intubated in view of having status epilepticus. Aside from seizure, this patient also presented with abnormal movements (that lasted for 5 days), specifically intermittent jerky movements

Table I: Patient demographics and peri-operative clinical data

Variables	Total patients n= 68	Patients with ANC n= 13	Patients without ANC n= 55	p-value
Sociodemographic and preoperative data				
Age at TOF repair (months)	26.5 (13)	28 (15)	26 (13)	0.894
Gender				
Male, n(%)	41 (60.3)	7 (53.8)	34 (61.8)	0.597
Female, n(%)	27(39.7)	6 (46.2)	21 (38.2)	
Gestation (n=67)				
Preterm	11 (16.2)	2 (15.4)	9 (16.7)	1.000
Term	56 (82.4)	11 (84.6)	45 (83.3)	
Developmental status				
No delay	55 (80.9)	8 (61.5)	47 (85.5)	0.109
Delayed	13 (19.1)	5 (38.5)	8 (14.5)	
Down syndrome				
Yes	7 (10.3)	0 (0.0)	7 (12.7)	0.331
No	61 (80.9)	13 (100.0)	48 (87.3)	
Preoperative haematocrit (%)	50.7 (16.1)	50.2 (17.2)	52.0 (15.4)	0.749
Preoperative haemoglobin (g/dl)*	17.1 (3.5)	16.7 (4.0)	17.2 (3.4)	0.630
Preoperative oxygen saturation (%) *	83.7 (7.3)	82.5 (8.1)	83.9 (7.1)	0.519
Mc Goon Index	1.8 (0.4)	1.8 (0.5)	1.8 (0.5)	0.974
Intraoperative and postoperative data				
CPB time (min)	176 (32)	174 (53)	178 (33)	0.938
ACC time (min)*	121.8 (24.1)	127.3(23.1)	120.7 (24.5)	0.457
Minimal postoperative pH	7.32 (0.08)	7.31 (0.04)	7.33 (0.08)	0.110
Highest postoperative lactate*	3.9 (1.5)	3.8 (1.0)	3.9 (1.6)	0.814
Presence of Bleeding				
Yes	35 (51.5)	6 (46.2)	27 (49.1)	0.849
No	33 (48.5)	7 (53.8)	28 (50.9)	
LCOS				
Yes	43 (63.2)	9 (69.2)	9 (69.2)	0.754
No	25 (36.8)	4 (30.8)	21 (38.2)	
Right ventricular dysfunction				
Yes	35 (51.5)	11 (84.6)	24 (43.6)	**0.008**
No	33 (48.5)	2 (15.4)	31 (56.4)	
JET				
Yes	22 (32.4)	6 (46.2)	16 (29.1)	0.324
No	46 (67.6)	7 (53.8)	39 (70.9)	
ECMO use				
Yes	7 (10.3)	2 (15.4)	5 (9.1)	0.611
No	61 (89.7)	11 (84.6)	50 (90.9)	
Inotropic score	20 (21.6)	30 (31.3)	15.5 (20.0)	0.107
Vasoactive inotropic score	40 (42.5)	67.5 (50.5)	37.5(26)	0.145
Duration of inotropic support (day)	6 (6)	7 (4)	5 (5)	**0.018**
Length of ICU stay (day)	8 (8)	15 (8)	7 (6)	**0.002**
Duration of mechanical ventilation (day)	5 (6)	9 (6)	4 (6)	**0.003**
Length of hospital stay (day)	13 (9)	20 (13)	12 (6)	**<0.001**
Mortality				
Alive	64 (94.1)	13 (100)	51 (92.7)	1.000
Dead	4 (5.9)	0	4 (7.3)	

*Abbreviation: ANC = acute neurological complications, CPB – cardiopulmonary bypass, ACC = aortic cross-clamp, LCOS = low cardiac output syndrome, JET = junctional ectopic tachycardia, ECMO = extracorporeal membrane oxygenation, ICU = intensive care unit

*Categorical data were presented as frequency (percentage). All continuous data was presented as median (interquartile range) except preoperative haemoglobin, preoperative oxygen saturation, aortic cross clamp time and highest postoperative lactate.

Table II: Frequency of acute neurological complications (n=13)

Neurological complications	Frequency n (%)
Single ANC observed	
Delirium/ Postoperative encephalopathy	7 (10.3)
Clinical seizures	2 (2.9)
Abnormal movements/ choreoathethosis	1 (1.5)
Multiple ANC observed	
Delirium with abnormal movement	2 (2.9)
Delirium with clinical seizure	1 (1.5)
Clinical seizure with abnormal movement	1 (1.5)

*Abbreviation: ANC = acute neurological complications

Table III: Spectrum of postoperative delirium (n=10)

Spectrum of postoperative delirium	Frequency
Main Features	
Change in personality or behaviour (e.g., Less communicative with parents/surrounding)	7
Deterioration in cognitive functioning (e.g., Inattentiveness)	4
Alteration in conscious level	2
Disturbance in circadian rhythm	0
Impairment in perception	0
Others	
Developmental regression/stasis [statomotoric development]	1
Visual disturbances	7
Blank stare	5
Upward gaze	2
Neurological signs	7
Difficulties with sucking and swallowing/dysphagia	1
Weakness of 4 limbs/ paraparesis	1
Hypertonia	1
Hyperreflexia	4

of both lower limbs with repeated lip-smacking but no abnormal eye movements or loss of consciousness. He was also sent for a computed tomography (CT) scan of the brain, but no abnormality was detected. In all four patients with seizures, there was no recurrence of seizure during this hospitalisation. One patient had both delirium and the presence of abnormal movements. The abnormal movements in this patient lasted for two days and comprised of oral dyskinesia, repeated pouting of lips, and stereotypic movements of both thumbs.

The clinical features of postoperative encephalopathy (delirium) is summarised in Table III. It was the most common neurological complication observed following TOF repair in our study group and had a median duration of seven days (range 3 to 33 days). Changes in personality and behaviour (70%) were the most frequent complaint noted from the caregivers/parents. For instance, these patients were less interactive with their parents and surroundings. Another unusual feature that was observed in half of these patients was a blank stare. Besides that, 40% of the patients presented with deterioration in cognitive functioning whereby they were unable to maintain their focus and attention. Altered consciousness level was also seen in another two cases. All these patients had self-limiting delirium that resolved before discharge.

Two magnetic resonance imaging (MRI) and two CT scans of the brain were done in patients with significant neurological complications. Findings of intracranial bleeding was detected in two patients and both these cases were referred to the neurosurgical team which opted for conservative management. One patient with a finding of cerebral atrophy on MRI which was performed at two weeks after the operation had persisting weakness of all four limbs and difficulties with sucking and swallowing. Preoperatively, this patient had delayed milestones, especially in gross motor development, that may suggest cerebral atrophy may already present before the surgery. The neurological deficit of this patient back to preoperative state during the follow-up review, which was two weeks after hospital discharge. There was no brain imaging done in the remaining patients as there was no evidence of neurological deficit and any symptoms that were present, had rapid improvement.

Perioperative Risk Factors and the Predictors for Acute Neurological Complication (ANC)

Compared to patient without neurological complication, patients with ANC had more right ventricular dysfunction (11(84%) vs. 24(43.6%), p=0.008), requiring longer duration of inotropic support (median 7 days IQR of 4 days vs. 5 days IQR of 5 days, p=0.018)), longer duration for mechanical ventilation (median 9 days vs. 4 days, IQR of 6 days for both; p=0.003), longer ICU (median 15 days IQR of 8 days vs. 7 days IQR of 6 days, p=0.002) and hospital stay (median 20 days IQR of 13 days vs. 12 days, IQR of 6 days, p<0.001) (Table I). A total of four deaths (5.9%) following primary repair occurred during our study period.

Table IV shows the result of univariate and multivariate logistic regression analysis comparing the values of captured variables to determine the predictor for the development of ANC. In univariate analysis, we found that the presence of RV dysfunction, prolonged duration of inotropic support (≥7 days), prolonged duration of mechanical ventilation (≥7 days), longer length of ICU stays (≥7 days) and longer length of hospital stay (≥14 days) were significantly associated with the presence of neurological deficit (p<0.05). However, multivariate analyses did not show any significant association between these variables and the development of ANC (p>0.05).

Another analysis was performed to identify possible predictors for the commonest ANC found in our study namely postoperative delirium and the findings are presented in Table V. In univariate analysis, we found that low baseline oxygen saturation (<75%), prolonged duration of inotropic support (≥7 days), ICU stay (≥7 days) and mechanical ventilation (≥7 days) were significantly associated with the presence of neurological deficit (p<0.05). Multivariate analyses noted that prolonged ventilation (≥7 days, OR=13.20, 95%CI: 1.20, 144.98) and low baseline oxygen saturation (<75%, OR=16.90, 95%CI: 1.36, 209.71) were the predictors for the development of postoperative delirium.

DISCUSSION

The overall incidence of acute neurological complications following primary TOF repair was 19.1% with postoperative

Table VI: Predictors of acute neurological complications (ANC) (N=68)

Variable	ANC		Univariate analysis			Multivariate analysis		
	Yes	No	OR	95%CI	p-value	OR	95%CI	p-value
Demographic and preoperative data								
Age at TOF repair								
<24 months	6 (22.2)	21 (77.8)	1.00					
≥24 months	7 (17.1)	34 (82.9)	0.72	0.21-2.44	0.598			
Developmental status								
No delay	8 (14.5)	47 (85.5)	1.00					
Delay	5 (38.5)	8 (61.5)	3.63	0.96-14.10	0.058			
Preoperative haematocrit								
<45	4 (25.0)	12 (75.0)	1.43	0.35-5.79	0.617			
45.00-49.99	2 (13.3)	13 (86.7)	0.66	0.12-3.61	0.631			
≥50	7 (18.9)	30 (81.1)	1.00					
Preoperative haemoglobin								
<12	2 (50.0)	2 (50.5)	4.29	0.51-35.91	0.180			
12.00-17.99	8 (20.0)	32 (80.0)	0.75	0.20-2.86	0.668			
≥18	3 (12.5)	21 (87.5)	1.00					
Preoperative oxygen saturation								
<75%	3 (42.9)	4 (57.1)	3.83	0.74-17.83	0.110			
≥75%	10(16.4)	51 (83.6)	1.00					
Mc Goon Index(n=66)								
<2	9 (19.6)	37 (81.4)	0.97	0.26-3.63	0.967			
≥2	4 (20.0)	16 (80.0)	1.00					
Intraoperative and postoperative data								
CPB (n=51)								
<3 hours	5 (18.5)	22 (81.5)	1.00					
≥3 hours	3 (12.5)	21 (87.5)	0.63	0.13-2.97	0.557			
ACC (n=53)								
<2 hours	4 (18.2)	18 (81.8)	1.00					
≥2 hours	5 (16.1)	26 (83.9)	0.87	0.20-3.67	0.845			
Lowest postoperative pH (n=66)								
<7.35	11(25.0)	33 (75.0)	3.33	0.67-16.61	0.142			
≥7.35	2 (9.1)	20(90.9)	1.00					
Highest postoperative lactate (n=67)								
<4	8 (20.5)	31 (79.5)	1.00					
≥4	5 (17.9)	23 (82.1)	0.84	0.24-2.91	0.786			
LCOS								
Yes	9 (20.9)	34 (79.1)	1.39	0.38-5.09	0.619			
No	4 (16.0)	21(84.0)	1.00					
ECMO use								
Yes	2 (28.6)	5 (71.4)	1.81	0.31-10.62	0.507			
No	11(18.0)	50 (82.0)	1.00					
VIS								
<40	3 (9.1)	30 (90.9)	1.00	0.99-16.14	0.051			
≥40	10(28.6)	25 (71.4)	4.00					
Duration of inotropic support								
<7 days	3 (7.5)	37 (92.5)	1.00			1.00		
≥7 days	10(35.7)	18(64.3)	6.85	1.67-28.00	**0.007**	3.10	0.098-99.70	0.521
Duration of mechanical ventilation								
<7 days	3 (7.3)	38 (92.7)	1.00			1.00		
≥7 days	10(37.0)	17 (63.0)	7.54	1.82-30.56	**0.005**	0.87	0.18-102.61	0.936
Right ventricular dysfunction								
Yes	11(31.4)	24(68.6)	7.10	1.44-35.12	**0.016**	2.62	0.42-16.32	0.302
No	2(6.1)	31(93.9)	1.00			1.00		
Length of hospital stay								
<14 days	2(5.3)	36(94.7)	1.00			1.00		
≥14 days	11(36.7)	19(63.3)	10.42	2.09-51.92	**0.004**	5.55	0.78-39.64	0.088
Length of ICU stay								
<7 days	1(4.2)	23(95.8)	1.00			1.00		
≥7 days	12(27.3)	32(72.7)	8.63	1.05-71.08	0.045	0.89	0.052-15.30	0.936

*Abbreviation: TOF = tetralogy of Fallot, OD = odds ratio, CI = confidence interval, CPB = cardiopulmonary bypass, ACC = aortic cross clamp, LCOS = low cardiac output syndrome, ECMO = extracorporeal membrane oxygenation, VIS = vasoactive inotropic score

Table V: Predictors of postoperative delirium

Variable	Postoperative delirium		Univariate analysis			Multivariate analysis		
	Yes	No	OR	95%CI	P value	OR	95%CI	P value
Demographic and preoperative data								
Age at TOF repair								
<24 months	4 (5.9)	23 (33.8)	1.00					
≥24 months	6 (8.8)	35 (51.5)	0.97	0.25-3.90	0.984			
Developmental status								
No delay	6 (8.8)	49 (72.1)	1.00					
Delay	4 (5.9)	9 (13.2)	3.63	0.85-15.49	0.082			
Preoperative haematocrit								
<45	3 (4.4)	13 (19.1)	1.19	0.26-5.51	0.822			
45.00-49.99	1 (1.5)	14 (20.6)	0.37	0.04-3.36	0.376			
≥50	6 (8.8)	31 (45.6)	1.00					
Preoperative haemoglobin								
<12	1 (1.5)	3 (4.4)	2.33	0.18-30.37	0.518			
12.00-17.99	6 (8.8)	34 (50.0)	1.24	0.28-5.48	0.781			
≥18	3 (4.4)	21 (30.9)	1.00					
Preoperative oxygen saturation								
<75%	3 (4.4)	4 (5.9)	5.79	1.07-31.40	**0.042**	16.90	1.36 -209.71	**0.028**
≥75%	7 (10.3)	54 (79.4)	1.00					
Mc Goon Index								
<2	7 (10.6)	39 (59.1)	1.02	0.23-4.41	0.982			
≥2	3 (4.5)	17 (25.8)	1.00					
Intraoperative and postoperative data								
CPB								
<3 hours	4 (7.8)	23 (45.1)	1.00					
≥3 hours	3 (5.9)	21 (41.2)	0.82	0.16-4.11	0.811			
ACC								
<2 hours	4 (7.5)	18 (34.0)	1.00					
≥2 hours	4 (7.5)	27 (50.9)	0.67	0.15-3.01	0.598			
Lowest postoperative pH								
<7.35	9 (13.6)	35 (53.0)	5.40					
≥7.35	1 (1.5)	21 (31.8)	1.00	0.64-45.70	0.122			
Highest postoperative lactate								
<4	5 (7.5)	34 (50.7)	1.00					
≥4	5 (7.5)	23 (34.3)	1.48	0.38-5.70	0.570			
LCOS								
Yes	7 (10.3)	36 (52.9)	1.43	0.33-6.10	0.632			
No	3 (4.4)	22 (32.4)	1.00					
ECMO use								
Yes	2 (2.9)	5 (7.4)	2.65	0.44-16.04	0.289			
No	8 (11.8)	53 (77.9)	1.00					
VIS								
<40	2 (3.1)	31 (47.7)	1.00					
≥40	8 (12.3)	24 (36.9)	5.17	1.01-26.60	**0.049**	2.02	0.25-16.25	0.508
Duration of inotropic support								
<7 days	2 (2.9)	38 (55.9)	1.00					
≥7 days	8 (11.8)	20 (29.4)	7.60	1.47-39.23	**0.015**			
Duration of mechanical ventilation								
<7 days	2 (2.9)	39 (57.4)	1.00					
≥7 days	8 (11.8)	19 (27.9)	8.21	1.59-42.48	**0.012**	13.20	1.20- 144.98	0.035

*Abbreviation: TOF = tetralogy of Fallot, OD = odds ratio, 95%CI = confidence interval, CPB = cardiopulmonary bypass, ACC = aortic cross clamp, LCOS = low cardiac output syndrome, ECMO = extracorporeal membrane oxygenation, VIS = vasoactive inotropic score

delirium being the most frequent complication observed in our study at a rate of 14.7%. It was considerably lower than the earlier study done by Anita et al., which reported that nearly 1 in 2 children developed delirium after cardiac bypass surgery. Our study population, that included only TOF patients, may have contributed to this disparity. Another significant difference found between our study and other similar studies was the utilisation of Cornell Assessment of Paediatrics Delirium (CAPD) as an assessment tool to diagnose delirium. The paediatric intensive care unit in our centre do not routinely screen for delirium, and the diagnosis of delirium was made on clinical description without the aid of a standard tool. The incidence of delirium may be, therefore under-estimated and under-recognised in the absence of an appropriate objective test. Nevertheless, our result was consistent with the 10-30% delirium rates as observed in the general population in critically ill children in many other previous studies.[5,9,10]

The criteria for the diagnosis of paediatric delirium depends on the presence of disturbances in one or more of the five categories of executive functions: behaviour, circadian

rhythm, cognition and mood, consciousness, and perception.[11] In our study, we reported that disturbances in both personality (70%) and cognition (40%) were the most common criteria used to aid in diagnosing paediatric delirium in this cohort of patients. Most of the delirium cases were transient and resolved rapidly, with a median duration of 7 days. The occurrence of delirium was longer compared to the median duration of two days in a previous study.[5] This disparity can be explained by the fact that persisting delirious state, coupled with focal neurological signs, might suggest a more sinister underlying diagnosis as in our study. For instance, in our study, the findings of intracranial bleed and atrophy in three of our patients could have contributed to the longer duration of delirium that we noted.

Delirium is no doubt a syndrome involving a multifactorial process that includes preoperative patient vulnerability, intraoperative insults, and iatrogenic factors during post-operative PICU stay.[12] Importantly, we noted that prolonged mechanical ventilation of more than seven days as a predictor of for the development of delirium following TOF repair. A similar result was also obtained from a previously published report which showed that mechanical ventilation was associated with a higher risk for the occurrence of paediatric delirium.[13,14] As the patient who requires prolonged ventilation means the need to be on sedation for a longer period, it is important to consider the effect of this prolonged used of sedation in the development of delirium. In our centre, benzodiazepine and fentanyl are the main sedation and analgesia used in ventilated patients. A study by Pandharipande et al., had shown that the choice of sedatives used and its associated level of sedation as a trigger for increasing the risk of delirium development.[15] This was further confirmed by the significant correlation between mechanical ventilation and deeper levels of sedation in another study.[13]

Low baseline systemic oxygen saturation was another predictor for the development of postoperative delirium in our study. The degree of hypoxia experienced by the patient is dependent on the extent of RVOT obstruction that is present in the patient. Preoperative hypoxemia in patients with significant RVOT obstruction may render them more vulnerable to the effects of CPB surgery. Hypo-perfusion during CPB will thereby increase the risk of developing cerebral ischemia or dysfunction to these previously identified vulnerable patients.[4] This, in a nutshell, increases the risk of delirium and potentially may have long term neurological sequelae.

Previous studies had shown a significant relationship between delayed developmental status of the patients subjected to primary TOF repair and the likelihood of having postoperative delirium.[5,13] In these studies, it was noted that the presence of atypical brain morphology made the bearer extra susceptible to develop delirium postoperatively compared to those with a normal brain morphology. Our study potentially supports the fact that delayed development of patients might show some correlation with delirium. However, this association was not achieved a statistically significant finding (p=0.082). The small sample size may explain why premorbid neurological conditions like delayed development and syndromic condition, i.e., Trisomy 21 were not significant contributing factors to ANC in our series. Furthermore, children with developmental delays are more difficult to assess in the acute care setting and possibly, more attention needs to be given to determine the presence of these conditions prior to the surgery. In this study, seizures were noted in 4 patients (4.4%), which was comparable to previously published case series that had rates of 1.4% to 8%.[16,17] Seizure control was achieved with single AED in two of our patients. The finding was similar to the study done by Messinger et al., which showed that 50% of their patients required only a single AED for satisfactory control of their seizures.[18]

The long waiting time for TOF repair in this country is primarily due to a lack of trained paediatric cardiac surgeons and PCICU beds. In our study, the median age of the patient who underwent TOF surgery was 26.5 months (range 1- 155 months), compared with a developed country where the majority of this primary TOF repair are performed between 3-6 months of age.[19] This may have explained a higher rate of complications, especially low cardiac output syndrome that may related to severe right ventricular dysfunctions or restrictive RV physiology. This may also have contributed to a higher mortality rate of 5.9% in our cohorts, compared with European and American congenital cardiothoracic surgery registries who have reported peri-operative mortality below 3% in recent years.[20]

The statistically significant association between the development of neurological complications and prolonged ICU stay emphasized the importance of reduction in post-operative complications following TOF surgery by improving perioperative and ICU management. Performing TOF surgery promptly on time is crucial as early surgery able to reduce the risk of pre-operative severe hypoxemia and post-operative complications related to RV dysfunction that may lead to prolonged inotropic support and mechanical ventilation requirement. Our findings also suggest the need for neuroprotective strategies such as early identification and prompt intervention to any neurological sequelae to improve the overall patient care and, at the same time, to optimise the utilisation of hospital resources.

This study has a few notable strengths. First, it was the first study in a relatively new referral paediatric cardiac centre in Malaysia with lack of trained surgeons for congenital heart surgery to identify the risk factors and predictors of acute neurological complications following TOF repair. Secondly, we managed to capture all the data of the patients that satisfied the inclusion criteria without encountering any missing data. Our study was limited by its retrospective design, which involved only a single centre with a relatively small sample size that may cause the findings cannot be extrapolated for the general population. Besides that, potential predictor for neurological sequelae like younger age at operation may have been overlooked in our study as most of our patients had their surgery done after the age of 12 months (93%). The lack of utilisation of an objective assessment tool to aid in the diagnosis of delirium may also result in under-recognition of delirium. Our results also may not predict long term neurodevelopmental outcomes, and this should serve as a basis for future study.

CONCLUSION

Acute neurological complications following TOF repair were significantly higher in patients with RV dysfunction and in those who required a longer duration of inotropic support, mechanical ventilation, ICU and hospital stay. Postoperative delirium is the most common manifestation of acute neurological sequelae. Low pre-operative systemic oxygen saturation and prolonged mechanical ventilation requirement are predictors for developing delirium. Therefore, reduction in postoperative complications following TOF surgery and routine screening for delirium using an objective assessment tool should be performed on these high-risk patients to enable early diagnosis and appropriate intervention to improve the overall surgical outcome.

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ETHICAL APPROVAL

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. This study was approved and registered by Ministry of Health's Medical Research and Ethics Committee (MREC) with NMRR ID: NMRR-18-3079-43586.

CONFLICT OF INTEREST

The authors declare that they have no conflict of interest.

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