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Original Article

Hepatitis Post Cardiopulmonary Bypass in Children: Single Center Experience in Egypt

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Abstract:

Background: Cardiopulmonary surgery is associated with risk of liver dysfunction due to hypoperfusion, release of mediators by macrophages and drug induced liver injury.

Aim of the work: to assess liver functions and sonographic changes post- cardiopulmonary bypass in children.

Methods: Fifty children with congenital heart diseases who underwent cardiac surgery were assessed. Liver function tests, abdominal ultrasound and echocardiography were performed for those with impaired liver functions at 6 months and up to 18months postoperatively.

Results: Among 50 studied children (30 males and 20 females); 40 underwent cardiopulmonary bypass (CPB) and 10 underwent closed heart surgery. Twelve (24%) patients had elevated liver transaminases (aspartate transaminase (AST) and alanine transaminase (ALT)). They all proved to have anti-hepatitis C virus (HCV) antibodies and positive HCV by polymerase chain reaction (PCR). Brightness of liver (20 cases), hepatomegaly (12 cases) and congested hepatic veins (10 cases) were the most important sonographic findings. Significant relation was found between elevated liver enzymes and HCV (p=0.012). There was no correlation between CPB or congenital structural defect or surgical procedure and hepatic affection (p>0.05).

Conclusion: Open heart surgery may be associated with increased risk of hepatitis C infection. Increased liver brightness is the most common sonographic finding. Pre-cardiac surgery screening for HCV is mandatory in children.

Level of Evidence of Study: IIB (*1*).

Keywords: cardiopulmonary bypass; liver function test; congenital heart diseases; hepatitis C virus; HCV.

Abbreviations: ALP: alkaline phosphatase; ALT: alanine transaminase; ASD: atrial septal defect; AS: aortic stenosis; AST: aspartate transaminase; AR: aortic regurgitation; AV: aortic valve; CAVC: complete atrioventricular canal defect; CPB: cardiopulmonary bypass; COA: coarctation of aorta; DORV: Double outlet right ventricle; GGT: gamma glutamyl transpeptidase; HCV: hepatitis C virus; MS: mitral stenosis; PCR: polymerase chain reaction; PDA: patent ductus arteriosus; PS: pulmonary stenosis; TGA: transposition of great arteries; TR: tricuspid regurgitation; VSD: ventricular septal defect.

Introduction

Major forms of congenital cardiovascular defects are recognized birth defects that occur between 4- 19 per 1000 live births. Surgical repair is often required during infancy. Despite improving mortality, risk of transplant or death in the first year of life remains 10-20% for complex interventions (*2*, *3*). Complications associated with cardiac surgery are related to type of underlying defect, type of surgery and use of cardiopulmonary bypass (CPB) and other risk factors.(*4*) Complications list is variable and affects variable body systems; cardiovascular, neurologic, hepatic, renal, blood, etc. (*5*, *6*). CPB might be employed to maintain circulation and tissue oxygenation during cardiac surgery (*7*). CPB is a non-physiologic circulation and the patients are subjected to a various degree of body organ dysfunction. As the number of patients undergoing cardiac surgery is increased; the need for CPB is also increased (*8*).

Hepatic injury post CPB results from centrilobular sinusoid ischemia, subsequent reperfusion injuries, the systemic inflammatory response syndrome and oxidative stress (*7*). Other mechanisms include drug induced hepatic injury or systemic inflammatory reaction by CPB (*9*). Consumption of coagulation factors during CPB and subsequent micro-thrombi formation in centrilobular hepatic sinusoids was also reported to compromise liver function post cardiac surgery (*6*). On the other hand, others demonstrated that short CPB time of less than two hours was not associated with compromised hepatic functions. Furthermore, an elevation of serum liver transaminases after uncomplicated CPB has also been reported in some studies. Hepatic injury associated with infections, hypo-perfusion and shocked liver is preventable (*10*). We aimed to study liver functions and sonographic changes after open heart surgery in pediatric patients with congenital heart diseases between 6- 18months postoperatively.

Subjects and Methods

This analytical cross-sectional study was conducted from September 2017 to July 2018. The study was approved by Higher Research Committee of Faculty of Medicine, Cairo University, Egypt. It was carried out in accordance with the Helsinki declaration (*11*).

Participants

The study included 50 pediatric patients with congenital heart disease who underwent cardiac surgery. They were assessed 6 months- 18 months postoperatively. They were recruited from Post-cardiac Intervention Clinic, Pediatric Cardiology Unit, Pediatrics Department, Faculty of Medicine, Cairo University. Pediatric patients with other associated congenital anomalies, known associated chronic liver disease, chronic kidney disease presenting prior to surgery were not included in the study.

Methods

Data Collection:

All relevant data were collected related to age, gender, consanguinity, history of similar conditions in family, type of congenital disease and type of repair, medications (type and dose), regularity of follow up, and the presence of complications related to cardiac surgery. All data of clinical examination was also collected.

Lab investigations:

Liver function tests: aspartate aminotransferase (AST), alanine aminotransferase (ALT), gamma glutamyl transpeptidase (GGT), alkaline phosphatase (ALP), albumin, total protein, total and direct bilirubin and coagulation profile: international normalized ratio (INR), prothrombin time (PT) and partial thromboplastin time (PTT) were performed.

Imaging:

Abdominal U/S: images were obtained using Toshiba model Nemio XG probe PVM375AT,3.75 MHZ and another model is Toshiba Xario 100.

Echocardiography: Images were obtained using 3.0-MHz or 5.0-MHz phased-array transducer of the Vivid 5 echocardiographic scanner (GE Ultrasound, Horten, Norway). The choice between transducers depended on the age of the child.

Other investigations that were deemed necessary by clinical judgment suggesting hepatic affection as were performed (viral screening, metabolic screening etc.)

Statistical Analysis

Data were coded, tabulated and analyzed using the statistical package SPSS (Statistical Package for the Social Sciences) version 25. Data were summarized as mean, standard deviation, median, minimum and maximum for quantitative data. For categorical data frequency (count) and relative frequency (percentage) were employed. Statistical tests of significance were used; comparisons between quantitative variables were done using the non-parametric MannWhitney test. For comparing categorical data, Chi square (χ^2) test was performed. Exact test was used instead when the expected frequency was less than 5. Correlations between quantitative variables were done using Spearman correlation coefficient. P-values less than 0.05 were considered as statistically significant.

Results

The mean age of the enrolled children was 3.14 ±2.1 years, of them 30 were males and 20 were females. 26 were products of consanguineous marriages. Table 1 cites the type of underlying congenital heart disease for which they underwent cardiac surgery. The age at time of operation ranged from 0.10 - 10 years with a mean ± (SD) of 2.39 ±2.2 years. Forty underwent open heart surgery with CPB (group I) and 10 underwent closed heart surgery (group II). The post-operative duration of follow up ranged from (6 to 18) months with a mean ± SD of 10.00 ±2.7 months. Weight for age percentile ranged from (3rd percentile to 90th) with a mean ± SD of 44.44 ±22.8; while height for age percentile ranged from (3rd percentile to 75th) with a mean ± SD of 35.00 ±25.8.

Table 1: Type of Congenital Heart Disease among the studied cohort.

	Number	%		Number	%
ASD-VSD	6	12	PS-VSD	1	2
VSD	3	6	PDA-ASD	1	2
COA	6	12	VSD-MS	1	2
ASD-PS	1	2	VSD-MS-TR	1	2
Fallot Tetralogy	7	14	VSD-PS	1	2
MS	1	2	ASD-VSD-MR-TR	1	2
TGA	6	12	PDA-AR-PFO	1	2
CAVC	7	14	COA-AS-Bicuspid AV	1	2
DORV	5	10			

AR: aortic regurgitation; ASD: atrial septal defect; AS: aortic stenosis; AV: aortic valve; CAVC: complete atrioventricular canal defect; COA: coarctation of aorta; DORV: Double outlet right ventricle; MS: mitral stenosis; PDA: patent ductus arteriosus; PFO: patent foramen oval; PS: pulmonary stenosis; TGA: transposition of great arteries; TR: tricuspid regurgitation; VSD: ventricular septal defect.

Table 2: Comparison between liver function tests in studied groups.

	With CPB; n=40 (open heart)		Without CPB; n=10 (closed heart)		P value
	Mean ±SD	Range (Min-Max)	Mean ±SD	Range (Min-Max)	
ALT	62.07 ±89.6	(12.00 - 498.00)	49.40 ±39.9	(12.00 - 122.00)	0.729
AST	64.67 ±59.2	(13.00 - 312.00)	56.70 ±30.3	(34.00 - 138.00)	0.607
GGT	32.75 ±38.1	(15.00 - 150.00)	15.60 ±6.9	(5.00 - 25.00)	0.356
ALP	258.43 ±120.5	(16.00 - 838.00)	261.70 ±67.2	(181.0 - 356.0)	0.729
Albumin	4.00 ±0.3	(3.40-4.50)	3.98 ±0.5	(3.20 - 4.60)	0.802
Total Protein	7.59 ±1.2	(6.40-13.90)	7.07 ±0.6	(6.10 - 8.20)	0.125
Direct Bilirubin	0.08 ±0.1	(0.00 - 0.20)	0.10 ±0.1	(0.00 - 0.20)	0.395
Indirect Bilirubin	0.35 ±0.2	(0.10 - 0.90)	0.34 ±0.2	(0.20 - 0.80)	0.952
PT	12.73 ±1.2	(10.80 - 15.80)	12.25 ±0.9	(11.10 - 14.10)	0.144
INR	1.06 ±0.1	(0.97-1.30)	1.04 ±0.04	(1.00 - 1.10)	0.465
RBS	98.70 ±10.4	(79.00 - 123.00)	101.50 ±16.3	(76.00 -125.00)	0.607

ALT: alanine transaminase; AST: aspartate transaminase; ALP: alkaline phosphatase; GGT: gamma glutamyl transpeptidase; INR: International normalized ratio; PT: Prothrombin Time; RBS: random blood sugar.

Twelve (24%) children were found to have elevated liver transferases (AST and ALT). Further investigations revealed that they all had antibodies to hepatitis C virus and polymerase chain reaction (PCR) confirmed the HCV infection. The findings did not correlate with CPB use intra-operatively. (Table 2). Further screening of HCV among studied population was not investigated, as it was beyond scope of current study. (Table 3). There was no correlation between age at operation or CPB use and liver function tests.

Twelve children (24%) were found to have renal calcification, 34% had echogenic kidneys with normal size. Calcification resolved by decreasing dose of furosemide or replacing it by other diuretics. Patients with cardiopulmonary bypass (group I) had significant lower prevalence of renal calcification (17.5%) vs. (50%) in patients without CPB (group II), (p value= 0.046). Other sonographic findings had no statistically significant differences between both groups; (p value >0.05). (Table 4). (Figure 1).

Table 3: Distribution of children with HCV among our studied cohort.

		With CPB; n=40		Without CPB; n=10	
		Count	%	Count	%
HCV	Yes	11	24.4%	1	20.0%
	Not screened	34	75.6%	4	80.0%

HCV: hepatitis C virus infection.

Table 4: Comparison between studied groups regarding hepatic and renal sonographic findings.

	FINDING	With CPB; n=40		Without CPB; n=10		P value
		Count	%	Count	%	
Liver Size	Enlarged	11	27.5%	1	10.0%	0.416
	Normal	29	72.5%	9	90.0%	
Bright Liver	Yes	16	40.0%	4	40.0%	>0.999
	No	24	60.0%	6	60.0%	
Dilated Portal Vein	Dilated	11	27.5%	2	20.0%	>0.999
	Normal	29	72.5%	8	80.0%	
Prominent Caudate Lobe	Yes	9	22.5%	0	.0%	0.174
	No	31	77.5%	10	100.0%	
Congested Liver	Congested	9	22.5%	1	10.0%	0.663
	Normal	31	77.5%	9	90.0%	
Splenomegaly	Yes	4	10.0%	0	.0%	0.571
	No	36	90.0%	10	100.0%	
Echogenic Kidney	Yes	12	30.0%	5	50.0%	0.277
	No	28	70.0%	5	50.0%	
Calcification in kidney	Yes	7	17.5%	5	50.0%	0.046*
	No	33	82.5%	5	50.0%	

Discussion

Our study aimed to define hepatic involvement beyond the immediate cardiac surgery in pediatrics after operation from 6 months up to 18month. Elevated transferases and HCV infection was encountered in 24% of the studied cohort. It is important to note that we did not screen for HCV among all the studied children, as it was beyond the scope of the study. It is not routine to investigate for HCV pre-operatively for cardiac surgery among children at our center.

The possibilities of how and when they were infected are immense. HCV incidence in Egypt was estimated to be 14.7% and dropped to be 10% in 2015 (*12*). Hence, the studied children with HCV might have contracted the HCV from their households or environments, yet the incidence among the general population is far less than the 24% encountered in our study. They might have contracted the HCV from the hospitals that they have been to, which underscores the importance of implementation of infection control practice (*13*). Again, they might have contracted it from the operative procedure, yet it is known that the risk of transmission following cardiac surgery is 1.27% (*14*). They might have contracted HCV from a previous blood transfusion. Nucleic acid amplification testing (NAT) (*15*) is applied to all donated blood in Blood Bank of Faculty of Medicine, Cairo University, Hospitals. After the implementation of blood donor screening, the risk for HCV infection after cardiac surgery in childhood dropped significantly from 14.6% to < 0.5% (*16*).

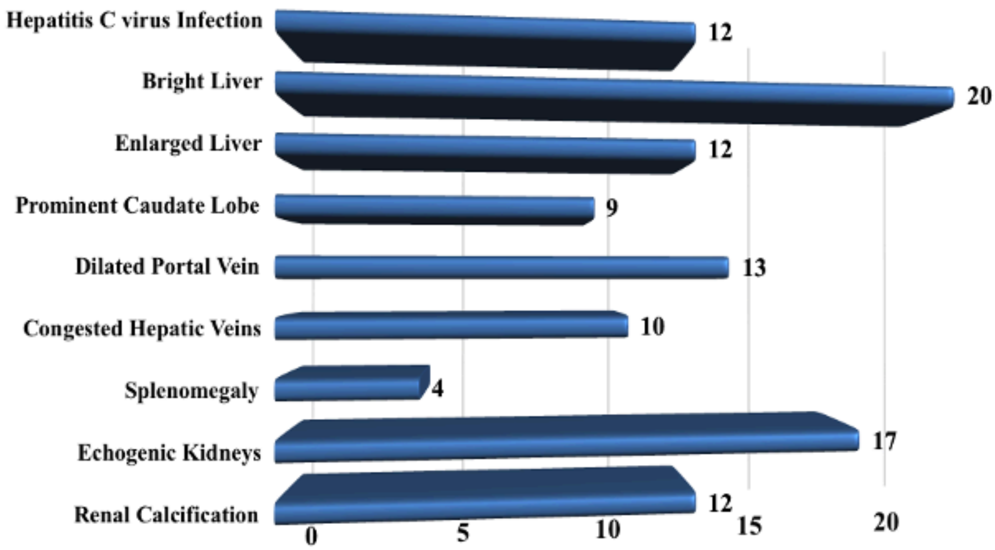

Figure 1: Hepatic and Sonographic Changes Post-cardiac Surgery**.**

Further studies are needed to verify the incidence of HCV among children with cardiac congenital anomalies and the mode of transmission of HCV. It is important to screen these children as direct antiviral treatment of HCV is approved and available for children 3 years old and above (*17*). It is important to implement routine screening as these cases are sources of infection to their households as they had a silent clinical picture. This means infection spread rapidly and would go largely unnoticed (*18*).

The sonographic findings in our study included hepatomegaly in 12 (24%), liver brightness in 60%, dilated portal vein in 26%, congested liver 20% and prominent caudate lobe in 18%. Congestion of liver improved upon change/ increase of drug induced diuresis among our studied cohort. We did not come across the cause of congestion apart from inadequate preload medication use. All children with congested enlarged livers encountered in our study post-operatively were related to insufficient control of systemic congestion following the intervention. Yet, the use of diuretics were found to be associated with renal calcification in 26% of our studied cohort. The fine tuning of dose to achieve control of systemic congestion and renal calcification needs regular follow up and sonographic imaging.

Fifty four percent of our studied cohort with congenital heart diseases were products of consanguineous marriages. Future studies are needed to verify the genetic mutations if any that underlie susceptibility to develop congenital heart diseases among consanguineous couples. Raising more awareness about consanguineous marriage and its effect on congenital abnormalities is a necessity.

Limitations of the study include the inaccessibility to operative data and the lack of screening for hepatic viral infections before and after major cardiac surgery, hence we could not tell whether the infection was related to the procedure or otherwise. Again another limitation was lack of screening of those with normal transaminases for HCV infection as it was not within the scope of this cross-sectional study.

Conclusion

Abnormal liver functions are not uncommon in patients 6-18 months post cardiac surgery. Abnormal liver functions might be related to hepatitis C affection. Open heart surgery may be associated with increased risk of hepatitis C infection. Increased liver brightness is the most common sonographic finding. Pre-cardiac surgery screening for HCV is mandatory in children.

Author Contributions: All authors shared in conceptualization, supervising, data curation, data analysis, writing original draft, data interpretation, writing original draft, supervising and revising. All authors reviewed the final manuscript. All authors have read and agreed to the published version of the manuscript.

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CONFLICT OF INTEREST

The authors declare no conflict of interest in connection with the study.

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