

## Sedation for children undergoing cardiac catheterization: A review of literature

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### Abstract

Management of children with congenital heart disease has been a great challenge for anaesthesiologists especially during cardiac catheterization. General anaesthesia with positive pressure ventilation can alter the intra-cardiac pressures as well as shunt fraction. Therefore deep sedation with pain free and spontaneously breathing patient on room air is preferred by the cardiac interventionist. A wide variety of drug regimens have been used for both general anaesthesia and monitored anaesthesia care. We reviewed the most common drugs used during the last 50 years for this procedure. The advent of new drugs has given better control on the level and duration of sedation with decreased untoward effects. A complete understanding of pathophysiology of the disease as well as the effects of intervention in a particular individual can provide a safe anaesthetic management.

**Keywords:** Congenital heart disease, Cardiac catheterization, Sedation, Anaesthesia.

### Introduction

The history of catheterization dates back to 1844, when Claude Bernard<sup>1</sup> inserted a mercury thermometer into the carotid artery of a horse and advanced it through the aortic valve into the left ventricle to measure blood temperature.

Later in 1929, a German surgical trainee, Werner Forssmann,<sup>2</sup> inserted a urological catheter in his own forearm and guided it into his right atrium. In return, he was fired from his position at the hospital but later won the Nobel Prize in 1956.

The use of cardiac catheterization and angiography as a diagnostic tool was first described in man by Cournand<sup>3</sup> and in children with congenital heart disease by Bing et al<sup>4</sup> in 1947. Interventional catheterization was first performed in 1953 by Rubio-Alvarez<sup>5</sup> to treat pulmonary stenosis. In 1966 the balloon atrial septostomy was developed by Rashkind and Miller<sup>6</sup> which was the first paediatric and the first intra cardiac transcatheter procedure.

Cardiac catheterization in children with congenital heart disease can be performed under general anaesthesia, but monitored anaesthesia care (MAC) with spontaneously breathing patient on room air is the preferred method by the cardiologist.

### Preoperative Assessment:

The preoperative evaluation of children with congenital heart disease undergoing cardiac catheterization, is a challenging task because of the wide range of anatomic and physiologic abnormalities. A thorough understanding of the anomalies enables the anaesthetist to choose a suitable technique for a particular patient.

A detailed history includes the gestational age, feeding reluctance, playing activities, cyanotic spells, continuous cough, failure to gain weight and bronchospasm. Physical examination should include the airway abnormalities, measurement of SpO<sub>2</sub>, blood pressure, and assessment of pulses in all extremities and difficulty for vascular access. Compromised heart may show signs of failure i.e. tachycardia with low volume pulse, a gallop rhythm, tachypnoea, difficulty in feeding, excessive perspiration, jugular venous distention, pulmonary congestion or hepatomegaly. Presence of increased respiratory rate, diaphoresis, intercostals muscles retraction, nasal flaring, and use of accessory respiratory muscles indicate poor respiratory reserve. Nearly 28% of patients show associated anomalies or syndromes which include musculoskeletal abnormality (8.8%), neurological defects (6.9%), and genitourinary irregularities (5.3%) but the most common is the Down's syndrome (9%). Atlanto - occipital subluxation is common in Down's syndrome which can lead to quadriplegia during laryngoscopy and tracheal intubation. Pharmacologic therapy usually includes diuretics and drugs for afterload reduction. Prostaglandin E1 (PGE1) infusion to maintain the patency of ductus arteriosus may be present. Need for supplemental oxygen or respiratory

**Table-1: Common procedures in catheterization laboratory.**

A. Diagnostic catheterization
B. Interventional catheterization
Pulmonary artery angioplasty
Aortic coarctation angioplasty
Patent ductus arteriosus (PDA) occlusion or stenting
Ventricular septal defect closure
Atrial septal defect dilation
Atrial septal defect closure
Balloon atrial septostomy
Aortic valve dilation
Pulmonary valve dilation
Mitral valve dilation
Pericardiocentesis
Stent in pulmonary vein.

**Table-2: Common drugs for premedication.**

Drugs	Doses mg/kg
Ketamine	PO 2-10 IV .25-1.0 - IM 1-4.0
Chloral Hydrate	PO: 25-100
Promethazine	PO 0.1-1.0
Midazolam	PO 0.25-0.75 - Intranasal 0.1-0.3
Diazepam	PO 0.1-0.4

PO: Per OS. IM: Intramuscular.

**Table-3: Ramsay Score.**

Score	Description
0	Awake, oriented
1	Agitated, anxious
2	Awake, co-operative
3	Sleeping, but co-operative
4	Deep sedation, quick reaction to pain stimuli
5	Deep sedation, slow reaction to pain stimuli
6	Deep sedation, no reaction to pain stimuli.

support may be necessary if pulmonary congestion or pulmonary oedema is severe.

The plans for pre medication, (Table-2) provision of deep sedation along with the possibility of general anaesthesia, with tracheal intubation, blood transfusion, and postoperative care including the possibility of ventilatory support should be discussed with the family.

If the patient has a permanent pacemaker in place, the indications for pacing, underlying rhythm, device type and its functional status must be reviewed.

Appropriate laboratory studies include complete blood count (CBC), blood urea nitrogen (BUN), creatinine, electrolytes, coagulation studies, a screen for antibodies, and a cross match for appropriate blood products. Diuretic therapy may result in dehydration, hypochloremic metabolic alkalosis, or hypokalaemia.

The chest radiograph and transthoracic Echo report gives a valuable information regarding the cardiac anatomical abnormalities as well as pressure in different chambers of heart and great vessels.

American society of anesthesiologist (ASA) fasting guidelines, should be followed as in any case for general anaesthesia.

Unlike adults, paediatric group need moderate to deep sedation (Table-4, Ramsay Score) to keep them immobile during the procedure. Although there is no ideal deep sedation technique which is widely accepted but the advent of new short acting drugs have given better control on sedation. Since acidosis hyperoxaemia, hypoxia and positive pressure ventilation all exert significant disturbance in the haemodynamic calculations, a spontaneously breathing

**Table-4: Commonly use Opioids for Sedation.**

Drug	IV Bolus Dose	Infusion
Morphine	0.1-0.2 mg/kg	10-40 µg/kg/h
Fentanyl	1-3 µg/kg	1-10 µg/kg/h
Remifentanyl	1 µg/kg	0.5-6 µg/kg/h
Alfentanil	15-25 µg/kg	0.4-2µg/kg/min

patient on room air, stable haemodynamics and normal blood gases are required with an appropriate immobility.

### Monitoring:

Standard monitoring should be used as defined by ASA guidelines. Baseline ECG, SpO<sub>2</sub>, noninvasive blood pressure should be taken before starting sedation. Respiratory monitoring can be performed via lateral flow CO<sub>2</sub> measurement tube placed closed to the mouth or in the oropharynx. Serial arterial blood gas should be checked once arterial line is established by the cardiologist.

Clinical scores like Ramsay score is the most common tool for monitoring the levels of sedation. However, during last one decade electroencephalographic findings, such as the bispectral index (BIS), auditory evoked potentials have become popular methods for objective assesment of the level of consciousness.

### DPT Mixture:

The combination of Meperidine(M), Promethazine(P), and Chlorpromazine(C) (MPC, Cardiac Cocktail) has been widely used for more than 40 years for paediatric sedation in a variety of cases. It comprises of Meperidine 25 mg/ml, Promethazine 6.5 mg/ml, and chlorpromazine 6.5 mg/ml which was used in a dose of 0.1 ml/kg.<sup>7</sup> In 1958 Smith<sup>8</sup> used this mixture intramuscularly in 670 patients. He found it a very promising method as only one patient had depressed breathing, only 5-10 mm Hg fall in MAP and a few mm Hg increase in PAP. One death was reported directly related to the mixture of drugs due to the use of full dose in a very sick child.

In 1969 Goldberg et al<sup>9</sup> found an increase in pulmonary vascular resistance resulting in increased right to left shunt. It has a slow onset of action, prolonged effect and a failure rate as high as 29%. Tarndrup et al reported 19 ± 15 hours to regain normal behaviour. Restlessness and respiratory depression is common with DPT. In 1985 Nahata<sup>7</sup> reported 4% incidence of life threatening complications. Snodgrass<sup>10</sup> called for "rational and safe alternatives" in 1989. The American academy of Pediatrics Committee on drugs, issued a critical re-appraisal of lytic cocktail<sup>11</sup> in 1995. Later significant respiratory depression, prolonged sedation were also mentioned by other investigators. In 1987 Mario et al showed significant variation in percent haemoglobin-oxygen saturation pertaining to DPT mixture.<sup>12</sup>

In 2000, Auden et al<sup>13</sup> compared intramuscular DPT with oral ketamine/midazolam in 51 children having cardiac catheterization, ages 9 months to 10 years. They claimed oral Ketamine/midazolam is better tolerated and provides superior sedation, less respiratory depression and stable haemodynamics. With the introduction of new and safer drugs in anaesthesia practice, DPT use has been declined significantly during the last two decades.

### **Ketamine:**

Ketamine has been widely used in anaesthetic practice for about 4 decades in a variety of cases. It was first used for cardiac catheterization in 1971.<sup>14</sup>

The combination of sedation and analgesia with the maintenance of respiratory drive and airway reflexes makes it a preferable choice outside the main operating room. The increase in heart rate helps to maintain rate dependent cardiac output in paediatric group.

Despite of its well known side effects i.e. increase in salivation, emergence delirium, delayed awakening and non purposeful movements, tachycardia, hypertension and tendency to increase pulmonary vascular resistance, it remained the drug of choice for sedating children for cardiac catheterization,<sup>15</sup> radiological procedures,<sup>16</sup> procedural sedation in Emergency department and burns dressings.<sup>17</sup>

After the initial bolus of 1-2 mg/kg IV slowly over 3-5 minutes, an infusion of 25-100  $\mu$ g/kg/min has been used by many investigators.<sup>18</sup> In a retrospective review of interventional cardiac procedures in 107 children, an increase in heart rate and mean arterial pressure by more than 20% from baseline values were seen in 10 and 9 patients. Transient apnoea and excessive salivation were seen in two patients each. Excessive movement of extremities was seen in six patients.<sup>19</sup>

In a comparative study of propofol and ketamine infusion for cardiac catheterization procedure Oklu et al<sup>20</sup> found a decrease in systemic vascular resistance with propofol leading to increased right to left shunting, whereas ketamine did not produce these changes.

Ketamine combined with propofol and midazolam not only reduces the involuntary movements but also preserves better haemodynamics without affecting the recovery.<sup>21</sup>

### **Propofol:**

Propofol (2,6-diisopropylphenol) is structurally unrelated to other sedative hypnotic agents which has rapid onset, predictable level of sedation, rapid recovery and a low incidence of nausea and vomiting with minimal adverse effects. Although propofol was licensed by the Food and Drug Administration for use in children greater than 3 years of age only, the efficacy and safety of Propofol in children has been

reported by several investigators.<sup>22,23</sup>

It has been used widely to provide deep sedation in the children for cardiac catheterization in a dose 1.5-2.5 mg/kg as a slow bolus over 30-60 seconds followed by 50-200  $\mu$ g/kg/min infusion. It decreases the blood pressure and heart rate by 10-30 % and systemic vascular resistance by 15-20 % which can have serious consequences in patients with severe aortic stenosis, cyanotic heart disease and compromised myocardial function.

Although many investigators have reported a decrease in systemic vascular resistance and increase in right-to-left shunting with propofol.<sup>20,24</sup> Gozal et al reported an insignificant change of intracardiac shunt with its use.<sup>14</sup>

Combination of propofol and ketamine has been used by several investigators with satisfactory results. Kogan et al<sup>25</sup> used a mixture of propofol (4 mg/mL) and ketamine (2 mg/mL) in 45 patients aged 6 months to 16 years undergoing cardiac catheterization. They experienced 20% change in heart rate in 4 patients and blood pressure in 5 patients, whereas only 3 patients desaturated due to hypoventilation that required manual assistance of ventilation. No major complications occurred in this study. Similarly Akin et al<sup>22</sup> used propofol (5 mg/mL) and ketamine (1 mg/ml) solution at a rate of 0.5 ml/kg in 60 children undergoing cardiac catheterization. In this study 20% decrease in blood pressure and heart rate, requirement of additional doses of propofol and fentanyl were significantly less than the control group.

In 2007, Gayatri et al<sup>26</sup> used two doses of ketamine 12.5  $\mu$ g/kg/min and 25  $\mu$ g/kg/min with fixed dose of propofol (25  $\mu$ g/kg/min). They found both combinations efficacious, safe and good option in paediatric group under going cardiac catheterization.

### **Dexmedetomidine:**

Dexmedetomidine is a unique and selective  $\alpha$  2-adrenoceptor agonist, which inhibits neuronal firing in the brain and spinal cord resulting in hypotension, bradycardia and sedation.<sup>27</sup>

Presynaptic stimulation of  $\alpha$  2 receptors in the spinal cord increases the release of norepinephrine which is responsible for its analgesic effect. It possesses a biphasic haemodynamic response (high, then low) for BP and vascular resistances which results from direct activation of  $\alpha$  2 receptors in the vascular smooth muscles.<sup>28</sup> Senzaki et al<sup>29</sup> claimed dexmedetomidine a better option for sedation in TOF patients (particularly small infants) with hypercyanotic spells. Large doses of dexmedetomidine causes vasoconstriction by activating these receptors in peripheral blood vessels which results in systemic and pulmonary hypertension. There is also an increased incidence of bradycardia and atrioventricular blocks. Dexmedetomidine does not depress respiratory drive

and provides a dry oral field because of its antisialogogue property.

Dexmedetomidine is currently approved by US FDA only for the sedation of intubated and mechanically ventilated adults in the intensive care unit.<sup>30</sup> However, it has been used for paediatrics sedation in cardiac catheterization,<sup>21</sup> radiological procedures,<sup>31</sup> dental procedures<sup>32</sup> and mechanical ventilation for ICU patients.<sup>33</sup> It has also been used to control withdrawal symptoms of opioids and benzodiazepines as well as for the prevention of emergence delirium after general anaesthesia.

Although the current literature lacks dose response guidelines but investigators have used it in a dose of 0.2 to 0.75 µg/kg/h in various paediatric case reports.<sup>34,35</sup>

Munro et al<sup>27</sup> used a loading dose of 1 microg x kg(-1) dexmedetomidine administered over 10 min followed by an infusion rate of 0.5-2 µg x kg(-1) x h(-1). In this study of 20 patients heart rate and blood pressure remained within 20% of baseline. None of their patients developed significant bradycardia or hypotension. They found dexmedetomidine, a suitable alternative for sedation in spontaneously breathing patients undergoing cardiac catheterization.

Mester et al<sup>18</sup> found combination of ketamine and dexmedetomidine as an effective means for paediatric sedation in cardiac catheterization procedures.

On the contrary, Tosun et al<sup>21</sup> found the propofol-ketamine combination superior to a combination of dexmedetomidine-ketamine which not only produced insufficient sedation and analgesia but also resulted in a longer recovery time.

### **Benzodiazepines:**

Since benzodiazepines lack any analgesic effects, therefore they are used with ketamine or opioids. The combination of benzodiazepines with Ketamine not only reduces its emergence delirium but also provide better sedation and amnesia. Midazolam is the most commonly used benzodiazepine because of its shorter duration of action and inactive metabolites. Benzodiazepines produce dose-dependent respiratory depression, which is more marked in patients with respiratory disease, congenital heart disease and when combined with opioids.

### **Opioids:**

Very few studies are available regarding the use of opioids during cardiac catheterization. In different studies Rautiainen<sup>36,37</sup> described the use of fentanyl and alfentanil as an effective method of sedation in catheterization lab. Because of their well known respiratory depression, they are generally used in conjunction with benzodiazepine or propofol. Newer opioids like fentanyl, alfentanil and remifentanil have rapid

onset of action, shorter duration and provide better haemodynamics stability.

### **Conclusion**

A variety of drugs regimens can be used for the cardiac catheterization procedures in children with congenital heart disease. A good preoperative assessment, thorough understanding of the disease and the procedure to be performed enable the anaesthesiologist to choose and use the right drug regimen for a safe anaesthetic management. Ketamine with or without benzodiazepines has remained the drug of choice for about 4 decades. Propofol with ketamine has provided near to ideal combination to provide deep sedation with adequate analgesia and stable haemodynamics in a spontaneously breathing patient.

### **Reference**

1. Bourassa MG. The history of cardiac catheterization. *Can J Cardiol* 2005; 21: 1011-4.
2. Forsmann W. Die soniderung des rechten herzens. *Klin. Wschr* 1929; 8: 2085.
3. Courmand A, Ranges HA. Catheterization of the right auricle in men. *Proc Soc Exp Bio Med* 1941; 46: 462.
4. Bing RJ, Vandam LD, Gray FD Jr. Physiological studies in congenital heart disease procedures. *Bull Johns Hopkins Hosp* 1974; 80: 107-20.
5. Rubio-Alvarez V, Limon R, Soni J. Intracardiac valvulotomy by means of a catheter. *Arch Inst Cardiol Mex* 1953; 23: 183-92.
6. Rashkind WJ, Miller WW. Transposition of the great arteries. Results of palliation by balloon atrioseptostomy in thirty-one infants. *Circulation* 1968; 38: 453-62.
7. Nahata MC, Clotz MA, Krogg EA. Adverse effects of meperidine, promethazine, and chlorpromazine for sedation in pediatric patients. *Clin Pediatr (Phila)* 1985; 24: 558-60.
8. Smith C, Rowe RD, Vlad P. Sedation of children for cardiac catheterization with an anarectic mixture. *Canad Anaesthet Soc J* 1958; 5: 35-40.
9. Goldberg SJ, Linde LM, Wolfe RR, Griswold W, Momma K. The effects of meperidine, promethazine, and chlorpromazine on pulmonary and systemic circulation. *Am Heart J* 1969; 77: 214-21.
10. Snodgrass WR, Dodge WF. Lytic "DPT" cocktail. Time for rational and safe alternatives. *Pediatr Clin North Am* 1989; 36: 1285-91.
11. American Academy of Pediatrics Committee on Drugs. Reappraisal of lytic cocktail/ Demerol, Phenergan, and Thorazine (DPT) for the sedation of children. *Pediatrics* 1995; 95: 598-602.
12. Saravia ME, Currie WR, Campbell RL. Cardiopulmonary Parameters During Meperidine, Promethazine and Chlorpromazine Sedation for Pediatric Dentistry: *Anesth Prog* 1987; 34: 92-6.
13. Auden SM, Sobczyk WL, Solinger RE, Goldsmith LJ. Oral ketamine/midazolam is superior to intramuscular meperidine, promethazine, and chlorpromazine for pediatric cardiac catheterization. *Anesth Analg* 2000; 90: 299-305.
14. Gozal D, Rein AJ, Nir A, Gozal Y. Propofol does not modify the hemodynamic status of children with intracardiac shunts undergoing cardiac catheterization. *Pediatr Cardiol* 2001; 22: 488-90.
15. Malviya S, Burrows TA, Johnston AE, Benson LN. Anaesthetic experience with paediatric interventional cardiology. *Can J Anaesth* 1989; 36: 320-432.
16. Mason KP, Michna E, DiNardo JA, Zurakowski D, Karian VE, Connor L, et al. Evolution of a protocol for ketamine-induced sedation as an alternative to general anesthesia for interventional radiologic procedures in pediatric patients. *Radiology* 2002; 225: 457-65.
17. Howes MC. Ketamine for paediatric sedation/analgesia in the emergency department. *Emerg Med J* 2004; 21: 275-80.
18. Mester R, Easley RB, Brady KM, Chilson K, Tobias JD. Monitored anesthesia care with a combination of ketamine and dexmedetomidine during cardiac catheterization. *Am J Ther* 2008; 15: 24-30.
19. Singh A, Girotra S, Mehta Y, Radhakrishnan S, Shrivastava S. Total intravenous anesthesia with ketamine for pediatric interventional cardiac procedures. *J Cardiothorac Vasc Anesth* 2000; 14: 36-9.

20. Oklu E, Bulutcu FS, Yalçın Y, Ozbek U, Cakali E, Bayindir O. Which anesthetic agent alters the hemodynamic status during pediatric catheterization? Comparison of propofol versus ketamine. *J Cardiothorac Vasc Anesth* 2003; 17: 686-90.
  21. Tosun Z, Akin A, Guler G, Esmoğlu A, Boyacı A. Dexmedetomidine-ketamine and propofol-ketamine combinations for anesthesia in spontaneously breathing pediatric patients undergoing cardiac catheterization. *J Cardiothorac Vasc Anesth* 2006; 20: 515-9.
  22. Akin A, Esmoğlu A, Guler G, Demircioğlu R, Narin N, Boyacı A. Propofol and propofol-ketamine in pediatric patients undergoing cardiac catheterization. *Pediatr Cardiol* 2005; 26: 553-7.
  23. Hertzog JH, Campbell JK, Dalton HJ, Hauser GJ. Propofol anesthesia for invasive procedures in ambulatory and hospitalized children: experience in the pediatric intensive care unit. *Pediatrics* 1999; 103: e30.
  24. Baysal A, Polat TB, Yalçın Y, Celebi A. The use of basic parameters for monitoring the haemodynamic effects of midazolam and ketamine as opposed to propofol during cardiac catheterization. *Cardiol Young* 2008; 6: 1-8.
  25. Kogan A, Efrat R, Katz J, Vidne BA. Propofol-ketamine mixture for anesthesia in pediatric patients undergoing cardiac catheterization. *J Cardiothorac Vasc Anesth* 2003; 17: 691-3.
  26. Gayatri P, Suneel PR, Sinha PK. Evaluation of propofol-ketamine anesthesia for children undergoing cardiac catheterization procedures. *J Interv Cardiol* 2007; 20: 158-63.
  27. Munro HM, Tirota CF, Felix DE, Lagueruela RG, Madril PR, Zahn EM, et al. Initial experience with dexmedetomidine for diagnostic and interventional cardiac catheterization in children. *Paediatr Anaesth* 2007; 17: 109-12.
  28. Bhana N, Goa KL, McClellan KJ. Dexmedetomidine. *Drugs* 2000; 59: 263-8.
  29. Senzaki H, Ishido H, Iwamoto Y, Taketazu M, Kobayashi T, Katogi T, et al. Sedation of hypercyanotic spells in a neonate with tetralogy of Fallot using dexmedetomidine. *J Pediatr (Rio J)* 2008; 84: 377-80.
  30. Hammer GB, Drover DR, Cao H, Jackson E, Williams GD, Ramamoorthy C, et al. The effects of Dexmedetomidine on cardiac electrophysiology in children. *Anesth Analg* 2008; 106: 79-83.
  31. Fahy CJ, Okumura M. Sedation for paediatric stereotactic radiosurgery: the Dexmedetomidine experience. *Anaesth and Intensive Care* 2004; 32: 809-11.
  32. Ogawa S, Seino H, Ito H, Yamazaki S, Ganzberg S, Kawaai H, et al. Intravenous Sedation With Low-Dose Dexmedetomidine: Its Potential for Use In Dentistry. *Anesth Prog* 2008; 55: 82-8.
  33. Berkenbosch JW, Wankum PC, Tobias JD. Prospective evaluation of dexmedetomidine for noninvasive procedural sedation in children. *Pediatr Crit Care Med* 2005; 6: 435-9.
  34. Tobias JD, Berkenbosch JW, Russo P. Additional experience with dexmedetomidine in Pediatric Patients. *South Med J* 2003; 96: 871-5.
  35. Mukhtar AM, Obayah EM, Hassona AM. The use of dexmedetomidine in pediatric cardiac surgery. *Anesth Analg* 2006; 103: 52-6.
  36. Rautiainen P. Alfentanil infusion for sedation in infants and small children during cardiac catheterization. *Can J Anaesth* 1991; 38: 980-4.
  37. Meretoja OA, Rautiainen P. Alfentanil and fentanyl Sedation in infants and small children during cardiac catheterization. *Can J Anaesth* 1990; 37: 624-8.
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