INTRODUCTION

Patent arterial duct (PDA) is a muscular artery connecting two elastic arteries (aorta and pulmonary artery). Neonates with certain complex congenital heart diseases are dependent on the PDA for blood flow to their systemic circulation or the pulmonary vascular bed. Blalock-Taussig Shunt (BTS) for palliation of cyanotic babies has revolutionized the management of these sick subset of patients. However, a lot of adverse effects are noted with BTS even after gaining a vast experience. Some of the concerns with BTS include early shunt thrombosis, chylothorax, diaphragmatic paralysis, and distortion and stenosis of branch PAs in the long term. The mortality following neonatal BTS is as high as 7.2% with a composite morbidity of 13.1% according to STS data(1)(2)(3). Hence alternative procedures were sought.

PDA stenting has been recognized as a reasonable alternative to BTS following the initial report by Gibbs et al in 1992(4) and reports of the outcomes of a large cohort in 2004(5). More recently, multiple metaanalysis have documented the benefits of PDA stenting compared to BTS in duct dependent pulmonary circulation and hence is being preferred in these sick subset of patients(6)(7)(8). Stenting of PDA was conventionally performed using bare metal stents (BMS). Bare metal stents of the sizes needed for PDA stenting have slowly gone out of market because of the established advantages of drug eluting stents in coronary artery disease. Hence, DES are being used for ductal stenting although the drug levels eluted and their effects have been primarily tested in adult population. The rapamycin group of drugs are used in drug eluting stents, which have immunosuppressive actions when levels are systemic. It has been shown to attain toxic blood levels in neonatal population although with no clinically relevant adverse effects.

PDA stenting is performed using DES in SCTIMST on a compassionate basis, as BMS are not available (BMS are currently not used for stenting coronary arteries because of established benefits of DES). Since the rates of neonatal infections and sepsis are higher in our population compared to Western population, it is important to characterize the safety, drug levels attained and consequences of immunosuppression due to systemic drug levels.

REVIEW OF LITERATURE

Stent implantation in the PDA is a recognized management option in maintaining arterial duct patency in newborns with duct dependent pulmonary or systemic blood flow. In a recent systematic review and meta-analysis, it has been found to be a viable alternative to BTS with no significant differences in terms of early or late mortality but had more reinterventions on follow up(8). A study by the Congenital Catheterization Research Collaborative compared 106 patients with a PDA stent and 251 patients with a BT shunt, where there were no differences in the primary composite outcome of death or unplanned reintervention to treat cyanosis. The PDA stent group had lesser procedural complications, intensive care unit stay, larger symmetrical pulmonary arteries on follow up but with higher incidence of reinterventions (hazard ratio, 29.8)(7).

Conventionally bare metal stents (BMS) have been used for PDA stenting because of the unknown drug concentrations attained when drug eluting stents(DES) are used in neonates. The reintervention rate following BMS implantation (redilation or need for a surgical shunt) is 17% to 25% at 6 months(5). The neointimal proliferative process after stent implantation compromises the luminal diameter. Lee et al in a study comparing BMS and DES in piglets demonstrated complete histological occlusion in the ductal lumen at minimum 1 level, in 9 out of 14 pigs(9). This was documented at 4 weeks in 1 (17%), and 5 (83%) pigs at 6 weeks. Early clinical studies have reported stent thrombosis or stenosis rates post BMS implantation in PDA in the range of 12-16%(5,10)(11). In the animal model by Lee et al, the difference in BMS and DES were noted at 4 weeks when the median luminal diameters of the BMS were 87%, 54% and 77% of the DES at various levels (aortic, pulmonary end and mid stent)(9). It was found that pigs who received a rapamycin eluting stent had lesser luminal loss on follow up and there were 50% lower proliferation rates in rapamycin-treated invitro cultures of duct-derived smooth muscle cells.

Drug-eluting stent technology enables topical drug delivery with therapeutic drug concentrations locally within the blood vessel wall, with substantially lower systemic blood levels. The use of DES is established in the treatment of coronary

artery disease. Sirolimus drug eluting stents (SES) are effective and documented to be safe in adults. In animal models with a DES containing 185 g of sirolimus, the whole-blood concentration of the drug was found to peak at 1 hour (mean, 2.63 0.74 ng/mL) and then fell below the lower limit of detection by 3 days while achieving therapeutic arterial tissue concentrations. In adults implanted with 150 and 178 g/18 mm DES, peak drug concentration occurred between 3 and 4 hours at a level of 0.57 and 1.05 ng/mL with 1 or 2 stents, respectively, and blood levels were undetectable at day 7. Based on the clearance rates of sirolimus in renal transplant recipients the estimated steady-state concentration of the drug in an average neonate was 3.3 ng/mL in the first week after implantation.

Sirolimus-eluting stents may have clinical advantages over BMS in the extremely proliferative environment of the neonatal arterial duct. However, sirolimus has immunosuppressive actions and little is known regarding sirolimus pharmacokinetics in the newborn. Lee et al reported pharmacokinetics of sirolimus in neonates after SES implantation where peak sirolimus levels were 20 times higher and clearance rates 30 times lower than previously reported in older children and adults(12). Sirolimus levels were within the immunosuppressive range for a prolonged period. The levels were >5 μg/L (trough level used in transplant recipients) for a variable time (mean 8.4 to 15.9 days) depending on the total dose of sirolimus in the implanted stents. They did not note any clinically significant adverse outcomes although immunosuppression was prolonged. Sivakumar et al have reported the serum sirolimus levels attained in 12 neonates following ductal stenting using a third-generation cobalt chromium DES(13). Their cohort involved 11 neonates with duct dependent pulmonary circulation and one with pulmonary atresia and rhabdomyoma. The sirolimus levels were less than 5 ng/ml in patients who received a single stent or even 2 stents where the total length was less than 22 mm. However immunosuppressive levels were documented in neonates with stent length > 22 mm which decreased to acceptable levels by 7^{th} day of implantation.

Abluminal drug coating is a technological improvement which helps controlled release of the drug onto the vessel wall. Prior studies have demonstrated delivery of sirolimus to the coronary artery in a controlled way with abluminal drug delivery(14)(15). The stent preserved a safe and effective local drug concentration

without significant toxicity. There are no studies on the use of abluminal drug eluting stents in the pediatric population. However, it seems prudent that the total sirolimus levels eluted being lesser in an abluminal delivery system, the blood levels achieved also may be lower with the use of such stents.

Patients post PDA stenting requires diligent follow up and the definitive or palliative procedure has to be performed within a stipulated period of time so as to avoid attrition in the interim period. The time period on PDA stent depends on the indication for stenting and the final treatment pathway- univentricular palliation, biventricular repair or close follow up in view of complex and difficult to treat anatomic substrates. Patients planned for univentricular pathway will have to undergo bidirectional Glenn procedure early as the PDA flow may be detrimental in the long term by elevating pulmonary vascular resistance. Patients destined for definitive biventricular repair may need prolonged palliation depending on the availability of conduits. Such patients also need close follow up as the PDA stent is their life line and any alterations in the hemodynamic mileu can have dire consequences (diarrhoeal disease with dehydration and stent thrombosis). Neonates with poor PA anatomy also requires prolonged palliation and reassessment for PA growth and accordingly, planning for surgical palliation or corrective repair. Neonates with transient PDA dependency such as Severe Ebsteins anomaly with functional pulmonary atresia who undergo PDA stent requires only a short period of ductal flow. These patients may be advised to stop antiplatelet drugs so that stent occlusion occurs. Sivakumar et al reported interstage mortality of 18% in a cohort of 22 patients who underwent ductal stenting(16). They also concluded that conduit repair had to be performed relatively early in patients with biventricular anatomy.

Many series have reported on the short and long term outcomes following ductal stenting(5)(10,11). Table 1 depicts the acute and long term complications following ductal stenting.

Although the previous published series do not report on adverse effects following sirolimus eluting stents, there have been reports of toxicity following use of rapamycin group of drugs for other indications in the pediatric population. The other indications where sirolimus or everolimus is used in current practice include renal transplant recipients, ependymomas in tuberous sclerosis and off label use in cardiac

rhabdomyomas. Saffari and colleagues characterized the adverse effects following systemic use of everolimus in a cohort of 17 patients with tuberous sclerosis(17). Recurrent infections, transient neutropenia and lymphopenia, transient anemia, increase in cholesterol/ triglyceride levels, elevation of lactate dehydrogenase, transient stomatitis and worsening of infantile acne were the reported side effects.

Table 1: Complications following ductal stenting

Acute Complications • Failure to negotiate the PDA • Dissection • Spasm of ductus • Stent occlusion by thrombus • Overflow- Acute lung hyperperfusion and heart failure • Stent dislodgement/ embolization	Intermediate complications • Sepsis • NEC • Access site issues
Late Complications • Instent stenosis • Pulmonary HTN (hyperkinetic) • Branch PA stenosis (mostly LPA) • Surgery post PDA stenting • Removal of stent • Needs LPA plasty almost invariably	

Reintervention rates following PDA stenting are higher compared to BTS. In a recent metaanalysis, reintervention rates were higher in the stented patients (Hazard ratio 1.77(1.39-2.26)) with no significant differences in early or medium term mortality(6). The various reinterventions reported from the Congenital Catheterization Research Collaborative group included balloon angioplasty of stent, re-stenting, PA balloon angioplasty, stenting of PAs, pulmonary valvuloplasty and need for emergency surgeries(7). Vida et al documented that the patients with ductal stents requires additional surgical maneuvers on pulmonary arteries in 53% of the patients on follow up. Ductal stents were completely retrieved in 3 patients (23%) and partially removed in 10 (77%) due to the fusion of the stent to the vascular wall(18).

PDA stenting is performed using DES in SCTIMST on a compassionate basis, as BMS are not available. This study is designed to characterize the safety, drug levels attained and consequences of immunosuppression due to systemic drug levels along with the long term outcomes after ductal stenting.

OBJECTIVES AND METHODOLOGY

Study design: Prospective observational study

Study period: Jan 2020 to Nov 2020

Setting: Tertiary referral centre, a university - level hospital (SCTIMST).

Place of study: Dept. of Cardiology, Sree Chitra Tirunal Institute for Medical Sciences and Technology (SCTIMST)

Hypothesis:

- Drug eluting stent implantation for stenting of PDA is safe in neonates with duct dependent circulation and is not associated with significant immunosuppressive complications.

Objectives:

Primary

- To evaluate the trend of blood sirolimus concentrations in neonates following PDA stenting.
- To evaluate the incidence of infections in neonates who undergo PDA stenting with DES

Secondary

- To determine the immediate and long term outcomes of PDA stenting in neonates.

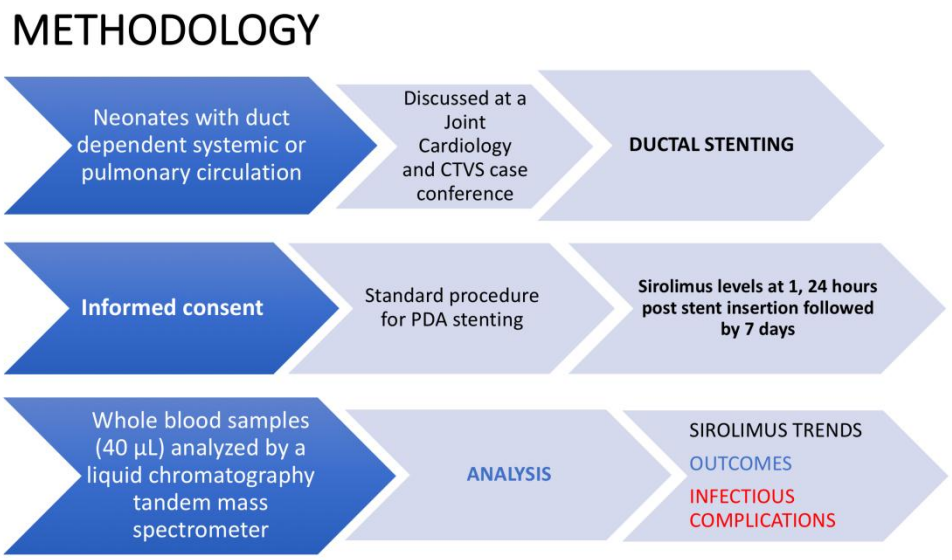
Methodology

The study was cleared by the Technical Advisory Committee of SCTIMST and the Institute Ethics Committee. Neonates with duct dependent systemic or pulmonary circulation and planned for ductal stenting were discussed at a Joint Cardiology and Cardiovascular Surgery case conference before catheterization. Routine informed consent for use of a SES was obtained from parents. Consent for a protocol of serial sirolimus measurements coordinated with routine blood samples taken for other clinical reasons was also signed by parents. Standard procedure for PDA stenting according to the Institute protocol was followed.

The usual procedure of PDA stenting involves use of stents of 3.5-4 mm diameter, the sirolimus dose being dependent on the stent length(19). Drug eluting stents have a drug-free polymer layer applied on top of the drug-polymer matrix as a diffusion barrier to prolong the release of the drug with 50% of the sirolimus eluted over the first week, 80% over 30 days, and 100% over 90 days.

Blood sampling for sirolimus levels was coordinated with sampling for other clinical reasons and drawn at ≈1 hour, 24 hours post stent insertion followed by every 7 days until the sirolimus level was below the limit of quantification (<2.27 µg/mL) where feasible. Sirolimus levels from whole blood samples (40 µL) of patients was analyzed by a liquid chromatography tandem mass spectrometer (DDRC SRL Diagnostics Ltd, Thiruvananthapuram in collaboration with SRL Diagnostics Ltd, Mumbai). Complete blood counts, liver and renal function was also assessed at 24 hours and repeated if abnormal.

Figure 1 represents the flow chart of the study methodology.



Participants:

All consecutive neonates with an indication for ductal stenting (duct dependent pulmonary or systemic circulation) were enrolled in the study

Inclusion criteria:

- All consecutive neonates with an indication for ductal stenting (duct dependent pulmonary or systemic circulation)
- Calculated Sample size (based on the 2018-19 SCT records) – 15 neonates
- However, this sample size could not be attained because of restricted admissions and long periods of lock down during the COVID-19 pandemic. It is also of note that a significant population of ductal stenting patients in the previous years were hailing from Tamil Nadu. Hence the COVID 19 pandemic and the restrictions imposed made it difficult for patients to travel to our Institute.

Exclusion criteria:

Parents of neonates not willing to participate in the study

Data collection and analysis

The data on the cardiac diagnoses, procedural aspects of the PDA stent implantation and any other subsequent catheter or surgically based cardiac interventions were collected. The clinical outcomes, including procedural complications, and ductal stent patency on follow up determined by echocardiography were studied. Drug concentrations were measured as described and the participants were followed up for at least 1 month, up to 6 months and beyond. Specific aspects on follow up included incidence of major/ minor infections, oxygen saturation, patency of the stent and any further interventions.

Data was collected based on the predesigned proforma and data entry was done in Microsoft Excel 2013 (Microsoft, Redmond, WA, USA). The statistical analysis was performed on SPSS software version 21 (IBM Corp. 2012, IBM SPSS Statistics for Windows, Version 21.0, Armonk, NY, USA). The baseline categorical variables were summarized as frequency (percentage) and continuous variables were summarized as mean (SD) or median (IQR). Line diagrams were used to represent the drug concentration of each patient and the growth in size of individual pulmonary arteries. A statistical test was not performed because of the low sample size.

OBSERVATIONS

A total of 6 patients were enrolled till November 2020.

Baseline parameters

There were 4 males and 2 female neonates. The average age at the time of PDA stenting was 11.3 ± 11.1 days with an average weight of 2.83 ± 0.1 kg. All the patients underwent ductal stenting for duct dependent pulmonary circulation. The various anatomic diagnosis with duct dependency and the outcomes of the patients are depicted in Table 1. All except two neonates had usual atrial arrangement, and one of them had dextrocardia. Three neonates had pulmonary atresia and 2 of them had severe pulmonary stenosis; the 1st patient required PDA stenting because of non-confluent PAs and the LPA was arising from the PDA. The aortic arch was right sided in 2 neonates.

Table 2: Characteristics of patients who underwent stent implantation

Neonate	Age (days)	Sex	Weight (kg)	Diagnosis
1	4	F	2.8	Left Isomerism, Double outlet Right ventricle, VSD, Non-Confluent PAs, PDA continuing as LPA
2	4	M	2.8	Congenitally corrected TGA, VSD, Pulmonary Atresia, Confluent PAs
3	30	M	2.9	TOF, critical PS, Confluent PAs, with recurrent spells, large conal crossing RVOT
4	3	M	2.7	VSD, Pulmonary Atresia, Confluent PAs
5	7	M	2.8	D-TGA, VSD, Severe PS, restrictive ASD
6	20	F	3	Unbalanced Atrioventricular canal defect, RV dominant, left isomerism, short segment Pulmonary Atresia, Confluent PAs, Interrupted IVC

Abbreviations: VSD-Ventricular septal defect, PA- Pulmonary artery, PDA-patent ductus arteriosus, LPA- Left pulmonary artery, TGA- Transposition of great arteries, TOF- Tetralogy of Fallot, PS-Pulmonary stenosis, IVC-Inferior vena cava, ASD- Atrial septal defect

Procedural Characteristics

The average stent size used was 3.5 ± 0.4 mm, and the average length of stent used was 16.3 ± 5.1 mm. Two of our patients required 2 stents as the aortic end was uncovered following the first stent deployment. The Abluminus stent (Concept Medical, Florida, USA) was used in 5 patients, and one of the neonates received a Yukon Choice PC (Translumina Therapeutics, New Delhi, India) stent. The details of the procedure have been summarized in Table3 and the characteristics of the 2 stents are depicted in Table 4.

Table 3: Procedural characteristics and Stents used

Neonate	Access site	Access sheath (Fr)	Stent size (mm)	Stent length: mm	STENT	DILATED TO (mm)	Sirolimus eluted
1	RA	4	3	12	ABLUMINUS	3.25	25.2
2#	LA	4	3.5 3.5	16 8	ABLUMINUS	3.8	58.8
3	RFA	4	3.5	12	ABLUMINUS	3.8	29.4
4	RA	4	3.5	18	YUKON PC	3.7	113.4
5	RA	4	3.5	20	ABLUMINUS	3.6	49
6#	RFA	5	4 3.5	12 20*	ABLUMINUS	3.7	33.6

Abbreviations: RA- Right axillary, LA-Left axillary, RFA- Right femoral artery,

#2 stents used; *2nd stent was everolimus eluting stent

Table 4: Characteristics of the stents used in the present study

Abluminus Facilitate mono directional drug release and less systemic exposure of drug leading to faster re-endothelistation	• Cobalt Chromium Alloy L605 with strut thickness of 73 µm • Sirolimus at concentration of 0.7 µg/mm² • Strut width 80 µm (hinge)- 120 µm (strut)
Yukon Choice PC	• 316 Stainless steel platform with poly (d,l) lactic acid • Strut thickness 87 µm • Sirolimus concentration- 1.80 µg/mm2

Characteristics post ductal stenting and Sirolimus level trends

The mean oxygen saturations increased from a mean of 69.5% to 84.3% following the procedure. The patients stayed in the hospital for a mean of 6 ± 4.2 days. Prolonged admission up to 2 weeks was required in Neonate 4 for completion of antibiotics for sepsis.

The serum sirolimus levels were documented at 1 hour, 24 hours and 7 days' post procedure. Since none of the patients had levels >4 ng/ml at 7 days (below therapeutic concentration in transplant recipients), a repeat sampling at 1 month was not performed. Table 5 shows the sirolimus levels for individual patients, and the Figure 2 represents the trends in sirolimus levels.

The mean sirolimus concentrations at 1 hour, 24 hours and 7 days' post procedure were 41.8± 6.93 ng/ml, 15.2 ± 7.1 ng/ml and 3.1± 0.85 ng/ml respectively. Two patients had undetectable sirolimus levels at 7 days, both of them had a 12-mm stent implanted. Sirolimus level less than 4 ng/ml is considered less than therapeutic range for immunosuppression. The amount of sirolimus eluted depended on the length of the stent implanted. The mean drug amount eluted was 51.56 ± 32.1 µg. The mean drug elution by Abluminus stents was 39.2 ± 14.2 µg.

Table 5: Serum sirolimus levels in individual patients taken at 1 hour, 24 hours and 7 days post ductal stenting

Sirolimus levels ng/ml	1 hour	24 hours	7 days
Neonate 1	38.84	Sample not taken	<2.27
Neonate 2 2 stents	>49.6	13.78	3.8
Neonate 3	42.38	15.3	3.3
Neonate 4	33.84	9.38	3.28
Neonate 5	>49.6	29.0	3.92
Neonate 6 1 sirolimus stent,1 everolimus stent	36.8	12.4	<2.27

Figure 2: Graphical representation of serum sirolimus levels in individual patients taken at 1 hour, 24 hours and 7 days post ductal stenting

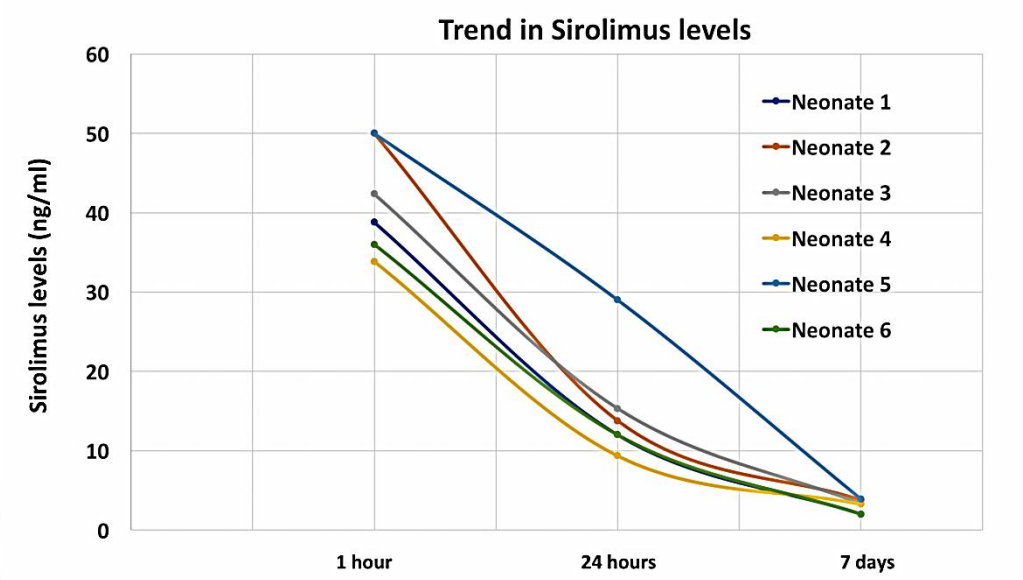
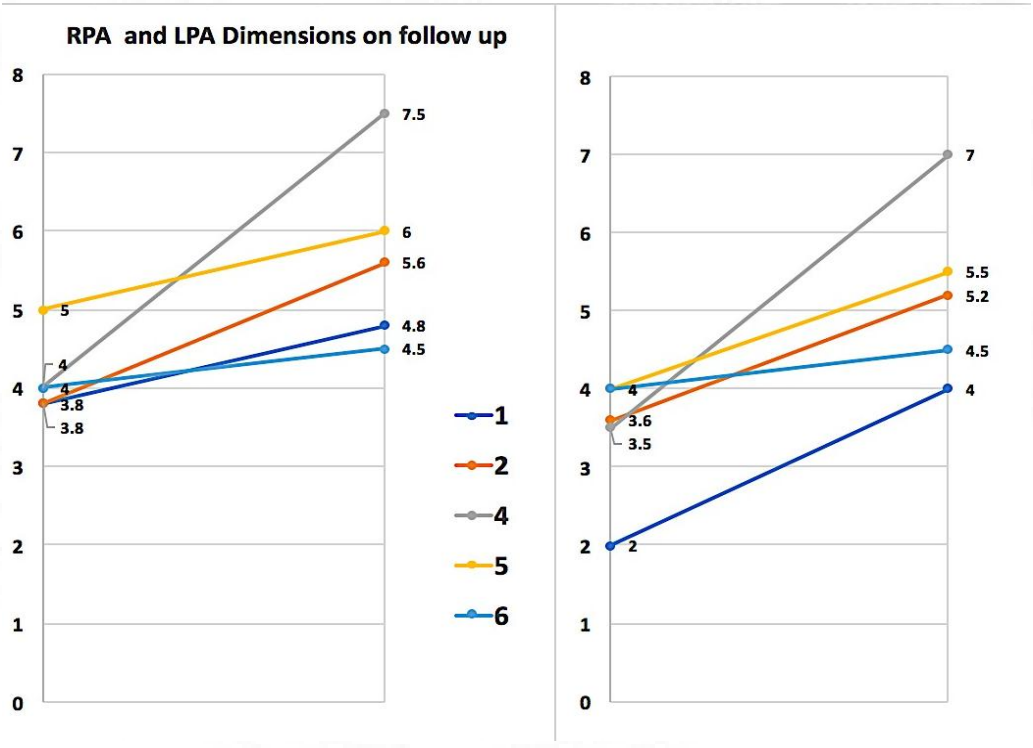


Figure 3: Follow up data of ductal stenting patients demonstrating growth of both RPA and LPA



RPA-Right pulmonary artery, LPA-Left pulmonary artery

Follow up data

The patients were regularly followed up and weight gain, saturations, status of PDA stent, growth of pulmonary arteries were assessed. All the patients were on regular dual antiplatelet therapy with 3mg/kg of aspirin and 0.5-1 mg/kg of clopidogrel. There were no significant bleeding complications related to antiplatelet use. The mean weight at a follow up of 159.1 ± 103 days was 5.2 kg with average saturation of 78.8 ± 5.4%. The patient no.3 had an uneventful post procedure period and was discharged on dual antiplatelets. However, there was sudden unresponsiveness 6 days after discharge with deepening cyanosis and the baby succumbed on the way to hospital. An autopsy could not be performed. Out of the 5 neonates on regular follow up, mothers of 2 of the patients did not report any complaints, while there was worsening cyanosis in 2 and mild respiratory distress in one of them. All the infants had appropriate development of age. Echo performed on follow up showed patent stent in all the 5 neonates, with good growth of both branch pulmonary arteries (Figure 3).

There was no significant branch PA stenosis noted in any patient. All the patients had good compliance to dual antiplatelets, and they were planned for definitive repair/ Bidirectional Glenn on follow up (Table 6). Patient No 1 with left isomerism and non-confluent PAs developed complete heart block and is planned for pacemaker implantation along with BDG.

Table 6: Complications following ductal stenting and long term outcomes

Neonate	Complications	Outcome	Follow up(days)
1	Suspect NEC, Anemia	Patent stent; CHB, planned BDG and pacemaker implantation	287
2	Nil	Patent stent, planned for BDG later	236
3	Sepsis	Sudden death after 6 days of discharge	12
4	Sepsis, NEC, Acute kidney injury	Patent stent Good PA growth planned for BDG later	216
5	Nil	Patent stent Planned for BDG	104
6	Nil	Patent stent Planned for BDG	100

Abbreviations: CHB- Complete heart block, BDG- Bidirectional Glenn, NEC- Necrotizing enterocolitis

DISCUSSION

This was a prospective observational study which planned to enroll at least 15 patients based on the previous years' data. However, the number of patients enrolled was 6 because of various reasons. The COVID 19 pandemic, restrictions imposed on travel and focus on COVID patients in peripheral hospitals caused a decrease in the number of referrals to our Institute during the period of the study. Hence it is difficult to draw any meaningful conclusions based on this small cohort of patients. There were quite a few worthy observations which merits attention.

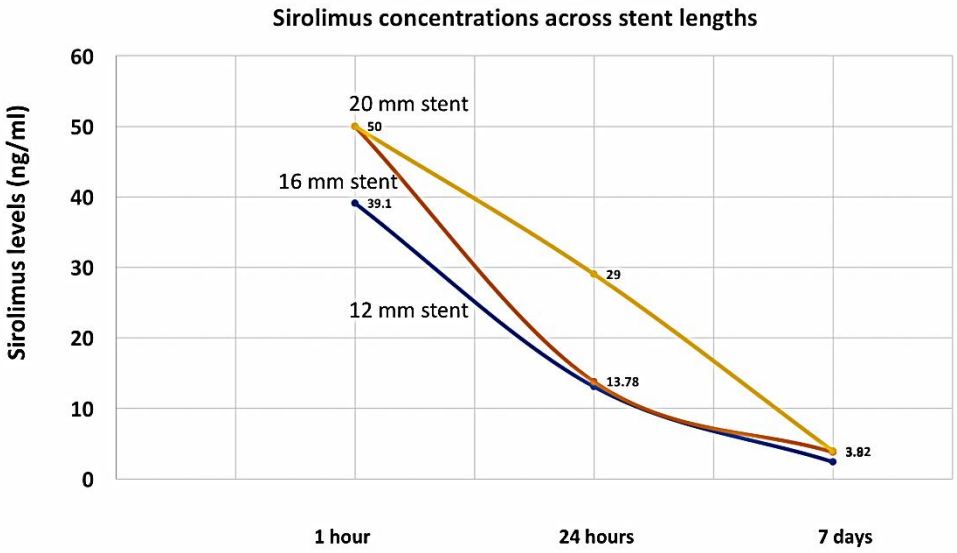
Our cohort of patients is comparable to the other series on PDA stenting in general and series specifically on drug levels after implantation of DES. The procedure is performed in very young patients and the average age of our cohort was 11.3 days with a mean weight of 2.8 kg. The weight of the neonates is lower than the average weight of 3 and 3.2 kg in the other series(12,13). An axillary approach was used in two thirds of the patients. The indication for stenting was for duct dependent pulmonary circulation. It was done to rehabilitate the LPA in one patient with non-confluent PAs and PDA continuing as LPA.

Bare metal stents are currently not available in our centre because the primary indication was coronary stenting. It has been established that DES fares much better than BMS in terms of long term patency/ luminal loss.

The stent sizes and length of the stent are comparable to those by Lee et al and Sivakumar et al. There are certain characteristics of the stent which is unique in the present study. We had implanted Abluminus stent in 5 out of 6 patients. This stent and similar stents with abluminal drug delivery facilitates drug release only into the abluminal surface where their action is needed most to prevent neointimal proliferation and thus decreases the systemic exposure of drug. This is very relevant in the population studied because the drug is originally designed for adult coronary arteries and hence the concentration of drug attained in neonates is high. It was seen that the drug levels attained depends on the original level of sirolimus eluted per stent which in turn depends on the length of the stent (Figure). Abluminal drug delivery systems reduces the drug amount to almost half compared to a similar length of a

luminal drug coated stent (sirolimus concentration 0.7 µg/mm² in Abluminus versus 1.80 µg/mm2 in Yukon Choice PC stent). Thus, the amount of sirolimus administered is significantly reduced. Whether this transforms to lower drug concentrations in blood requires further consideration as we had only one patient where luminal drug coated stent was used. The study by Sivakumar et al on 12 neonates used BioMime SES (Meril Life Sciences, Gujarat, India) which contains sirolimus at a dosage of 1.25 µg per square millimeter of stent surface area and elutes the drug luminally too(13).

Figure 4: Graphical representation of serum sirolimus levels at 1 hour, 24 hours and 7 days post ductal stenting in stents of various lengths (all Abluminus stents).



Sirolimus levels are considered to be therapeutic (for immunosuppression in renal transplant recipients) when the levels are 4 to 20 ng/ml as estimated by tandem mass spectrometry(20). All of our patients had sirolimus levels reaching more than 33 ng/ml immediately post stenting. Two of our patients with longer stents had sirolimus concentrations which were above the upper limit of detection (>49.7 ng/ml). Lee et al documented a biphasic release of sirolimus in the first 12 hours in 4 subjects. We did not observe this phenomenon in any patient. In fact, there was more than 30% fall in sirolimus levels in all 6 patients by 24 hours. It is possible that this phenomenon is missed because of the 24-hour period between our first 2 samples. Lee et al attributed this phenomenon to biphasic sirolimus elution or an enterohepatic recirculation. Sirolimus is predominantly metabolized in the liver and intestine, with <3% of oral

sirolimus cleared by the kidneys. Liver and intestinal metabolism of sirolimus is predominantly by cytochrome P450-3A4, 3A5, and a small percentage by CYP 2C8. The metabolism of sirolimus in neonates varies from adults because of the predominant hydroxylation pathway compared to O-methylation in adults. Neonatal liver is immature to handle these toxic products and thus leads to decreased clearance of the drug.

It is concerning to note that sirolimus levels remains much above the recommended therapeutic range immediately and remains in the immunosuppressive concentrations at 24 hours after stent implantation. The levels at 24 hours documented in our study are much higher than that noted by Sivakumar et al. They have not evaluated sirolimus concentrations at 1 hour. However, the median sirolimus level at 24 hours was 4.49 ng/ml compared to a much higher level of 15.2 ng/ml in our cohort. It is also noteworthy that the 7-day concentration of sirolimus also differs significantly between our patient cohort and those in the study by Sivakumar et al (3.1 ng/ml vs 0.4 ng/ml). This is despite the fact that the original concentration of sirolimus eluted is higher in their population because of use of a luminal drug coated stent with higher drug content for surface area. They have documented therapeutic concentration of 5-15 ng/ml. It is possible that there are differences in the method of estimation in different labs and the lower and higher limit of detection may be different. The lower and higher limits prescribed by our laboratory was 2.27 ng/ml and 49.7 ng/ml respectively.

Sirolimus is used as an immunosuppressive agent and it is well known that recurrent infections or flare up of indolent infections like tuberculosis can occur during sirolimus treatment. Our group of patients are more susceptible to infections compared to other children receiving sirolimus. Neonatal period, immaturity of immune system, intensive care unit stay, use of invasive catheters and lines, hypoxemia and specific associations like Di George syndrome or asplenia in right isomerism are some of the factors increasing the susceptibility to infection in newborns with duct-dependent pulmonary blood flow. Presence of a large PDA itself have been recognized to be a contributing factor to the development of necrotizing enterocolitis in these sick neonates(21)(22). Hence infection, necrotizing enterocolitis, abnormalities of leucocyte counts and liver function tests are not uncommon clinical

problems in such patients. It is difficult to attribute such episodes to the presence of systemic sirolimus in immunosuppressive levels or even toxic doses. We did not note any alteration in leucocyte counts or liver and kidney function parameters.

In our cohort, out of the 2 patients who had sepsis, neonate 3 had prolonged hospital admission in another hospital prior to the stenting procedure. Sepsis which was acquired prior to the procedure might have been detected in the post procedure period. Since almost all the patients have been admitted elsewhere for stabilization prior to shifting to our tertiary level centre, the risk of contracting infection is high and the exact contribution of sirolimus cannot be determined. One patient had suspected NEC while the neonate 4 with sepsis had frank features of NEC. There were no long-term clinical consequences from any of these complications and none of the patients required admission for treatment of infectious complications in the follow up period. Consideration should be given to delay live vaccine administration, while sirolimus levels remain in the immuno- suppressive range, especially when 2 SES are used or stent lengths more than 16 mm is used. It was observed that the sirolimus levels remain in the immunosuppressive range for up to 7 days after stent implantation. This is a critical period wherein the neonate requires close monitoring in hospital or at home for features of frank infection or early signs like poor feeding or activity. The cause for death in neonate 3 is unlikely due to an immunosuppression induced major infection because the blood levels of sirolimus at the time of discharge itself was 3.3 ng/ml which is below the therapeutic range.

All the patients on follow up had patent stents and good growth of pulmonary arteries. Although mean follow up was only 159 days, that is the time period when most patients who undergo ductal stenting are taken up for the definitive/palliative surgical procedures. It is reassuring to note that there were no significant stent occlusions requiring emergency interventions/surgeries. The patient who developed CHB at 5 months of age had an anatomical substrate for heart block with left isomerism and hence is not related to the intervention. No reinterventions were required in this cohort as the stents were patent and infants were clinically well. Although it is difficult to comment based on the small numbers in our study, it is probably a better option to use DES than BMS because of prolonged patency rates especially in those patients requiring long term palliation on PDA stent. This study

demonstrates good patency rates when patients are compliant with dual antiplatelet therapy. It has been reported that patency rates and unplanned reinterventions due to luminal narrowing are comparably less with DES compared to bare-metal stents(22). A study using 3rd generation SES demonstrated patency of DES upto 8–16 months in univentricular lesions and 21–27 months in patients destined for biventricular repair(13).

LIMITATIONS

This is a prospective study with a small sample size. There were significantly lesser number of patients than expected because of the COVID 19 pandemic and lockdowns imposed. This was because of the reduction in the total number of procedures and a significant reduction in patients from far away districts/ Tamil Nadu.

The availability of various diameters and specifically, lengths of sirolimus eluting stents was a concern. In certain cases, we had to use other available everolimus or zotarolimus eluting stents as the specific length of SES were not available. These cases could not be enrolled.

There were no objective tests performed to document immunosuppression. However, there was no major infectious complications which could be attributed to the presence of the drug, as there was no neutropenia/leucopenia.

Although abluminus stents were used in 5 of 6 patients, there was no simultaneous comparison group to document sirolimus levels. Hence it may be overzealous to make any conclusions regarding the better safety in terms of drug levels in abluminal drug delivery systems although it suggests that drug concentration is lower.

The maximum reduction in drug levels occurs in the first 24 hours after implantation. Hence introduction of another sampling point before the 24-hour sample would have further clarified the drug kinetics in the 1st day following implantation.

CONCLUSIONS

This prospective observational study of a cohort of 6 neonates who underwent ductal stenting for PDA dependent pulmonary circulation demonstrates that although sirolimus levels attained are high and in the immunosuppressive range, they are safe in neonates as there were no clinically significant immunosuppressive complications. There were no life threatening infectious complications/ hematological evidence of infection.

This study documents high sirolimus levels in the first week after stent implantation and hence appropriate precautions (antibiotic cover and heightened surveillance) may be recommended for such neonates. Routine immunisation must be offered only after one week following stenting as drug levels fall to low values by one week.

Stents with abluminal drug delivery may be better for ductal stenting because of the lower sirolimus levels in the stent, although there were no major differences in actual drug concentrations based on contemporary studies.

The use of DES has preserved long term patency following ductal stenting and thus may be helpful in prolonged palliation. There is adequate symmetrical growth of pulmonary arteries following neonatal intervention by ductal stenting.

Randomized studies are required to confirm our speculations on the selection of abluminal drug delivery stents over other stents.

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Technical Advisory Committee (Clinical Studies)

SREE CHITRA TIRUNAL INSTITUTE FOR MEDICAL SCIENCES & TECHNOLOGY
THIRUVANANTHAPURAM – 695011, INDIA

TAC Registration No: SCT-/S/2020/1076 **Date: 07.07.2020**

Project title: SAFETY OF DRUG ELUTING STENTS FOR STENTING PATENT ARTERIAL DUCT IN NEONATES

Principal Investigator:	
Dr.Harikrishnan K N, Fellow, Department of Cardiology, SCTIMST	Degree: M.D. (Pediatrics), D.M(Cardiology)
Co-Principal Investigator(s):	
Dr. K.M Krishnamoorthy, Professor and Head, Department of Cardiology, SCTIMST Degree: M.D(Pediatrics), D.M(Cardiology)	
Dr.Deepa S Kumar, Associate Professor, Department of Cardiology, SCTIMST	Degree: M.D, D.M(Cardiology)
Dr. Arun Gopalakrishnan, Assistant Professor, Department of Cardiology, SCTIMST	Degree: M.D, D.M(Cardiology)

Members who participated in the TAC meeting on 20/06/2020
Dr Harikrishnan S (Chairman)
Dr Manikandan S
Dr Narayanan Namboodiri
Dr Jayadevan E R
Dr Sylaja P N
Dr Ramshekhar N Menon
Dr Unnikrishnan K P
Dr Syam K
Dr Sanjay G
Dr Deepti A N
Dr Sabarinath Menon
Dr Jayanand Sudhir B
Dr Srinivas G (Member Secretary)

Dr Sabarinath Menon, Dr Ramshekhar N Menon, Dr Sylaja P N, Dr Deepti A N, Dr Manikandan S, Dr Narayanan Namboodiri, Dr Srinivas G, Dr Sanjay G, Dr Harikrishnan S, Dr Unnikrishnan K P, Dr Syam K and Dr Jayadevan E R stayed away from the proceedings when the projects in which they are involved as investigator were discussed (#1072,1087, 1089, 1092, 1093, 1095, 1096, 1097, 1098, 1099, 1100, 1101, 1103, 1107, 1108, 1111, 1113, 1114, 1116, 1118, 1119, 1120, 1121, 1122, 1123, 1127, 1129, 1130)

Risk Classification of the project (Minimum/ Moderate/ High): Minimum
Requirement of DSMB: No
Recommended members of DSMB: Not applicable

Recommendations of TAC:
Recommended for consideration of IEC.

The PI may note that there can be no additions / alterations in the documents approved by TAC when they are submitted to the IEC.

Dr Srinivas G **MEMBER SECRETARY**
TAC (Clinical Studies)
SCTIMST

Copy to IEC

श्री चित्रा तिरुनाल आयुर्विज्ञान और प्रौद्योगिकी संस्थान, त्रिवेन्द्रम
तिरुवनन्तपुरम - ६९५०११, केरल, इंडिया
SREE CHITRA TIRUNAL INSTITUTE FOR MEDICAL SCIENCES AND TECHNOLOGY, TRIVANDRUM
Thiruvananthapuram - 695 011, Kerala, India
(An Institute of National Importance under Govt. of India)
Grams : Chitramet, Phone : +91-471-2443152, Fax : +91-471-2550728 / 2446433, E-mail : sct@sctimst.ac.in, Website : www.sctimst.ac.in

Institutional Ethics Committee
(IEC Regn No. ECR/189/Inst/KL/2013/RR-16)

SCT/IEC/1198/APRIL-2018 07.09.2018

Dr. Harikrishnan K N
Senior Resident
Department of Cardiology
SCTIMST, Thiruvananthapuram

Dear Dr. Harikrishnan,

The Institutional Ethics Committee reviewed and discussed your application to conduct the study entitled "LONG TERM OUTCOMES OF BIDIRECTIONAL GLENN AND FONTAN PROCEDURES IN A TERTIARY CARE CARDIAC CENTRE IN SOUTH INDIA (IEC/1198)" on 21st April, 2018.

The following documents were reviewed:

Original submission

1. *Covering letter addressed to the Chairperson, IEC, SCTIMST dated 21.03.2018 with check list*
2. *TAC Approval Letter*
3. *IEC Application Form*
4. *Project Proposal*
5. *Patient Information Sheet and Informed Consent Form in English and Malayalam*
6. *CV of Principal Investigator and Co- Principal Investigators*

Revised submission

1. *Covering letter addressed to the Chairperson, IEC, SCTIMST dated 13.08.2018 with check list*
2. *TAC Approval Letter*
3. *IEC Application Form*
4. *Project Proposal*
5. *Protocol*
6. *Assent Form*
7. *Telephone Recruitment Script in English and Malayalam*
8. *Patient Information Sheet and Informed Consent Form in English and Malayalam*
9. *CV of Principal Investigator and Co- Principal Investigators*

The following members of the Ethics Committee were present at the meeting held on 21st April, 2018 at G. Parthasarathi Board Room, AMCHSS, SCTIMST

SL. No.	Member Name	Highest Degree	Gender	Scientific /Non Scientific	Affiliation with Institution(s)
1.	Dr. R V G Menon	M Tech, PhD	Male	Lay Person (Chairman)	No
2.	Dr. Rema M. N	MD	Female	Basic Medical Scientist	No
3.	Dr. Kala Kesavan. P	MBBS, MD	Female	Basic Medical Scientist	No
4.	Dr. K R S Krishnan	M.E., Ph.D.	Male	Medical Technology	Yes
5.	Dr. S S Giri Sankar	LL.M. Ph.D.	Male	Legal Expert	No
6.	Dr. Aneesh V Pillai	BA. LLB (Hons.), LLM, Ph. D, SET (Law)	Male	Legal Expert	No
7.	Mr. Satheesh Chandran	MSW, PGDPM	Male	Lay person/ NGO/ Social Scientist	No
8.	Dr. Harikrishna Varma PR	Ph.D(Materials Science)	Male	Medical Technology	Yes
9.	Smt. Sathi Nair	MA (English Literature)	Female	Lay Person	No
10.	Dr. Christina George	MD Psychiatry	Female	Clinician	No
11.	Dr. Harikrishnan S	MD, DM (Cardiology) DNB (Cardiology)	Male	Clinician	Yes
12.	Dr. Anand Kumar A	MD, DM	Male	Clinician	No
13.	Dr. V. Raman Kutty	M D, M Phil, M P H	Male	Health Sciences Expert/Clinician	Yes
14.	Dr. Mala Ramanathan	PhD	Female	Social Scientist (Member Secretary)	Yes

IEC Decision

The IEC approved the conduct of the study in the present form.

Remarks:
The Institutional Ethics Committee expects to be informed about the progress of the study, any SAE occurring in the course of the study, any changes in the protocol and patient information/informed consent and asks to be provided a copy of the final report.

There was no member of the study team who participated in voting / decision making process. The ethics committee is organized and operated according to the requirements of Good Clinical Practice and the requirements of the Indian Council of Medical Research (ICMR).

Sincerely,

Mala Ramanathan
Member Secretary, IEC

Page 2 of 2

PROFORMA

Safety of drug eluting stents for stenting patent arterial duct in neonates

Patient No:
Age: Days Sex: M/F H. No:
Home Town: Contact No:
Length: Weight: BSA:
Diagnosis: Situs S / I / A Cardiac position D/ L / M
Hypoplastic
SV morphology- LV/ RV
Ventricular function
Pulmonary Atresia/ Stenosis
RPA LPA
PDA size
Prostaglandin infusion?
Dose
Comorbidities:

CLINICAL FEATURES

- NYHA CLASS
- Cyanosis Present/ Absent SpO2

ECG Findings: Rhythm : Loop

- Heart Rate :
- QRS Duration:
- Axis

Procedural details
Access
Stent:
Stent size: 3 3.5 4
Stent length: mm
Sirolimus level in stent
Sirolimus levels 1 hour
24 hours
7 days
1 month
Complications:

Follow up Date:
Mortality on follow-up? Perioperative

Sudden/ Thromboembolic/ Heart failure/ Sepsis Others

Operative procedures:

STUDY CONSENT FORM

TITLE OF THE STUDY: Safety of Drug eluting stents for stenting patent arterial duct in neonates.

Study number:

Participant's name: Date of Birth / Age (in years):
I_____ _____,
mother/father/guardian of _____ (Please tick boxes).

[ ] Declare that I have read the above information provided to me regarding the study: "**Safety of Drug eluting stents for stenting patent arterial duct in neonates.**" and have clarified any doubts that I had.
[ ] I also understand that participation of my child in this study is entirely voluntary and that I am free to withdraw permission to continue to participate at any time without affecting mine/my child's usual treatment or my legal rights.
[ ] I understand that the study staff and institutional ethics committee members may not need my permission to look at records of my child even if I withdraw from the trial. I agree to this access.
[ ] I understand that my/ my child's identity may not be revealed in any information released to third parties or published.
[ ] I voluntarily agree to take part in this study.
[ ] I received a copy of this signed consent form.

Name:	Name of witness:
Signature:	Relation to participant:
Date:	Date:

I attest that the requirements for informed consent for the medical research project described in this form have been satisfied. I have discussed the research project with the participant and explained to him or her in nontechnical terms all of the information contained in this informed consent form, including any risks and adverse reactions that may reasonably be expected to occur. I further certify that I encouraged the participant to ask questions and that all questions asked were answered.

_____ _____

Name and Signature of Person Obtaining Consent
Dr. Harikrishnan K N, Fellow in Pediatric Cardiology, Dept. of Cardiology SCTIMST

For any technical clarifications, please contact Dr. Mala Ramanathan, Member Secretary, IEC, SCTIMST and Additional Professor, AMCHSS, SCTIMST (Email: iec.mem.sec@sctimst.ac.in, Phone no. 0471-2524234)

SREE CHITRA THIRUNAL INSTITUTE FOR MEDICAL SCIENCES AND TECHNOLOGY, TRIVANDRUM

PATIENT INFORMATION SHEET

TITLE: Safety of Drug eluting stents for stenting patent arterial duct in neonates.

Name of Investigators:
Dr. Harikrishnan K N, Dr. K.M Krishnamoorthy, Dr Deepa S Kumar, Dr Arun Gopalakrishnan

Dear Patient/Parent

We welcome you and thank you for your interest in your/ your child's participation in this research project titled "**Safety of Drug eluting stents for stenting patent arterial duct in neonates.**". We hope to include 20 neonates from this hospital in the study. Before your baby participates in this study, it is important for you to understand why this research is being carried out. This form will provide you all the relevant details of this research. It will explain the nature, the purpose, the benefits, the risks, the discomforts, the precautions and the information about how this project will be carried out. It is important that you read and understand the contents of the form carefully. This form may contain certain scientific terms and hence, if you have any doubts or if you want more information, you are free to ask the study personnel or the contact person mentioned below before you give your consent and also at any time during the entire course of the project.

WHAT IS PDA STENTING PROCEDURE?

The normal human heart has four equal-sized pumping chambers; two atria (a right and left) and two ventricles (right and left). The right-side pumps blood to the lungs, and the left side pumps blood to the rest of the body.

Patent arterial duct (PDA) is a muscular artery connecting two major arteries (aorta and pulmonary artery) and is normally present in fetal life. It usually constricts within first 3 days of life and becomes a chord like structure. However, there are many children born with cardiac chambers which are smaller than they are supposed to be; or when one of the valves connecting the chambers is so small or absent. In such conditions, PDA may be the only source of blood to the lungs or to the body. Stent implantation is a recognized management option in maintaining patency of the PDA in newborns with duct- dependent pulmonary or systemic blood flow.

WHAT STENTS ARE USED FOR PDA STENTING CURRENTLY?

Conventionally bare metal stents(BMS) have been used for PDA stenting. These stents do not have any medications within the struts. Drug eluting stents(DES) have a coating of a drug to

prevent excessive cell growth within the stent. When DES are used in neonates, the drug concentration attained is not known. The medications used in stents like sirolimus, everolimus has multiple other effects on the cells of the body, particularly of the immune system.

WHAT DOES THE PRESENT STUDY INVOLVE?

This study is aimed at finding the drug (sirolimus) concentrations in blood after PDA stenting in babies for various indications. The records of the your child's condition will be collected from the hospital records. A specialist doctor will explain the proposed study design to you and ask you to sign the consent form to confirm that you understand the procedure and agree to go ahead with it. Please ask any questions you want.

Following the decision to perform PDA stenting (as discussed in a multidisplinary meeting involving cardiologists and cardiac surgeons) your child will be enrolled into the study. Your baby's blood will be collected to check the serum sirolimus levels. The blood collection is timed such that it will be done at the same time when other routine investigations are carried out (1 hr, 24 hours and 7 days post procedure). The records of the baby's course in hospital and any other relevant factors including infections will be collected. Any particular event and the condition of the baby at the time of routine follow ups will be included for documentation.

HOW LONG DOES IT TAKE?

The hospital stay and follow ups are not changed for the study purpose. The blood collection will also be timed with the routine blood investigations.

WHAT ARE THE RESPONSIBILITIES OF PARTICIPANTS?

Your decision to to allow your child to participate in this study is voluntary, your own personal choice. You may choose not to continue at any time, for any reason, without notice.

WHAT ARE THE EXPECTED RISKS FOR THE PARTICIPANTS?

The study involves collection of blood samples for detecting drug levels. There will be a follow up evaluation to assess the functional status and outcome of PDA stenting. There will be less than minimal risk for the participants because of collection of a small volume of blood. They will be managed according to the hospital protocol. No specific intervention will be done as part of the study.

WHAT ARE THE EXPECTED BENEFITS OF THE RESEARCH TO THE PARTICIPANTS?

The study may provide insights into the safety of DES in neonatal age group. Since the procedure undertaken is palliative in nature, a follow up examination and evaluation may be helpful in identification of any risk factors for poor outcomes or functional deterioration. It may be helpful in detecting patients who require early intervention. The data derived from the study may be helpful in planning appropriate strategies for patients with similar conditions in the future.

WILL PARTICIPANTS BE COMPENSATED FOR PARTICIPATION IN THIS TRIAL?

You will not be paid for participation in the study.

WILL MINE/MY CHILD'S PARTICIPATION IN THIS STUDY BE KEPT CONFIDENTIAL?

All records of your child's study will be kept confidential. Your child's personal identity will not be revealed in any publication or release of results. Study records will be kept indefinitely for analysis and follow-up.

CAN I WITHDRAW FROM THE STUDY AT ANY TIME DURING THE STUDY PERIOD?

Yes, you can. Your decision will not affect your regular medical care.

IF THERE ARE ANY NEW FINDINGS / INFORMATION, WOULD I BE INFORMED?

Yes.

WHAT HAPPENS IN CASE OF A STUDY RELATED INJURY?

There will be no study related injury.

IS THERE ANY ALTERNATIVE TO THE TREATMENT MENTIONED?

Not applicable.

If you have any further questions, please ask: Dr. Harikrishnan. K.N (Principal investigator), Fellow, Department of Cardiology (Email: drhari.kurup@sctimst.ac.in Ph No: 9746869303)
For any technical clarifications, please contact Dr. Mala Ramanathan, Member Secretary, IEC, SCTIMST and Additional Professor, AMCHSS, SCTIMST (Email: iec.mem.sec@sctimst.ac.in, Phone no. 0471-2524234)

ശ്രീ ചിത്ര തിരുനാൾ ഇൻസ്റ്റിറ്റ്യൂട്ട് ഫോർ മെഡിക്കൽ സയൻസസ് ആന്റ് ടെക്നോളജി,
തിരുവനന്തപുരം
രോഗിക്കുള്ള കാര്യവിവരണപത്രം

പഠനശീർഷകം:
പേറ്റന്റ് ആർട്ടീരിയൽ രക്തനാളത്തിൽ സ്റ്റെന്റ് സ്ഥാപിക്കേണ്ട നവജാതശിശുക്കളിൽ മരുന്നു പുരട്ടിയ സ്റ്റെന്റിന്റെ സുരക്ഷിതത്വം.

ഗവേഷകരുടെ പേര്
ഡോ. ഹരികൃഷ്ണൻ കെ. എൻ, ഡോ. കെ.എം കൃഷ്ണമൂർത്തി, ഡോ. ദീപ എസ് കുമാർ, ഡോ. അരുൺ ഗോപാലകൃഷ്ണൻ

പ്രിയ രോഗി/രക്ഷകർത്താവേ,

"പേറ്റന്റ് ആർട്ടീരിയൽ രക്തനാളത്തിൽ സ്റ്റെന്റ് സ്ഥാപിക്കേണ്ട നവജാതശിശുക്കളിൽ മരുന്നു പുരട്ടിയ സ്റ്റെന്റിന്റെ സുരക്ഷതത്വം" എന്ന പഠനത്തിൽ താങ്കൾ/താങ്കളുടെ കുട്ടി പങ്കെടുക്കാൻ താത്പര്യപ്പെടുന്നതിനെ സ്വാഗതംചെയ്യുകയും നന്ദിപ്രകാശിപ്പിക്കുകയും ചെയ്യുന്നു. ഈ ആശുപത്രിയിൽനിന്നും 20 നവജാതശിശുക്കളെ ഈ പഠനത്തിൽ ഉൾപ്പെടുത്താമെന്ന് ഞങ്ങൾ പ്രതീക്ഷിക്കുന്നു. താങ്കളുടെ കുട്ടിയെ ഈ പഠനത്തിൽ പങ്കെടുപ്പിക്കുന്നതിനുമുമ്പ് ഈ ഗവേഷണം എന്തിന് നടത്തുന്നു എന്ന് മനസ്സിലാക്കിയിരിക്കേണ്ടത് പ്രധാനമാണ്. ഈ പത്രിക ഗവേഷണത്തെപ്പറ്റിയുള്ള പ്രസക്തമായ വിവരങ്ങൾ നൽകും. ഇത്, ഈ പദ്ധതി നടപ്പിലാക്കുന്നതെങ്ങനെയെന്നും, അതിന്റെ സ്വഭാവം, ഉദ്ദേശം, നേട്ടങ്ങൾ, അപായസാദ്ധ്യതകൾ, അസ്വസ്ഥതകൾ, മുൻകരുതലുകൾ എന്നിവ വിശദീകരിക്കും. താങ്കൾ ശ്രദ്ധയോടെ ഈ പത്രിക വായിക്കുകയും മനസ്സിലാക്കുകയും ചെയ്യേണ്ടത് പ്രധാനമാണ്. ഈ പത്രികയിൽ ചില ശാസ്ത്രിയ പദങ്ങളുണ്ടായേക്കാം അതിനാൽ താങ്കൾക്കെന്തെങ്കിലും സംശയമോ, അല്ലെങ്കിൽ കൂടുതൽ വിവരങ്ങൾ ആവശ്യമുണ്ടെങ്കിലോ പഠനസംഘത്തിലുള്ളവരോട് ചോദിക്കുകയോ അല്ലെങ്കിൽ ബന്ധപ്പെടാനായി താഴെ നൽകിയിരിക്കുന്നവരെ ഈ പഠനാവസാനം വരെ ഏതുസമയത്തും ബന്ധപ്പെടാൻ താങ്കൾക്ക് സ്വാതന്ത്ര്യമുണ്ട്.

എന്താണ് പേറ്റന്റ് ഡക്ടസ് ആർട്ടീരിയോസിസ് (പിഡിഎ) സ്റ്റെന്റിംഗ് നടപടികൾ?
മനുഷ്യ ഹൃദയത്തിന്, സാധാരണ തുല്യവലുപ്പമുള്ള നാല് അറകളുണ്ട്, രണ്ട് എട്രിയകളും (വലതും ഇടതും) രണ്ട് വെൻട്രിക്കിളുകളും (വലതും ഇടതും). വലതുവശം ശ്വാസകോശത്തിലേയ്ക്ക് രക്തം

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പമ്പുചെയ്യുകയും ഇടതുവശം ശരീരത്തിന്റെ മറ്റുഭാഗങ്ങളിലേയ്ക്ക് രക്തം പമ്പുചെയ്യുകയും ചെയ്യുന്നു. രണ്ട് പ്രധാന ആർട്ടറികളെ (അയോർട്ടയെയും പൾമനറി ആർട്ടറിയെയും) ബന്ധിപ്പിക്കുന്ന പേശികൊണ്ടുള്ള ആർട്ടറിയാണ് പേറ്റന്റ് ആർട്ടീരിയൽ രക്തനാളി. അത് ഗർഭാവസ്ഥയിൽ സാധാരണയായി ഉള്ളതാണ്. അത് സാധാരണയായി ജനിച്ച് ആദ്യ മൂന്ന് ദിവസത്തിനുള്ളിൽ ചുരുങ്ങുകയും ചരടുപോലുള്ള ഒരു രൂപമാകുകയും ചെയ്യും. എന്നിരുന്നാലും അനേകം കുട്ടികൾ ഹൃദയ അറകൾ വേണ്ടതിലും ചെറിയതായോ, അറകളെ ബന്ധിപ്പിക്കുന്ന വാൽവുകളിലൊന്ന് ചെറുതോ അല്ലെങ്കിൽ ഇല്ലാതെയോ ജനിക്കാറുണ്ട്. അത്തരം ഒരു അവസ്ഥയിൽ രക്തം ശ്വാസകോശത്തിലേയ്ക്കോ ശരീരഭാഗങ്ങളിലേക്കോ പോകാൻ പിഡിഎ മാത്രമാണ് ഏക മാർഗ്ഗം. നവജാതരിൽ രക്തനാളിയെ ആശ്രയിക്കുന്ന പൾമനറി അല്ലെങ്കിൽ സിസ്റ്റമിക് രക്തപ്രവാഹത്തിനായി പിഡിഎയുടെ പേറ്റൻസി നിലനിർത്താനുള്ള അംഗീകൃത നടപടിയാണ് സ്റ്റെന്റ് സ്ഥാപിക്കൽ.

ഇപ്പോൾ പിഡിഎ സ്റ്റെന്റ് സ്ഥാപിക്കുന്നതിന് ഏതു സ്റ്റെന്റുകളാണ് ഉപയോഗിക്കുന്നത്?

സാധാരണയായി വെറും ലോഹ സ്റ്റെന്റുകളാണ് പിഡിഎ സ്റ്റെന്റ് സ്ഥാപിക്കലിനായി ഉപയോഗിക്കുന്നത്. ഈ സ്റ്റെന്റുകളുടെ കമ്പികളിൽ ഒരു മരുന്നും ഇല്ല. സ്റ്റെന്റിനുള്ളിൽ അധികമായി കോശങ്ങൾ വളരുന്നതിനെ തടയുന്ന മരുന്നിന്റെ ഒരു കവചം ഡ്രഗ് എല്യൂട്ടിംഗ് സ്റ്റെന്റിലുണ്ട് (ഡിഇഎസ്). നവജാതരിൽ ഡിഇഎസ് ഉപയോഗിക്കുമ്പോൾ നേടുന്ന മരുന്നിന്റെ സാന്ദ്രത എത്രയെന്ന് അറിവില്ല. സിറോലിമസ്, എവറോലിമസ് എന്നീ സ്റ്റെന്റുകൾക്ക് ശരീരത്തിലെ കോശങ്ങളിൽ അനേകം മറ്റ് പ്രഭാവങ്ങളുണ്ട്, പ്രത്യേകിച്ചും രോഗപ്രതിരോധ സംവിധാനത്തിൽ.

ഈ പഠനത്തിൽ ഉൾക്കൊള്ളുന്നതെന്ത്?

പിഡിഎ സ്റ്റെന്റ് സ്ഥാപച്ചതിനു ശേഷം കുട്ടികളിലെ വ്യത്യസ്ഥ സൂചകങ്ങളിൽ സിറോലിമസ് മരുന്നിന്റെ രക്തത്തിലെ സാന്ദ്രത കണ്ടെത്താനാണ് ഈ പഠനം ലക്ഷ്യമിടുന്നത്. ആശുപത്രി രേഖകളിൽ നിന്നും താങ്കളുടെ കുട്ടിയുടെ അവസ്ഥയെപ്പറ്റിയുള്ള വിവരങ്ങൾ ശേഖരിക്കും. ഒരു വിദഗ്ധ ഡോക്ടർ താങ്കളോട് ഉദ്ദേശിക്കുന്ന പഠന രൂപരേഖ വിശദീകരിക്കുകയും താങ്കൾ നടപടികൾ മനസ്സിലാക്കി അതിന് സമ്മതം നൽകുന്നു എന്നുറപ്പാക്കാൻ ഒരു സമ്മതപത്രം ഒപ്പിടാനാവശ്യപ്പെടും. താങ്കൾക്ക് ആവശ്യമുള്ള ഏതുചോദ്യവും ദയവായി ചോദിക്കുക.

സ്റ്റെന്റ് സ്ഥാപിക്കാനുള്ള തീരുമാനത്തെ (കാർഡിയോളജിസ്റ്റുകളും കാർഡിയാക് ശസ്ത്രക്രിയാവിദഗ്ദ്ധരുമടങ്ങുന്ന വ്യത്യസ്ഥ വിഭാഗങ്ങളിലുള്ളവർ ഉൾപ്പെടുന്ന യോഗത്തിലെ ചർച്ച പ്രകാരം) തുടർന്ന് താങ്കളുടെ കുട്ടിയെ പഠനത്തിൽ ഉൾപ്പെടുത്തും. സിറം സിറോലിമസ് നിലവാരം പരിശോധിക്കാൻ താങ്കളുടെ കുട്ടിയുടെ രക്തം ശേഖരിക്കും. മറ്റ് പതിവ് പരിശോധനകൾ നടത്തുന്ന സമയത്തായിരിക്കത്തക്കവിധം രക്തം ശേഖരിക്കുന്നത് ക്രമപ്പെടുത്തും (ശസ്ത്രക്രിയയ്ക്കുശേഷം 1 മണിക്കൂർ, 24 മണിക്കൂർ, 7 ദിവസം). കുട്ടിയുടെ ആശുപത്രിയിലെ വിവരങ്ങൾ അണുബാധപോലുള്ള പ്രസക്തമായ വിവരങ്ങൾ എന്നിവ ശേഖരിക്കും. പതിവ് തുടർചികിത്സയിൽ കുട്ടിയുടെ അവസ്ഥയെപ്പറ്റിയുള്ള എതെങ്കിലും പ്രത്യക സംഭവങ്ങളും രേഖപ്പെടുത്തും.

എത്ര സമയം ഇതിനെടുക്കും?

പഠനത്തിനായി, ആശുപത്രിവാസത്തിലോ തുടർചികിത്സയിലോ മാറ്റമുണ്ടാകില്ല. പതിവ് രക്തപരിശോധനകൾക്ക് ഒപ്പം രക്തശേഖരണവും ക്രമപ്പെടുത്തും.

പങ്കെടുക്കുന്നവരുടെ ഉത്തരവാദിത്വങ്ങളെന്തെല്ലാം?

ഈ പഠനത്തിൽ പങ്കെടുക്കാൻ താങ്കളുടെ കുട്ടിയെ അനുവദിക്കുന്നത് തികച്ചും സ്വമേധയായാണ്, അത് താങ്കളുടെ വ്യക്തിപരമായ തീരുമാനമാണ്. മുൻകൂറായി അറിയിക്കാതെ ഏതുസമയത്തും എന്തു കാരണത്താലും താങ്കൾക്ക് പഠനത്തിൽ നിന്നും പിൻമാറാം.

പങ്കടുക്കുന്നവർക്ക് പ്രതീക്ഷിക്കപ്പെടുന്ന അപായങ്ങളെന്തെല്ലാം?

മരുന്നിന്റെ അളവ് കണ്ടെത്താനായുള്ള രക്തശേഖരണം മാത്രമാണ് പഠനത്തിലുൾക്കൊള്ളുന്നത്. പിഡിഎ സ്റ്റെന്റ് സ്ഥാപിച്ചതിന്റെ പ്രവർത്തനപരമായ നിലയും നേട്ടവും തുടർ അപഗ്രഥനവും വിലയിരുത്തലും ഉണ്ടാകും. ചെറിയ അളവ് രക്തം ശേഖരിക്കുന്നതുകൊണ്ടുള്ള കുറഞ്ഞ അളവിലും താഴെയുള്ള അപായമേ പങ്കാളികൾക്കുണ്ടാകൂ. അവ ആശുപത്രി നടപടിക്രമപ്രകാരം കൈകാര്യം ചെയ്യും. പഠനത്തിന്റെ ഭാഗമായി പ്രത്യേകിച്ച് ഇടപെടലൊന്നുമുണ്ടാകില്ല.

ഗവേഷണംകൊണ്ട് പങ്കാളികൾക്ക് പ്രതീക്ഷിക്കാവുന്ന നേട്ടങ്ങളെന്തെല്ലാം?
നവജാതശിശുക്കളുടെ പ്രായ വിഭാഗത്തിൽ ഡിഇഎസ്സിന്റെ സുരക്ഷിതത്വത്തെപ്പറ്റിയുള്ള ഉൾക്കാഴ്ച പഠനം നൽകിയേക്കാം. പരിചരണസ്വഭാവമുള്ള നടപടിയാണെന്നതിനാൽ, മോശം ഫലത്തിന്റെയും പ്രവർത്തനപരമായ തകരാറിന്റെയും കാരണം കണ്ടെത്താൻ തുടർ പരിശോധനയും വിലയിരുത്തലും സഹായകരമായേക്കാം. മുൻകൂട്ടിയുള്ള ഇടപെടൽ ആവശ്യമുള്ള രോഗികളെ കണ്ടെത്തുന്നതിനും അത് സഹായകരമായേക്കാം. സമാനമായ അവസ്ഥയിലുള്ള രോഗികൾക്ക് അനുയോജ്യമായ തന്ത്രങ്ങൾ ആസൂത്രണം ചെയ്യാൻ പഠനത്തിൽനിന്നും ലഭിക്കുന്ന വിവരങ്ങൾ ഭാവിയിൽ സഹായകമായേക്കാം.
ഈ പരീക്ഷണത്തിൽ പങ്കെടുക്കുന്നവർക്ക് പ്രതിഫലം നൽകുമോ?
പഠനത്തിൽ പങ്കെടുക്കുന്നതിന് താങ്കൾക്ക് പ്രതിഫലം നൽകില്ല.

എന്റെ/എന്റെകുട്ടിയുടെ ഈ പഠനത്തിലെ പങ്കാളിത്തം രഹസ്യമായി സൂക്ഷിക്കുമോ?
താങ്കളുടെ കുട്ടിയുടെ എല്ലാ രേഖകളും രഹസ്യമായി സൂക്ഷിക്കും. ഒരു പ്രസിദ്ധീകരണത്തിലും ഫലങ്ങളുടെ പ്രകാശനത്തിലും താങ്കളുടെ കുട്ടിയുടെ വ്യക്തിവിവരങ്ങൾ പ്രസിദ്ധീകരിക്കില്ല. പഠനരേഖകൾ അനന്തമായി വിലയിരുത്തലിനും തുടർ ചികിത്സകൾക്കുമായി സൂക്ഷിക്കും.

പഠനകാലത്ത് ഏതു സമയത്തും എനിക്ക് പഠനത്തിൽ നിന്നും പിൻവാങ്ങാനാകുമോ?

അതെ താങ്കൾക്ക് കഴിയും. താങ്കളുടെ തീരുമാനം താങ്കളുടെ പതിവ് വൈദ്യപരിചരണത്തെ ബാധിക്കില്ല.

പുതിയ ഏതെങ്കിലും കണ്ടെത്തലുകൾ/വിവരങ്ങൾ ഉണ്ടായാൽ എന്നെ അറിയിക്കുമോ?
അറിയിക്കും.

പഠനസംബന്ധിയായ പരുക്കുണ്ടായാലെന്ത് സംഭവിക്കും?
പഠനസംബന്ധിയായി പരുക്കൊന്നുമുണ്ടാകില്ല.

സൂചിപ്പിച്ചതിന് പകരമായി എന്തെങ്കിലും ചികിത്സയുണ്ടോ?
ബാധകമല്ല.
താങ്കൾക്ക് കൂടുതലെന്തെങ്കിലും ചോദ്യങ്ങളുണ്ടെങ്കിൽ ദയവായി ചോദിക്കുക, ഡോ. ഹരികൃഷ്ണൻ കെ എൻ (പ്രധാന ഗവേഷകൻ), ഫെല്ലോ, കാർഡിയോളജി ഡിപ്പാർട്ട്മെന്റ്, (ഇമെയിൽ: drhari.kurup@sctimst.ac.in ഫോൺ. 9746869303)

ഏതു വിശദീകരണത്തിനും ദയവായി ബന്ധപ്പെടുക ഡോ. മാല രാമനാഥൻ, മെമ്പർ സെക്രട്ടറി, IEC, SCTIMST, അഡീഷണൽ പ്രൊഫസർ, AMCHSS, SCTIMST (ഇമെയിൽ: iec.mem.sec@sctimst.ac.in ഫോൺ. 0471-2524234)

പഠന സമ്മതപത്രം

പഠനശീർഷകം:

പേറ്റന്റ് ആർട്ടീരിയൽ രക്തനാളത്തിൽ സ്റ്റെന്റ് സ്ഥാപിക്കേണ്ട നവജാതശിശുക്കളിൽ മരുന്നു പൂരട്ടിയ സ്റ്റെന്റിന്റെ സുരക്ഷിതത്വം.

പഠന നമ്പർ:

പങ്കാളിയുടെ പേര്.....ജനനതീയതി/വയസ്സ് (വർഷത്തിൽ).....

അച്ഛൻ/അമ്മ/രക്ഷകർത്താവ്.....

.....(ദയവായി കോളത്തിൽ ശരി അടയാളപ്പെടുത്തുക).

[ ] "പേറ്റന്റ് ആർട്ടീരിയൽ രക്തനാളത്തിൽ സ്റ്റെന്റ് സ്ഥാപിക്കേണ്ട നവജാതശിശുക്കളിൽ മരുന്നു പൂരട്ടിയ സ്റ്റെന്റിന്റെ സുരക്ഷതത്വം"എന്ന പഠന സംബന്ധമായി എനിക്കു നൽകിയ വിവരങ്ങൾ വായിക്കുകയും എനിക്കുണ്ടായ സംശയങ്ങൾ പരിഹരിക്കുകയും ചെയ്തു.

[ ] പഠനത്തിലെ എന്റെ കുട്ടിയുടെ പങ്കാളിത്തം സ്വമേധയാ ആണെന്നും. എന്റെ കുട്ടിയുടെ പതിവ് ചികിത്സയെയോ/നിയമപരമായ അവകാശങ്ങളെയോ ബാധിക്കതെ ഏതു സമയത്തും എന്റെ അനുവാദം പിൻവലിക്കാനെനിക്ക് സ്വാതന്ത്ര്യമുണ്ടെന്നും എനിക്ക് മനസ്സിലായി.

[ ] ഞാൻ പഠനത്തിൽ നിന്നും പിൻമാറിയാലും പഠനസംഘാംഗങ്ങൾക്കും ഇൻസ്റ്റിറ്റ്യൂഷണൽ എത്തിക്സ് കമ്മിറ്റി അംഗങ്ങൾക്കും എന്റെ കുട്ടിയുടെ ആരോഗ്യ രേഖകൾ പരിശോധിക്കാൻ എന്റെ അനുവാദം ആവശ്യമില്ലെന്നും ഞാൻ മനസ്സിലാക്കുന്നു. അതിന് ഞാൻ സമ്മതിക്കുന്നു.

[ ] മൂന്നാം കക്ഷികൾക്ക് നൽകുമ്പോഴോ പ്രസിദ്ധീകരിക്കുമ്പോഴോ എന്റെ കുട്ടിയുടെ വ്യക്തിവിവരങ്ങൾ നൽകില്ലെന്ന് ഞാൻ മനസ്സിലാക്കുന്നു.

[ ] ഞാൻ സ്വമേധയാ ഈ പഠനത്തിൽ പങ്കെടുക്കാൻ സമ്മതിക്കുന്നു.

[ ] ഈ സമ്മതപത്രത്തിന്റെ ഒപ്പിട്ട ഒരു പ്രതി എനിക്ക് ലഭിച്ചു.

പേര്	സാക്ഷിയുടെ പേര്
ഒപ്പ്	പങ്കെടുക്കുന്നയാളുമായുള്ള ബന്ധം
തീയതി	തീയതി

മെഡിക്കൽ റിസർച്ച് പ്രോജക്ടിനാവശ്യമായ സമ്മതപത്രത്തിനുവേണ്ടുന്ന എല്ലാ ഘടകങ്ങളും തൃപ്തികരമായി നിർവഹിച്ചിരിക്കുന്നുവെന്ന് ഞാൻ ബോധ്യപ്പെടുത്തുന്നു. പഠനപങ്കാളിയുമായി ഗവേഷണപദ്ധതിയെപ്പറ്റി സാങ്കേതികേതര പദങ്ങളുപയോഗിച്ച് എല്ലാ വിവരങ്ങളെപ്പറ്റിയും ചർച്ച നടത്തുകയും പ്രതീക്ഷിക്കാവുന്ന അപകടസാധ്യതകളും പാർശ്വഫലങ്ങളും വിശദീകരിക്കുകയും ചെയ്തു. പങ്കാളിയെ ചോദ്യങ്ങൾ ചോദിക്കാൻ പ്രേരിപ്പിക്കുകയും എല്ലാ ചോദ്യങ്ങൾക്കും ഉത്തരം നൽകുകയും ചെയ്തു എന്നും ഞാൻ സാക്ഷ്യപ്പെടുത്തുന്നു.

സമ്മതപത്രം വാങ്ങുന്ന ആളുടെ പേര്

ഒപ്പ്

ഡോ. ഹരികൃഷ്ണൻ കെ എൻ (പ്രധാന ഗവേഷകൻ), ഫെല്ലോ, കാർഡിയോളജി ഡിപ്പാർട്ട്മെന്റ്, (ഇമെയിൽ: drhari.kurup@sctimst.ac.in ഫോൺ. 9746869303)

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MASTER CHART

Patient No:	H No	CATH no	Age	Sex	wt	length	BSA	SPO2 prior	SPO2 post	SpO2 diff	DATE	Last follow up	Follow up	wt	Ht	Diagnosis	Dyspnoea	CYANOSIS	FC	LVEF	SpO2	RHYTHM	Situs	Cardiac Position	AV concordance	VA concordance
1	483777	79945	4	F	2.8	45	0.19	67	82	15	19/2/20	12/06/20	287	5.2	60	l isomerism, dorv, vsd, non confluent PAs	0	1	2	68	70	chb	A	L	C	DORV
2	484269	80062	4	M	2.8	47	0.19	75	85	10	03/04/20	30/11/20	236	4.8		CCTGA, VSD, PA, CONFL PAS, SMALL PDA	0	0	1		78	SR	S	D	D	pa
3	483241	80101	30	M	2.9	52	0.2	60	78	18	03/09/20	21/3/20	12			TOF, CRITICAL PS, SPELLS, CONFL PAS, LARGE CONAL CROSSING RVOT						SR	S	L	C	C
4	484595	80100	3	M	2.7	50	0.19	72	88	16	03/09/20	15/11/20	216	5.7	60	VSD, PULM ATRESIA, CONFL PAS	0	0	1	56	80	SR	S	L	C	PA
5	487521	80532	7	M	2.8	50		70	85	15	25/8/20	12/09/20	104	5.3		DTGA, VSD, PS,RESTRICTIVE ASD, PDA DEPENDENT PULM CIRCULATION	0	1	1		82	SR	S	L	C	D
6	487258	80541	20	F	3	54		73	88	15	26/8/20	12/06/20	100	5		UNBALANCED AVCD, RV DOMINANT, LEFT ISOMERISM, SHORT SEGM PULM ATRESIA, CONFLUENT GOOD PA, D MALPOSED AO, INTERRUPTED IVC	0	1	1		84	LAR	S	L	C	PA

IVC drainage	PV drainage	Tricuspid valve	Mitral valve	Pulmonary Valve	Aortic valve	GA RELATION	Arch	CoA	COMMENT	Hospital stay	Mechanical ventilation	Access site	Access sheath	Stent size: 3 3.5 4	Stent length: mm	STENT	STENT 2	DILATED TO	Survival	Sirolimus eluted	Sirolimus levels 1 hour	24 hours	7 days	1 month	Complications:	RPA	LPA	RPA FL	LPA FL
Interrupted IVC	LA	N	H	N	N	RP	L	0	L isomerism	6		RA	4	3	12	ABLUMINUS	0	3.25	1	25.2	38.8		<2		NEC, 2 PRBC transfusions	3.8	2	4.8	4
N	LA	N	N	A	N	LA	R	0		3		LA	4	3.5	24	ABLUMINUS	3.5,8	3.8	1	58.8	**>49.6**	13.78	3.8		0	3.8	3.6	5.6	5.2
N	N	N	N	PS	N	RP	L	0		7		RFA	4	3.5	12	ABLUMINUS	0	3.8	0	29.4	42.38	15.3	3.3		SEPSIS				
N	N	N	N	A	N	NRGA	L	0		14		RA	4	3.5	18	YUKON PC	0	3.7	1	113.4	33.84	9.38	3.28		SEPSIS, NEC, AKI	4	3.5	7.5	7
N	LA	N	N	PS	N	RA	L	0	POST BAS	3		RA	4	3.5	20	ABLUMINUS	0	3.6	1	49	**>49.6**	29	3.92		? SELF LIMITING DISSECTION	5	4	6	5.5
Interrupted	LA	N	H	A	N	RA	R	0	L isomerism, LPA stenosis	3		RFA	5	4	12	ABLUMINUS	3.5,20 PROM	3.7	1	33.6			<2.27		0	4	4	4.5	4.5