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Perioperative Anaesthetic Management for an Isolated or Combined Tetralogy of Fallot (TOF) and Cleft Palate/Lip Repairs - A Systematic Review and Meta-Analysis

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Abstract

The prevalence of cleft lip is 0.3 in every 1000 live births and the combination of cleft lip (CL) and palate(P) in every 1000 live births is 0.45.[1] The CL/P is commonly associated with various cyanotic and noncyanotic cardiac anomalies including Tetralogy of Fallot's (TOF).[2,3] Severe congenital heart disease (CHD) forms are diagnosed and treated before cleft care.[4] Most of the patients with CL/P can be operated on at a median age of 11 months without any serious complications, and intensive care unit admission or mortality.[2] Nowadays, most of the CL/P repairs are managed under the smile train scheme. The Smile Train is the world's largest cleft-focused organization, that empowers local medical professionals with the training, funding, and resources to provide 100%-free cleft surgery and other comprehensive cleft care to children globally. Since 1999, the Smile Train Society have supported safe and quality cleft care for 2+ million children in 95+ countries. Various palliative procedures like Blalock- Taussig (BT) shunt, ductus arteriosus stenting, balloon dilatation or stenting of right ventricle outflow tract (RVOT) and pulmonary artery angioplasty in neonatal life as a bridge to TOF correction surgery should be performed before the cleft repair to avoid the life-threatening complications like Tet spells(cyanotic spells), increased blood loss, re-exploration, hemodynamic instability, arrhythmias, air embolism, seizures, and even mortality.[5] Under any circumstances, the severe form of TOF should be managed prior to the CL/P repair, and such cases should

be operated in a tertiary care centre with established expertise in the care of both paediatric cardiac and craniofacial lesions. The anaesthetic management of Children with uncorrected TOF undergoing CP repair is a challenge and requires a thorough understanding of the pathophysiology of TOF, clinical presentation, sequelae of chronic hypoxemia like polycythaemia, recurrent Tet spells, coagulopathy, systemic venous thrombosis, cerebral abscess, endocarditis, and multiple organ dysfunctions, and respiratory infection to avoid the morbidity and mortality. Ideally, the TOF pathology and palliative interventions should determine the anaesthetic induction agent, i.e. presence or absence of dynamic RVOT obstruction with hypertrophic muscle bundles, presence of patent ductus arteriosus (PDA) and major aortopulmonary collateral arteries (MAPCAS) or previous modified BT shunt.[6] Generally, ketamine has been considered the induction drug of choice in TOF owing to its effect of an increase in systemic vascular resistance(SVR) and a decrease in the right to left intracardiac shunt. In the author's experience, narcotic based balanced general anaesthesia technique comprising a combination of fentanyl, midazolam, etomidate, sevoflurane in 100% oxygen, and vecuronium as a muscle relaxant can be safely utilised in TOF with both dynamic and static RVOTO, keeping in mind the principles of maintenance of SVR and systemic blood pressure, and adequate intravascular volume, avoidance of increase in inotropy and HR and proper de-airing of all intravenous lines to avoid the paradoxical air embolism.[6] There are no clinical data available in the literature concerning the clinical outcome of the concomitant combined repair of the TOF and CL/P to date. However, nowadays, in high-volume tertiary care centres, several combined cardiac and non-cardiac surgical procedures are performed successfully. Similarly, both TOF and CL/P can be repaired concomitantly by the experienced multidisciplinary team of paediatric cardiac surgeon and oral maxillofacial surgeons and paediatric cardiac anaesthetist and intensivist. This systematic review and meta-analysis focus on the perioperative anaesthetic management of isolated CP/L repair or combined TOF and palate repair.

Keywords: Balanced GA, BT shunt, cleft palate, CPB, Coagulopathy, Combined TOF and Palate Repair, Hyper -viscosity, Tet spells, Total correction.

Introduction

Cleft lip / palate (CL/P) are the most common congenital anomaly affecting approximately 1 in 700 individuals. These are frequently associated with syndromic and non-syndromic CHD. [7,8,9] The prevalence of CHD in cleft patients varies from 5.4%-15%, and the commonly associated cardiac anomalies are atrial septal defect (ASD), ventricular septal defect (VSD), patent foramen ovale (PFO), PDA, TOF, truncus arteriosus, transposition of the great arteries, and pulmonary hypertension (PH). [10,11,12,13]. TOF is the most common cyanotic CHD associated with CL/P. TOF has four variants;1. classical TOF with PS; 2. TOF with complete atrioventricular (AV) canal defect; 3.TOF with absent pulmonary valve syndrome; 4. TOF with pulmonary valve atresia and major aortopulmonary collateral arteries (TOF/PA/MAPCAs).[14] The fourth category is the most extreme variant of TOF, in which complete atresia of the pulmonary valve replaces PS, and pulmonary blood flow is supplied by the MAPCAS or PDA. Consequently, the pathophysiology might range from a"pink" Fallot with normal saturation due to minimum RVOTO and left to right shunt across the VSD, to real "blue" babies with very low saturations and frequent Tet spells.[14] Patients of TOF can present for non-cardiac surgery either before or after the TOF

correction. Some authors have reported that the presence of CHD impacts the management and outcomes of cleft care, and therefore, the knowledge of the pathophysiology of the TOF is the key to deliver safe anaesthesia and manage perioperative complications.[4,7] Patients in group 4, with significant sequalae of chronic hypoxia require palliation with systemic to pulmonary shunt like BT shunt, or DA stenting or total correction for TOF under cardiopulmonary bypass (CPB) before CL/P repair to avoid the major morbidity and mortality.[5] The occurrence of TOF in a CP patient may increase risks of developing specific complications like Tet spells, increased bleeding requiring blood transfusions and re-explorations, arrhythmias, endotracheal bleed, paradoxical systemic air embolism, and multiorgan failure.[15,16] Following a successful intracardiac repair of TOF, the CL/P repair can be performed under standard balanced general anaesthesia technique without any added risk.[15] Indeed, recently, in high volume tertiary care centres several combined complex cardiac and non-cardiac surgical procedures have been possible with satisfactory short- and long-term survival.[16] Similarly, both TOF and CL/P can be repaired concomitantly by the experienced team. The surgical management should be dictated by anatomy regardless of genetics. This comprehensive systematic review and meta-analysis will highlight the perioperative anaesthetic management of a patient of TOF with CL/P undergoing CL/P repair surgery, or combined TOF and palate repair.

Methods

Electronic searches for this comprehensive systematic review and meta-analysis included PubMed, Medline, research gate, Google, google scholar and the Cochrane database and research gate up to May 2024. Selection criteria were case reports, case series randomized studies, meta-analysis, reviews, and clinical guidelines of TOF with cleft lip/ palate. The primary focus was on clinical presentation, pathophysiology, management of Tet spells, coagulopathy in TOF, initial management, anaesthesia for TOF/ CL/P repair, hemodynamic goals in severe TOF, associated congenital anomalies and syndromes, complications of chronic hypoxemia, combined TOF and palate repair, postoperative management, and early and long-term outcomes of TOF repair.

Discussion

The overall incidence of orofacial clefts is around 1 in 700 live births. The most of the orofacial clefts presents either isolated as unilateral cleft lip 22%, unilateral cleft lip and palate (23%), bilateral cleft lip and palate 12%, cleft palate alone (43%) or associated with other congenital malformations and syndromes (Table 1).[1,2,3,17] The commonest associated CHD are TOF, transposition of greater vessels, atresia of tricuspid valve, total anomalous pulmonary venous connection, truncus arteriosus, ebstein's anomaly, hypo- plastic left heart syndrome and pulmonary atresia, ASD, VSD, patent foramen oval (PFO), PDA, pulmonary stenosis, aortic stenosis and coarctation of aorta.[3,10,11,12,18] A systematic review of twelve series found an estimate of 7.42% of CHD among non-syndromic CL/P patients.[19]The CL/P has been associated with TOF / double outlet right ventricle (DORV) in approximately 6.4%and 15.7% respectively.[5] TOF was first described by bishop and anatomist Nicolas Steno in 1671, its anatomy was more extensively described first time by French physician Etienne Louis Fallot in 1888.[6] It is characterised by four cardinal features: 1.Non-restricted mal -aligned VSD; 2. RVOT obstruction, which can be fixed or often a dynamic due hypertrophic muscular bands in the RVOT; 3. overriding of the aorta, more than 50% is associated with significant desaturation(cyanosis)

; 4. consequent RVH as a sequalae of these three.(Fig.1a &1b) All derived from an embryonic antero cephalad deviation of the outlet septum.[6] There is a right to left shunt through the VSD redirecting blood to the aorta instead of the pulmonary artery resulting in low systemic arterial oxygen saturation. Hence, hypoxia is unresponsive to supplemental oxygen.[6] In addition, more than 50% patients of TOF with CL/P have been reported to be associated with several genetic syndromes, including trisomy 21 (Down syndrome), DiGeorge, CHARGE, Velocardiofacial Syndrome, Alagille syndrome' (trisomies 21, 18, 13), microdeletions of chromosome 22q11.2, and JAG1, NOTCH2 mutations, NKX2-5, methylenetetrahydrofolate reductase polymorphism, and mutations in TBX1 and ZFPM2.[5,6, 20,21]

Pathophysiology might range from a "pink" Fallot with almost normal saturations and only marginally impaired physiology with mild RVOTO and left to right shunt, to the real "blue" babies and frequent hypoxic spells due to very low saturations, because of severe RVOTO. [6,14,22,23,24]

Clinically, the classic presentation of TOF with CL/P is a progressive cyanosis (blue tinge most evident in the lips, nose, and extremities), depending upon the RVOTO, degree of aortic over-ride and systemic vascular resistant(SVR) and pulmonary vascular resistance(PVR).[6] Additional symptoms comprise as shortness of breath and rapid breathing especially during feeding or exercise, poor weight gain, easy fatiguability during play or exercise, irritability, crying for long periods of time, and fainting.[6,22] The patients with TOF and CL/P may present in any of the sequalae of chronic hypoxia like polycythaemia, Tet spells, coagulopathy, systemic venous thrombosis, cerebral abscess, endocarditis and organ failure. In addition, these children may have the specific features and complications of associated syndromes such as respiratory obstruction, congenital brain abnormalities, delayed motor and speech abnormalities (Table 1).[17,25,26,27] In addition, patients of TOF with CL/P may suffer from chronic rhinorrhoea secondary to reflux of feeds into the nasal passages, and upper respiratory tract infections, repeated chest infections and obstructive sleep apnoea, and neuromuscular disorders.[16]

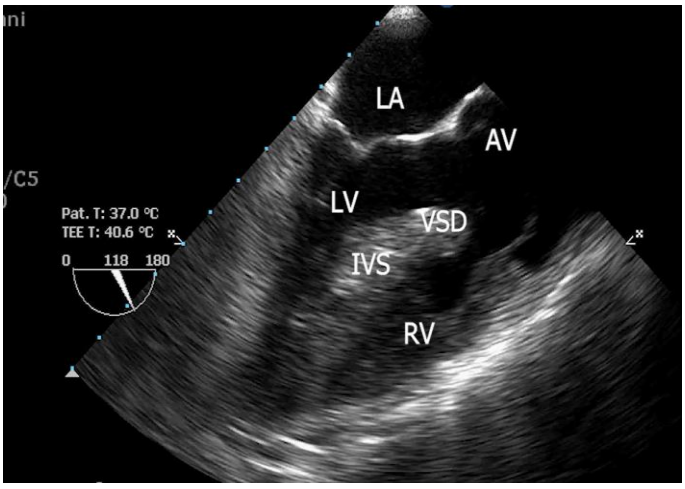

Fig. 1a: ME-LAX, TEE view at 118 Degree. 2-D examination reveals large subaortic VSD, about 50% aortic over-ride as aortic valve is shifted towards the RV. In addition, severe IVS and RV hypertrophic but having normal RV contractility. All the features suggestive of TOF (labelled). In addition, MV appears to be normal without any thickening and calcification and chordae are nicely seen attaching to both AML and PML.

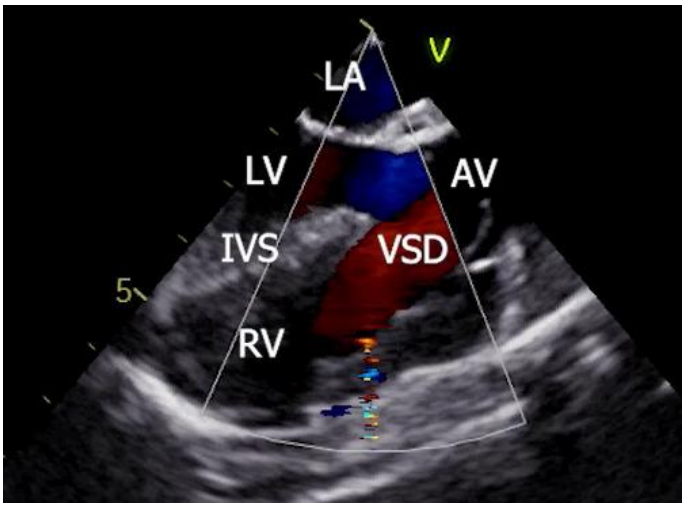

Fig. 1b: ME-LAX, TEE view at 121 Degree. The color doppler examination reveals large subaortic VSD with Bidirectional flow (red and blue jet) (Labelled).

ME-LAX TEE: mid eosphageal long axis Transesophageal Echocardiography, VSD: ventricular septal defect, RV: right ventricle, IVS: interventricular septum, TOF: tetralogy of fallot, MV: mitral valve, AML: anterior mitral leaflet, PML: posterior mitral leaflet.

S.No.	Name of the syndrome	Clinical features	Complications
1	Pierre Robin sequence	Triad of glossoptosis, micrognathia and airway obstruction	• Upper respiratory tract obstruction respiratory difficulty. • Hypoxic injury, cerebral impairement, • Cor pulmonale, pulmonary hypertension and hypoxaemia.
2	Van der Woude syndrome	Lower lip pits are the hallmark. hypodontia, missing maxillary or mandibular second premolar teeth, absent maxillary lateral incisor ankyloglosia. congenital heart defects, Hirschsprung disease popliteal web.	• Presence of rare limb abnormalities. • Presence of congenital brain abnormalities. • Presence of congenital Heart defects
3	Treacher collin syndrome	Hypertelorism, downward slanting of lower palpebral fissure malformation of external ears, parrot beak nose. Dysplasia or aplasia of minor salivary glands, Hypoplasia of zygomatic bone or maxilla, underdeveloped mandible, teeth agenesis and discolouration.	• Severe eye abnormalities which may cause vision loss. • Delay in motor and speech development
4	Stickler syndrome	Flattened facial appearance. eye abnormalities, hearing loss, and joint problems	• Tongue fully or partly blocks child's airway •Cardiac problems
5	Apert syndrome	Craniofacial deformities, acrcephaly, hyperteleorism, and flattened nose high-arched palate, maxillary hypoplasia, crowding in teeth, delayed dentition, ectopic teeth, abnormal arrangement of teeth, and crowding in teeth.	•Upper respiratory tract disorders, sleep apnea, and several mental disorders
6	Cerebro-costo mandibular syndrome	Combination of mandibular hypoplasia and gap in between the ribs tracheal cartilage abnormalities, elbow hypoplasia and spina biδidiaG	• Upper airway obstruction • Language disorder • Conductive hearing loss • Mental retardation
7	Klippel- Feil syndrome	Congenital fusion of at least two of seven cervical vertebrae in the cervical spine deafness, congenital heart disease, and renal anomalies.	•Difficult intubation should be anticipated due to severely limited flexion and extension of the cervical spine

Table 1: Syndromes associated with cleft lip and palate [17,25,26,27]

Preoperative considerations

Children with TOF and CL/P scheduled for the CL/P repair may present with previous surgical palliation like BT shunt or with cardiac catheterization laboratory interventions like ductus stenting, pulmonary valvuloplasty and pulmonary artery angioplasty, or subset of patients who have undergone total correction for severe TOF. Now a days, total correction can be performed safely in the neonatal period particularly in the high-volume centres, though some technical difficulty may be encountered. However, Some children are unsuitable for total correction and require palliation with systemic to pulmonary shunt i.e. modified BT shunt like neonates with pulmonary atresia, hypoplastic pulmonary annulus, hypoplastic pulmonary arteries, unfavourable coronary artery anatomy, age of 3 to 4 months old, weighing less than 2.5 kg or who have medically unmanageable hypoxic spells, and regressed or poor LV.[28,29] A child with CL/P with uncorrected severe TOF can be in one of the sequelae of chronic hypoxemia (polycythaemia, coagulopathy, Tet spells, systemic venous thrombosis, cerebral abscess, endocarditis, organ failure) that may complicate the perioperative course of CL/ P repair and represents an additional risk of increased morbidity and mortality.[30]. Therefore, it is recommended to address the sequelae of chronic hypoxemia.

Hyper- cyanotic Spells (Tet Spells)

Some conscious infants with TOF may suddenly develop episodes of intense blue skin, nails, and lips, and deeper and faster breathing. Most common age for Tet spells is 2 to 4 months, and can be triggered by crying, playing, feeding, or stooling or at times of stress, and long fasting. Even, various anaesthetic and surgical manipulations can trigger the Tet spells. The spells are caused by sudden increase in RVOTO due to increase in

cardiac inotropy or decrease in the SVR exaggerating the right to left shunt, leading to sudden and rapid fall in the PO2. The manifestation of Tet spells in OR varies from arterial desaturation to bradycardia, hypotension, RV distension, sweating, seizures, syncope, stroke or coma to brain damage, and death. Tet spells require a rapid and aggressive approach including positioning (knee-chest) to increase SVR, oxygen therapy to cause pulmonary vasodilation and systemic vasoconstriction, and intravenous fluid bolus (10-15 ml/kg) to improve the right ventricle filling and pulmonary flow; sedation with fentanyl (1-2 mcg/kg) or morphine sulphate,(0.2 mg/kg) suppresses the respiratory centre and abolishes hyperpnea (and thus breaks the vicious cycle) in awake patient. Intravenous beta-blockers (metoprolol, esmolol) have been used to reduce the RVOTO by relaxing the muscle, and intravenous phenylephrine (5-10 mcg/kg), norepinephrine (5-10 mcg) boluses to increase the SVR; Sodium bicarbonate (1-2 Meq/Kg) or based on the ABG analysis base deficit, (Base deficit x body weight x 0.3) as ml of sodium bicarbonate to correct acidosis. Intravenous calcium chloride (10mg / kg) can also be administered for a cardiac support. Refractory Tet spells under anaesthesia requires additional measures like administration of inhalational anaesthetics (halothane, sevoflurane) to decrease the RVOT contractility. Prostaglandin (PGE1, 0.05 -0.1 mcg/kg/min) infusion can be used to keep ductus arteriosus patent that helps maintaining pulmonary blood flow and so arterial oxygen saturation in the more severe extreme form of the TOF in the neonates. Dexmedetomidine (0.2mcg/kg/min) an alfa 2 agonist with sedation, anxiolysis, central sympatholytic, and decreasing catecholamine properties, may be able to control precipitating factors (catecholamines) of Tet spell like tachycardia, hypercontractile RVOT, and so ameliorate the life-threatening refractory Tet spell. Patients unresponsive to the pharmacological management, big arteries like abdominal aorta and femoral arteries may be compressed by the anaesthesiologist to increase the SVR and decrease the right to left shunt. Patients presenting with repeated Tet spells and unsuitable for TOF correction may be subjected to the cardiac catheterization interventions like RVOT dilatation, balloon Pulmonary Valvotomy, PA angioplasty, ductus arteriosus stenting to reduce the RVOTO to enable adequate pulmonary blood flow to allow oxygenation. [14,31,32,33] Gold standard for management of refractory Tet spells is either palliation in form of modified BT shunt to improve the pulmonary blood flow and PO2 or a total intracardiac repair under cardiopulmonary bypass. [34] Currently, most children are managed with a complete surgical repair with relief of RVOTO by either transannular patch or valve sparing repair techniques in infancy without preceding palliation.[6] In desperate scenarios and a fatal Tet spell that is refractory to conventional therapy may necessitate the use of ECMO as hemodynamic and respiratory support or as a bridge to palliation or total correction of the TOF.[14]

Some neonates develop compensatory changes in chronic hypoxia to maintain the oxygen saturation; polycythaemia, increased blood volume and haemoglobin, vasodilation, neovascularization, and alveolar hyperventilation to maintain systemic oxygen balance, and respiratory alkalosis to counter metabolic acidosis. [6,35]

Coagulopathy in TOF

Coagulation abnormalities have been reported at an early age and highest in children of under-fives.[36] Several clotting abnormalities have been described particularly when haematocrit exceeds 65%. Higher haematocrits are associated with a greater bleeding diathesis secondary to

coagulopathies. Elevated haemoglobin results in hyper-viscosity with resultant increased endothelial dysfunction, platelet activation and subsequently accelerated activation of the clotting cascade. Coagulation abnormalities which may have a serious adverse impact on the prognosis include thrombocytopenia, von Willebrand factor deficiency, fibrinolysis and disseminated intravascular coagulation (DIC).[6,37] Hypoxia leads to endothelial injury, and exposure of the sub-endothelial space to the platelets, with subsequent activation of the coagulation cascade and a state of low grade or subclinical DIC.[38] Uncorrected TOF patients require screening for preoperative platelet count, Prothrombin time (PT), activated partial thromboplastin time (APTT), and in addition, D-dimer assay in suspected DIC.[39] Artifactually elevated PT and PTT with erythrocytic blood as a result of decreased plasma volume in high haematocrit blood can result in spuriously elevated measures of the PT and PTT.[40]

Administration of platelets, fresh frozen plasma (FFP), cryoprecipitates and antifibrinolytics like tranexamic acid(20 mg/kg) and ε-aminocaproic acid(50- 100mg/kg) improve postoperative haemostasis in patients with cyanotic CHD.[6] Some adult and paediatric patients (>1 month of age) with significant coagulopathies undergoing surgery may require a topical application of Tisseel (fibrin sealant glue) as an adjunct to hemostasis when control of bleeding by conventional surgical techniques (such as suture, ligature, and cautery or friable tissue) is ineffective or impractical.[41] So, practically, Tisseel can be applied on the suture line bleeding of cleft palate repair. Patients with life threatening bleeding, and haemostasis with other measures fails or its due to Factor VII Deficiency then recombinant factor VIIa (15 to 30 mcg/kg) intravenous bolus, every 4 to 6 hours can be administered until haemostasis achieved.[42] Furthermore, rFVIIa is used to control the bleeding in severe thrombocytopenia, platelet function disorders, and impaired liver function, usually noticed in the patients of TOF with longstanding arterial desaturation.[43] However, serious arterial and venous thrombotic events have been reported following administration of this drug.[42,43] Selectively intravenous Desmopressin 0.3-0.4 mcg/kg over 30 min can be used, as it increases the release of tissue plasminogen activator, stimulate the release of von Willebrand factor and increases factor VIII levels up to 2 to six fold and enhances platelet aggregation and adherence and likely reduces the intraoperative blood loss and blood transfusion, but risk of hypotension needs to be mitigated.[44,45,46]

Hyper-viscosity

Chronic hypoxemia in a patient of TOF causes increased erythropoietin production in the kidney resulting in polycythaemia or erythrocytosis. Children with a haematocrit of > 65% often present with hyper-viscosity symptoms like headache, faintness, dizziness, blurred or double vision, fatigue, lethargy , myalgias, muscle weakness ,paraesthesia and dissociative mentation.[6] It's not the hematocrit number rather symptomatic hyper viscosity is the indication for therapeutic phlebotomy with a partial isovolumic exchange transfusion as a rescue therapy to lower down the hematocrit to approximately 45%.[47,48,49] An elective preoperative isovolumic exchange transfusion decreases the incidence of haemorrhagic complications of surgery.[50] Preoperative fasting of a child needs to be avoided in the presence of erythrocytosis, and administration of intravenous 5% dextrose in water with 0.45% NaCl (1-2 ml / kg /hr) during nil orally period to avoid the spur of the hyper viscosity symptoms and Tet spells. In Addition, hyper-viscosity and erythrocytosis in patients with TOF

can cause cerebral venous thrombosis in younger children.[6] Furthermore, patients of TOF with polycythaemia remains at the risk of development of brain abscess, stroke and seizures. Hyper-viscosity causes sluggish cerebral circulation blood flow resulting in microthrombi formation. [51, 52]

Sequences of the repairs in TOF with CL/P

Toubat O et al. have reported a cohort in 2021, including 127 patients with CL/P with CHD comprising: ASD, TOF or DORV, arch defects, truncus arteriosus, and total anomalous pulmonary venous communication (TAPVC). Nearly 2/3 of the patients underwent CHD interventions on CPB, and several required even deep hypothermic cardiac arrest for cardiac repair.[5] The authors have reported that the presence of CL/P did not impact the duration of CPB time and aortic cross clamp time (ischemia time) and mortality. However, increased morbidity as airway reintervention, postoperative mechanical support, diaphragmatic plication, pacemaker implantation, thoracic duct ligation, reoperation for bleeding have been reported.[5,53] The authors have also suggested that median interval of 199 days between CHD intervention and CL repair, and median 499 days between CHD repair and CP repair, interval between CL/P repair and CHD repair was 976 days.[5] Several other authors have also reported a successful cardiac surgery prior to the CL/P repair in post neonatal period.[5,54] Therefore, TOF correction should be performed prior to the CP/L repair.[5] Such a practice will prevent the perioperative complications during CL/CP repair like Tet spells, air embolism, uncontrolled bleeding due to coagulopathy, and sign and symptoms of hyper-viscosity. The authors also suggest that to avoid the complexity of the postoperative period in patients operated for isolated CHD surgery and CL/P left untreated, the postoperative complications may be prevented by performing a combined cardiac and CL/P surgery. It's further clarified that most of these reported complications and mortality are inherent to the complex cardiac surgery itself and not directly linked to the CL/P. [55]

A subset of pink TOF, physiologically behaves like a large unrestricted VSD with a left-to-right shunt and absence of cyanosis. So, Patients with minimum RVOTO or "Pink TOF "can undergo CL/P repair safely before TOF correction, considering the normal sinus rhythm is maintained, and tachycardia, sympathetic stimulation and hypercontractility are avoided.[6,14] In addition, the focus should be to avoid the further exacerbation of the pre-existing PAH and RV dysfunction by avoiding the hypoxia, hypercarbia, acidosis and sympathetic stimulation, and administration of pulmonary vasodilators such as prostanoids, endothelin receptor antagonists, nitric oxide and phosphodiesterase inhibitors and furosemide also to decongest the lungs.[56]

Fortunately, anaesthesia and surgical practices are continually evolving with the innovations in preoperative evaluation and preparation, anaesthesia techniques and monitoring, surgical techniques like avoidance of transannular patch, and revamped perfusion management, availability of effective inodilators (levosimendan, milrinone), and cell salvage, and improved postoperative care makes it possible to conduct successful combined cardiac and noncardiac operations. Recently, the cardiac anaesthesiologists are becoming more accustomed and experienced in managing various combined surgeries. [57,58] Yang Y et al have reported a largest domestic single-centre report on several successful combined cardiac and lung operations involving several coronary artery bypass grafting (CABG)surgery with various procedures like lung surgeries, radical mastectomy, distal radical gastrectomy (Belot type II); colostomy,

transabdominal anterior resection of rectal cancer, and liver cancer radical resection, cholecystectomy, left renal and ureter radical resection, transurethral resection of bladder cancer. In addition, aortic and mitral valve replacement combined with lung surgeries. Even, the heart and gynaecological operations included mitral valve replacement (MVR), TV de-Vega repair, and radical hysterectomy, and aortic and mitral valve replacement with hysterectomy, atrial tumour thrombus and inferior vena cava tumour thrombus removal and hysterectomy. [16,58] The authors have concluded that simultaneous surgery is feasible and safe for patients suffering from cardiac and noncardiac diseases, especially for those early malignant tumour patients with severe CAD. [16,58]

So, the authors speculate that if such a complex combined cardiac and non-cardiac procedures can be performed successfully without any major morbidity and mortality, then there is always a possibility to perform combined TOF and CL/P repair safely by the experienced team. The sequences of the repairs should be as follow: First carry out TOF repair via median sternotomy approach. Anticoagulation for the CPB is accomplished with unfractionated heparin (300 units/kg) to achieve a target activated clotting time (ACT) of >480 seconds. A Standard moderate hypothermic(28^0c) CPB (aorto-bicaval venous cannulation) is used with antegrade del Nido potassium enriched cardioplegic myocardial protection. The surgical procedure involves the VSD patch-closure with Gore Tex patch in such a way that over-riding of aorta is corrected, and aorta exits from the LV. Followed by excision of hypertrophic muscle bundles and relief of the RVOT obstruction (Figure -2), and RVOT augmentation using pericardial patch, leaving an anatomically normalized heart. After achieving rewarming, haemostasis and deairing of cardiac chambers and normal sinus rhythm or paced rhythm, the patient is weaned off CPB, and heparin anticoagulation is reversed with protamine (1:1.3). The desired infusions of inodilators and vasopressors (Milrinone; 0.35-0.75mcg/kg/min, dobutamine; 2.5-5 mcg/kg/min or noradrenaline; 0.025-0.1mcg/kg/min) are administered for cardiac and hemodynamic support. FFP, Platelets and cryoprecipitates, antifibrinolytics, calcium chloride are also infused precisely. After ensuring the complete haemostasis, the chest is closed, and the CL/P is repaired as usual. However, the heparinised CPB circuit and both aortic and venous cannulas should be preserved sterile for emergency reinstitution of CPB if required during CL/P repair due to refractory hemodynamic deterioration. Finally, the patient is shifted to the cardiac ICU for elective mechanical ventilation. Once the patient maintains hemodynamic, normal arterial blood gas and serum electrolytes values and haemostasis of TOF and cleft repairs, he is weaned off the mechanical ventilation.

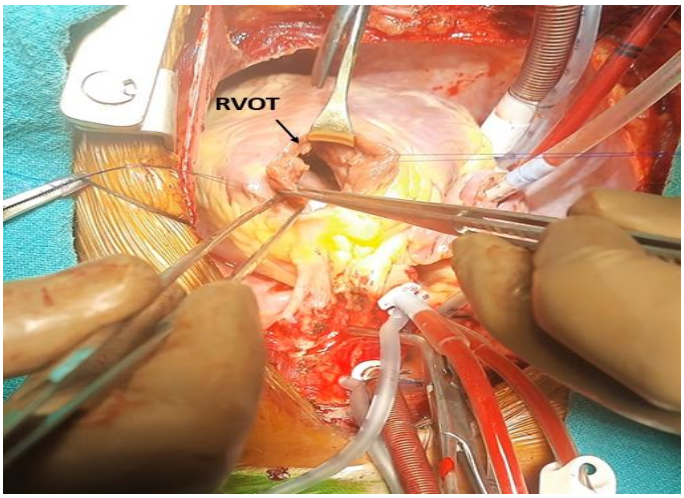

Fig. 2: The intraoperative photograph showing vertical right ventriculostomy for excision of hypertrophic muscular bands from the RVOT to relieve the RVOTO and RVOT augmentation using pericardial patch. RVOT- right ventricular outflow tract, RVOTO- right ventricular outflow tract obstruction.

The authors opine that the described protocol will prevent the repeated hospitalisations for two separate surgical procedures, will provide better post operative care as the patient is managed in postoperative well equipped cardiac ICU, and the healing would be faster after combined repair with improved tissue oxygenation, and patient will be on mechanical ventilation (oxygen therapy). Postoperative, TOF repair patients routinely receive blood products and antifibrinolytics, and calcium chloride for control of the medical bleeding secondary to the defects in the coagulation cascade, platelets, and fibrinogen, and same will be applicable for combined TOF and CL/P repair. Single antimicrobial course will also be sufficient for both the repairs. The common post cleft palate repair complication like air way obstruction would be 100% eliminated as patient will remain intubated for the routine 6- 12 hrs elective mechanical ventilation in the cardiac ICU following the TOF correction surgery. The post cleft repair bleeding control would also be superior as various measures used to control the cardiac bleeding would automatically take care of the cleft bleeding also, leading to the improved short-term outcome. There would be less psychological trauma, less burden on the family and better social acceptance and cost effective also. In addition, the patient stays in the hospital for at least 2-3 weeks, so post CL/P repair continuous followed up can be performed. Therefore, it is recommended to perform combined TOF and the CL/P repair in a tertiary care centre (Table 2).

Severity of TOF and CL/P	Clinical presentation	Procedure	Management
Severe symptomatic TOF with CL/P, 6 to 11 months age. [59,60,61,62]	Presents with Tet spells, dyspnoea, hyperviscosity, coagulopathy	Palliation: Ductus stenting or BT shunt Total correction of TOF under CPB CL/P repair after 3-6 months. [5,53]	Use opioids based balanced anaesthesia technique, with invasive montoring Hemodynamic goals: maintain SVR, normal sinus Rhythm, Low PVR, adequate IV volume Avoid tachycardia, hypercontractility Use Phlebotomy if HCT >65% Antifibrinolytics like Tranexamic acid, EACA, FFP, Platelets to control the bleeding Echocardiography reassessment for BT shunt patency and TOF correction for any residual lesions before CL/P repair Hemodynamic and anaesthetic goals after total correction: unbothered. [6,75,76,78,79,80]
Asymptomatic less severe TOF with absent to mild RVOTO. [6,14]	Pink TOF without Tet spells, or sequalae of chronic hypoxia Left to right shunt in VSD	CL/P repair is safe before TOF correction	Minimize increase in RVOTO by avoiding Prevent increase in PAH, inotropy and PVR and decrease in SVR To prevent right to left shunt across the VSD
Severe TOF with CL/P Age 6months to 11 months	Tet spells controlled with beta blockers	Consider for CL/P repair before TOF palliation or repair	Use narcotics-based GA with fentanyl, ketamine/ etomidate, midazolam, sevoflurane, dexmedetomidine Needs invasive monitoring Achieve the hemodynamic and anaesthetic goals Follow the bleeding control strategies Potential for the postoperative bleeding Needs haemostasis: gel foam, Tisseel - fibrin sealant, BP control and strain control TOF repair after 3-6 months. [6,57,58,75,76]
Severe symptomatic TOF with CL/P 6-11 months of age Associated respiratory syndromes. [59,60,61,67,68]	Uncontrolled Tet spells, coagulopathy, hyperviscosity syndrome	Combined TOF and CL/P repair in a tertiary care centre by multidisciplinary experienced Team	First TOF correction under standard narcotics based balanced anesthesia technique, invasive monitoring for CPB Using mid -sternotomy approach and heparin anticoagulation standard mild hypothermic CPB and K enriched myocardial protection technique Reverse heparin with protamine; achieve hemostasis Close chest Then Perform CL/P repair Less or no concerns about post op respiratory obstruction as endotracheal tube remains insitu for routine postoperative elective ventilation after TOF repair , better healing of CL/P repair due to improved arterial saturation and routine use of FFP, platelets, calcium and antibiotics Less strain and coughing Cost effective Better social acceptance

Table 2: Management strategies for a patient of TOF with CL/P

Timing of the repair

CL is classically repaired between 6 and 12 weeks but nowadays it can also be operated in neonatal period. CP is usually repaired later, between 3 and 9 months, in a one or two stage procedure to promote normal speech development and reduce nasal regurgitation. Most of the surgeons follow the rule of 10 for CL/P repair; the child is at least 10 weeks of age or older, 10 pounds of weight, 10gm% of haemoglobin, <10,000 /mm3 of white blood cell count at the time of surgery.[59,60,61] The American Cleft Palate - Craniofacial Association (ACPA) recommends palatoplasty prior to 18 months, with most centres performing palatoplasty between 6 and 14 months of the age. However, there are data to suggest that late palatoplasty is associated with poorer long-term speech outcomes.[62]

The optimal age for the elective repair of TOF with pulmonary stenosis appears to be between 3 and 6

months, closer to 3 months if pulmonary valve preservation is likely. Primary neonatal or early repair is the preferred approach for the treatment of symptomatic infants with TOF. [63,64] Transcatheter ductal stenting has been shown to be an appropriate alternative to the surgical palliation for patients with ductal-dependent pulmonary blood flow with equal to superior outcomes to surgical shunts, and success rates ranging from 80% to almost 100%.[65]. Eventually, the authors are of the opinion that the optimum timing for isolated or combined TOF and cleft palate repair is around 3-11 months of age.

Perioperative management

Preoperative evaluation and preparation

Perioperative anaesthetic management for patients with unrepaired TOF coming for CP/L repair is a challenge and represents an additional risk of increased perioperative morbidity and mortality.[5] The information about the associated genetic anomalies and various syndromes is most vital, as may have a negative impact on the postoperative outcome [Table 1]. Hence, a mandatory comprehensive preoperative evaluation of the patient by multidisciplinary team involving paediatric cardiologist and cardiac surgeon, otolaryngology, cardiac anaesthesiologist plays a major role in the perioperative management and outcome. Such children require proper evaluation and systemic examination regarding gestational and birth history, severity of cyanosis whether static, intermittent, dynamic, progressive, continuous depending upon the severity of RVOT obstruction. Many of these children will have SpO2 of 75 - 80% as 'normal' for their anatomy. Details about the medications, cyanotic spells, coagulopathy, and previous TOF palliations or total correction should be available, as these factors can determine the anaesthesia technique and major morbidity. Recent transthoracic echocardiography evaluation should be available to confirm the diagnosis of TOF (Figure 1a & 1b), associated cardiac anomalies like PDA, additional muscular VSD, ASD, and biventricular functions, direction of shunt across VSD particularly in children scheduled for combined TOF and cleft palate repair. In addition, cardiac cath. Study about the coronary arteries courses, RVOT gradient, MAPCAS, valvular lesions, and pressures and saturations in various cardiac chambers should be available. [6,66] ECG confirms the right axis deviation, tall R wave in V1: RVH, tall P waves (P pulmonale) for right atrial enlargement and any arrhythmias. Look for any atrial re-entrant tachyarrhythmias (AF), ventricular dysrhythmias, QRS duration > 180 MS as may be associated with increased morbidity and mortality. The detailed biochemistry values should be known such as hematocrit, platelet values, PT, PTT and INR values along with liver function and renal function tests, also total white blood cell count to rule out the infection due to associated cleft palate. Arterial blood gas analysis should be performed to know the baseline hematocrit, Pao2, absolute base excess or base deficit, metabolic acidosis with pH. Children with high hematocrit (>65%) and associated hyperviscosity syndrome may require phlebotomy in preoperative period.[6] Chest X-ray reveals a boot shaped heart due to hypoplastic pulmonary artery and RV hypertrophy, and oligemic lung field suggestive of decreased pulmonary blood flow because of RVOTO. (Figure 3) A proper airway assessment is required to assess any difficulty in face mask ventilation, placing the laryngoscope blade, and securing the airways with endotracheal intubation. [67,68]. Hyper-viscosity causes sluggish blood flow in cerebral circulation that results in micro-thrombi formation, even precipitates Tet spells. Therefore, nil orally period should be zero, and an intravenous infusion at a rate of 2ml/kg /hr should be initiated throughout the

fasting period to maintain adequate intravenous hydration.

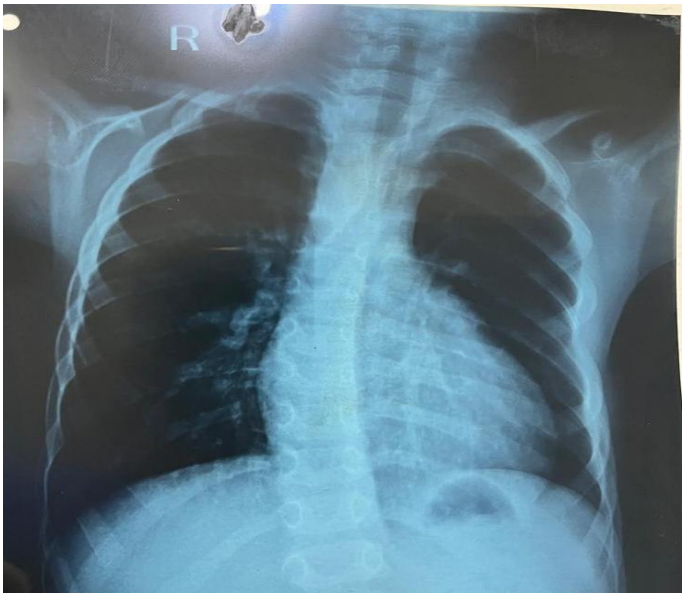

Fig 3: Chest X-Ray (PA) view showing boot shaped heart with upward pointing cardiac apex due to RVH of TOF. In addition, the lung fields are oligemic due to decreased pulmonary blood flows because of significant RVOTO causing right to left shunting across the VSD. The bronchovesicular markings are reaching up to < 1/3 of the lung's parenchyma. Note that this patient is also having scoliosis. TOF- tetralogy of Fallot, RVH- right ventricular hypertrophy, VSD- ventricular septal defect

Operated cases of modified BT shunt should be reassessed before cleft palate repair for its patency by clinically i.e. decrease in the severity of Cyanosis or absence of Tet spells, PaO2 of 75-85% on air, presence of the shunt murmur at the site of the BT shunt, and shunt flow and QP/QS ratio of 1.1: 1.8 confirmed by echocardiography or catheterization evaluation. If it is blocked by thrombus or kinked, the patient will present with sudden desaturation, low blood pressure and loss of shunt murmur and it requires urgent revision before subjecting the patient to the cleft palate repair.[28]Even operated cases of TOF should be reassessed before posting for CP/L repair, clinically for reduced exercise capacity, and transthoracic echocardiography to rule out significant pulmonary regurgitation, TR, restrictive RV physiology presenting with low cardiac output, and residual lesions like VSD, RVOTO and RV and LV dysfunctions.[6,69]

Anaesthetic Management:

Anaesthetic management of the patients with uncorrected TOF for noncardiac surgery is a challenge owing to the effects of the chronic hypoxia and decreased pulmonary blood flow, resulting in a significant modification of the physiology and neurological complications. Therefore, understanding the pathophysiology of the TOF and associated syndromes with CL/P involving the airway is vital to provide safe anaesthesia and manage complications. Prophylaxis against infective endocarditis should be administered in all patients with TOF with CL/P with 1 gm of cefazolin or ceftriaxone administered IV/IM for adults and 50mg/kg for pediatric patients prior to the surgery.

Anaesthesia technique is decided according to the planned surgical procedure i.e. BT shunt, total correction, combined TOF and CP/L repair or isolated CL/P repair before or after total correction of the TOF, and dynamic or fixed type of RVOTO. Ketamine (2mg/kg) is the preferred induction agent in TOF undergoing CL/P repair due to its property of increasing SVR which decreases right to left shunting and so improves the oxygen saturation.[70] Indeed, narcotic based balanced general anaesthesia technique comprising a combination of fentanyl (5- 10 mcg/kg), midazolam(0.03-0.05 mg/kg), etomidate(0.2-0.3 mg/kg), sevoflurane(2-3%) in 100% oxygen, and vecuronium(0.1-0.2 mg /kg) as a muscle relaxant can be safely utilised in the patients undergoing BT shunt palliation, total correction of TOF or combined TOF and CL/P repair. A balanced general anaesthesia technique for fast track extubation comprising fentanyl

(1-2 mcg /kg), etomidate (0.2- 0.3mg/kg) or ketamine (1-2mg/kg), midazolam(0.05mg/kg), sevoflurane (1-3%) in 100% oxygen and atracurium (0.5mg/kg)as a muscle relaxant, combined with regional anaesthesia by an infraorbital, external nasal, greater/ lesser palatine and nasopalatine nerve blocks have been used successfully for CL/P repair in unrepaired TOF patients or previously operated cases of BT shunt.[71,72,73,74] However, anaesthesia induction can easily be achieved with any of the available agents. It is crucial to prevent perioperative infundibular spasm precipitated by increased myocardial contractility, and decreased SVR to avoid the worsening of right to left shunting through the VSD. Maintenance of SVR with the use of vasopressors like phenylephrine, norepinephrine and vasopressin decreases right to left shunting and so diminishes the arterial desaturation, but at the expanse of RV or biventricular failure. β-Blockers and sevoflurane are often used to decrease inotropy. The systemic blood pressure should be maintained, as < 60 mmHg may trigger right to left shunt and Tet spells. The important anaesthetic goals are to maintain sinus rhythm and low HR (80-90 bpm), low PVR, maintain intravascular volume particularly in patients with increased haematocrit. If a patient has already been subjected to a palliation surgery like modified BT shunt, then these anaesthetic considerations do not play significant role. [6,75] In right-to-left shunts, the onset of intravenous agents is faster, because it takes less time to enter the systemic circulation. The situation is opposite for inhalation inductions, where the onset is slower in right-to-left shunts. However, with the newer, low-solubility volatile anaesthetic, this difference might not be clinically apparent until the degree of right-to-left shunting becomes significant. In addition, a proper deairing of all intravenous lines should be ensured to avoid the paradoxical air embolism. Even use of 0.2micron in-line filters can help prevent air, particle, and microbe introduction into the patient circulation via intravenous lines. [6,75]

Another problem in these patients is a intraoperative Tet spells usually triggered by two mechanisms either decrease in SVR or spasm of cardiac muscle in the region of RVOT due to sympathetic stimulation (infundibular spasm) as a result of various surgical and anaesthetic manipulations, that needs to be addressed promptly on the suggested guidelines.[14,31,32,33,76] RV diastolic dysfunctions usually exist in TOF with RVH causing a poor lusitropy, and needs optimization of preload by ensuring the appropriate intravascular volume, use of lusitropic agents like milrinone, levosimendan, dobutamine, and sinus rhythm and avoidance of myocardial ischemia to maintain adequate cardiac output.[14] For the CP repair, the endotracheal intubation should be performed with oral south pole, Ring – Adair – Elwyn (RAE) tracheal tube, and fixed in the midline below the lower lip to allow an optimal surgical access and to prevent the mouth gag from obstructing the tube when it is positioned. The throat packing should be done with a roll gauze to avoid the aspiration and to support the tube position in midline.

Perioperative monitoring: and postoperative care

Intraoperative monitoring is determined by the severity of TOF anatomy, secondary effects of chronic hypoxemia and associated other congenital anomalies and the type of surgical procedures. Intraoperative monitoring in patients undergoing BT shunt, total intracardiac repair for TOF or combined TOF and CL/P repair includes a standard ASA monitoring including a five lead ECG to detect any rhythm disturbances (bradycardia, tachycardia) and myocardial ischemia. Dysrhythmias can result from several factors, including

light anaesthesia, hypoxemia, hypercarbia, drugs, and electrolyte abnormalities and various surgical manoeuvres, even long incisions and chamber stretching for the total correction can precipitate re-entrant tachyarrhythmias and junctional ectopic tachycardia (JET). The patient may develop bradycardia or complete heart block particularly post- VSD patch repair and often requires single or dual chamber pacing. Careful attention must be paid to the ST-segment patterns because myocardial ischemia can occur in these infants after total correction or even with BT shunt overflow causing coronary insufficiency. Invasive arterial pressure using radial, or femoral artery for continuous BP monitoring and serial blood gas analysis, but radial artery opposite to the BT shunt should be used, as on the same side it will underestimate the blood pressure. Repeated arterial blood gas analysis should be performed pre and post BT shunt or total correction or combined TOF and CL/P repair to assess the improvement in the arterial oxygenation and other important parameters such as hematocrit, base excess, pH, PaCo2 levels, blood sugar, and serum electrolytes (Na, K, ca, and Mg). One should know the pulse oximetry overestimates arterial oxygen saturation as saturation decreases, end-tidal carbon dioxide readings underestimate $PaCO_2$, hence, arterial blood gas analysis values are more accurate.[77] Pusle oximetry for early detection of desaturation or Tet spell, and improvement after palliation or total TOF repair. Central venous pressure (CVP) line is used for assessment of vascular volume status, RV functions and administrations of various anaesthetic drugs, and inotropes and vasopressors. The other routine monitoring including capnography, NMT, airway pressure, temperature and urine output, activated clotting time (ACT) should also be measured.

In patients undergoing BT shunt or total correction before CL/P repair, Trans-esophageal echocardiography (TEE): Two- dimensional (2-D) echocardiography can also be used to assess BT shunt patency with QP/OS ratio, and residual defects, RVOTO, additional muscular VSD, and ASD, LSVC, Big MAPCAS, PR severity, the bi-ventricular functions, VSD patch, volume status after total correction. Also used to evaluate CO, SVR, PVR, LV/ RV filling and so it guides the fluid and drug therapy. [78,79,80]

Furthermore, the monitoring for isolated CL/P repair after the previously operated TOF for total correction includes usual standard ASA monitoring i.e. ECG, pulse oximetry, non-invasive BP, ETCO2, and airway pressures. Patient should be monitored for signs of airway obstruction throughout their recovery from anaesthesia.

The continuous, vigilant monitoring of hemodynamics during early postoperative management is paramount. There will be no risk of postoperative airway obstruction at all as endotracheal tube still be in situ for postoperative elective ventilation in ICU in patients who have undergone combined CL/P and TOF repair. However, in the patients undergoing isolated CL/P repair, there is a risk of postoperative airway obstruction particularly in children with pre-operative airway problems and subjected to the isolated CL/P repair.

Airway obstruction has been observed because of swelling of the tongue from gag pressure, laryngospasm, retained throat pack, blood clot or even a combination of these factors. Post- extubation, the child is turned in lateral or prone position for a short duration to improve the breathing pattern. Injection hydrocortisone and ondansetron are used as anti-inflammatory, and anti-emetic Just before the tracheal extubation. There are several strategies in use for providing post-operative

analgesia like fentanyl(0.25mcg/kg/hr) bolus or continuous infusions. diclofenac or paracetamol suppositories, as well as regular paracetamol and NSAIDS in young children. Paracetamol(15mg/kg) infusion every 6hourly postoperatively for pain control. [81,82] Dexmedetomidine (0.3 -0.5 mcg/kg/hr) infusion with $\alpha_2$agonist actions, has been used for arousable sedation, analgesia, control of Tet spell, control of JET. [83,84,85]

Conclusion

Our comprehensive systematic review and meta-analysis recommend that a subset of TOF with CL/P patients with severe arterial desaturation, and Tet spells refractory to medical therapy are unsuitable for CP /L repair surgery. These patients should undergo cardiac catheterization laboratory interventions (RVOT dilatation, PA angioplasty, balloon pulmonary valvuloplasty, ductus stenting) or need modified BT shunt or total Correction under CPB before CP repair surgery to avoid the morbidity and mortality. A balanced general anaesthesia technique for fast track extubation comprising fentanyl (3 mcg /kg), etomidate (0.2- 0.3mg/kg) or ketamine (1-2mg/kg), midazolam(0.05mg/kg), sevoflurane (1-3%) in 100% oxygen and atracurium(0.5mg/kg)as a muscle relaxant, combined with regional anaesthesia by an infraorbital, external nasal, greater/ lesser palatine and nasopalatine nerve blocks can be used successfully for CL/P repair in unrepaired TOF patients or previously operated cases of BT shunt or total correction.[71,72,73,74] We also recommend early corrective cardiac interventions for the children with severe TOF to improve oxygenation, prevent sequalae of chronic hypoxemia and safe CL/P repair. Now a days a combined cardiac and noncardiac surgeries are performed successfully without any significant increase in morbidity or mortality. Similarly, a Simultaneous surgery for TOF and CL/P repair is feasible and safe when performed in a tertiary care centre by the experience team. The sequence of procedure should be as follows; First repair TOF under standard CPB and after chest closure, CP is repaired, and baby is shifted to cardiac ICU for elective ventilation. This approach will prevent 100% postoperative airway obstruction after CP repair, and provide excellent bleeding control, healing of the scar and hemodynamic management. Future research, particularly larger, high-quality multicentre trials are needed to determine the exact timing of combined TOF and CL/P repair.

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