

## Propofol Infusion for Rapid Opiate and Benzodiazepine Wean to Extubation in a Child after Cardiac Surgery with Residual Mitral Regurgitation: Lessons from a Unique Case

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### Abstract

We present a case of a child who was in the cardiac intensive care unit after having undergone a mitral valve repair. Significant mitral valve regurgitation persisted post operatively and she had high requirements of sedating agents and opioids. A propofol infusion was used to facilitate rapid wean of sedation and opioids leading to subsequent successful extubation. This was done safely without hemodynamic compromise or increase in lactate.

**Keywords:** Propofol Infusion; Opiate; Benzodiazepine; Cardiac Surgery

### Introduction

Critically ill children, particularly those with congenital heart disease will often require sedating agents and opioids while recovering postoperatively or for medical admissions in the cardiac intensive care unit. When large amounts of sedating agents and opioids are needed, weaning can be particularly problematic and can result in significant withdrawal. Propofol, often used in the operating room, can be used in the intensive care unit to help wean from other sedating agents and opioids. Over the years, however, propofol infusions in the intensive care unit have developed an associated negative stigma. In fact, some pediatric cardiac intensive care units have adopted the policy of avoiding the use of propofol infusions, entirely [1]. Fears associated with propofol infusion include cardiovascular collapse and propofol related infusion syndrome [2]. The actual prevalence of these adverse effects is quite low and adequate monitoring of patients in the intensive care unit can allow early detection of such complications and cessation of propofol if needed.

Propofol infusions can be safely used in critically ill children and offer some marked advantages, such as allowing for rapid weaning of sedating agents and opioids and facilitating extubation [3]. While there is some published literature of the use of propofol infusions in the pediatric intensive care unit setting, there is a paucity of data regarding the use of propofol infusions in critically ill children with congenital heart disease.

We present a case of a young child who was in the cardiac intensive care unit recovering from cardiac surgery with residual mitral valve regurgitation who required high doses of sedating agents and opioids for a prolonged period of time. A propofol infusion, or so called "washout" was utilized to facilitate rapid weaning of sedating agents and opioids and facilitate extubation.

## Case Report

We present the case of a 16-month-old girl who presented to our institution for mitral valve repair due to severe mitral valve regurgitation. This young girl was born full-term and had respiratory distress shortly after birth secondary to meconium aspiration. She was also noted to have a patent arterial duct, cleft palate, bilateral syndactyly of the toes, and micrognathia. She required cannulation onto extracorporeal membrane oxygenation on day of life 11 due to worsening oxygenation and required extracorporeal membrane oxygenation for 7 days.

A cardiac catheterization was done at 4 months of life, which demonstrated a patent arterial duct with left to right shunt (Qp:Qs 1.37) and a mean pulmonary artery pressure of 32. She was also noted to have both tricuspid valve and mitral valve regurgitation. She underwent a ligation of the arterial duct and then was eventually discharged home on home oxygen, sildenafil, enalapril, and Flovent at \*\*\* months of age.

During outpatient follow up visits supplemental oxygen and sildenafil were weaned off. She presented to another hospital with chief complaint of perioral cyanosis and a “bulge” in her right neck and was hospitalized after being found to have a dissection in the ligated vein that had been used for extracorporeal membrane oxygenation. She was also found to have worsening mitral regurgitation with decreasing coaptation of the mitral valve leaflets. She was taken for a repeat cardiac catheterization which demonstrated persistent pulmonary hypertension and severe mitral valve regurgitation. The hospitalization was further complicated by a rhinovirus infection and the patient ultimately had issues with oxygenation and ventilation, requiring intubation.

With worsening mitral valve regurgitation in the setting of pulmonary hypertension, the young girl was transferred to our institution for further management and mitral valve repair. An echocardiogram after transfer demonstrated severe mitral valve insufficiency with dilation of the mitral valve annulus (24 mm, Z-score = 6.6). The jet of insufficiency was central and secondary to non-coaptation of the mitral valve leaflets. The papillary muscles were normal and there was no mitral stenosis. There was mild tricuspid valve insufficiency with a peak gradient that estimated systemic pulmonary hypertension with a right ventricular systolic pressure estimate of 80 mmHg.

The child remained intubated and on inhaled nitric oxide with aggressive diuresis until going to the operating room on the 9<sup>th</sup> day of admission at our institution. Intraoperatively she was found to have a very dilated heart with a mitral valve that had a central area of non-coaptation. There was also prolapse of the anterior leaflet of the mitral valve and short mitral valve chordae. She underwent mitral valve repair consisting of a commissuroplasty and an Alfieri stitch. An atrial septal communication was created as well. The mitral valve had moderate residual mitral valve regurgitation shortly, postoperatively.

The child was brought back to the cardiac intensive care unit intubated and had a high analgesic and sedative requirement. The day of surgery she was started on hydromorphone (60 mcg/kg/hr), midazolam (0.04 mg/kg/hr) and dexmedetomidine (1.2 mcg/kg/hr) infusions. She also received intermittent morphine boluses intravenously. Total daily doses of analgesic and sedative medications are outlined in table 1. Total morphine equivalent doses include hydromorphone (conversion factor of 6.8), ketamine (conversion factor of 1/3) and morphine (conversion factor of 1). The total morphine equivalent dose was 50.8 mg on postoperative day 0 and peaked on postoperative day 1 at 76.2 mg. She remained on high doses of analgesics and was persistently agitated for several days. Midazolam was also utilized although the child seemed to benefit minimally from it. Low-dose propofol infusion was utilized immediately postoperatively and on postoperative day 1 while a ketamine infusion was utilized on postoperative days 1 through 7. Quetiapine was also initiated for concern of delirium in the setting of high delirium scores. Hemodynamics remained stable throughout and the patient remained intubated.

On postoperative day 7, it was decided to initiate a propofol infusion and attempt to rapidly wean off other agents with a target duration of 24 hours for the washout. Immediately prior to the initiation of Propofol, the hydromorphone infusion was at 50 mcg/kg/hr, dexmedetomidine at 2.0 mcg/kg/hr, ketamine at 0.5 mg/kg/hr and Midazolam? 0.04 mg/kg/hr. Bispectral index monitoring was initiated and then a propofol infusion was started with the goal of weaning the other analgesic and sedative agents while maintaining a bispectral index reading of 30 to 60. Propofol infusion was initiated at 75 mcg/kg/min and both the ketamine and midazolam infusions were discontinued within the first hour of the propofol washout. The hydromorphone infusion was also weaned to 25 mcg/kg/hr within the first hour of the washout and dexmedetomidine was weaned to 1 mcg/kg/hr.

Table 1 demonstrates the daily doses of various sedating agents and opioids from postoperative day 0 to postoperative day 10.

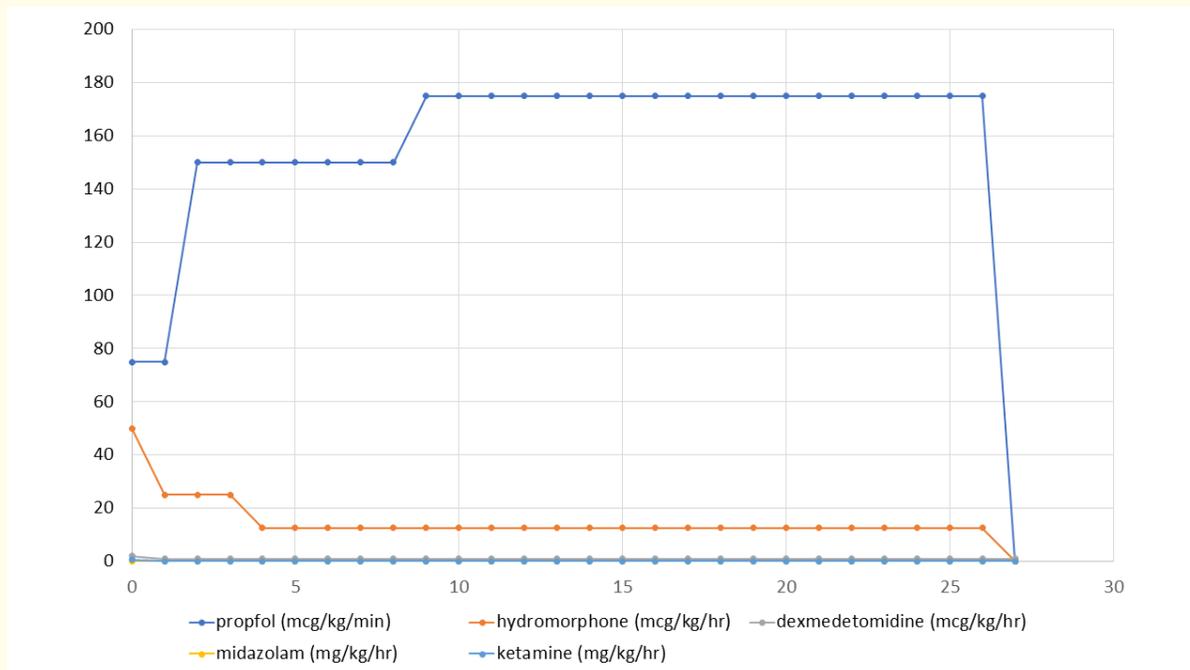
Postoperative day	Hydromorphone (mg)	Morphine (mg)	Midazolam (mg)	Ketamine (mg)	Dexmedetomidine (mg)	Propofol (mg)
0	74.8	0	1.6	0	0.2	636
1	107.2	0	8.6	10	0.2	182
2	62.6	0	9.1	22	0.3	0
3	52.8	0	10.6	25.4	0.2	0
4	55.4	0	11.9	72.4	0.3	0
5	52.3	0	11.5	74.8	0.3	0
6	51.4	0	5.9	74.8	0.1	0
7 (washout start)	16.6	0	0.8	10.4	0.1	1,206
8 (washout end)	2.8	6	1.7	0	0.1	379
9	0	6	0	0	0.2	0
10	0	7	0	0	0.2	0

**Table 1:** Doses of drugs.

Bispectral index values began to rise around hour 2 and the propofol infusion was increased to 150 mcg/kg/min. By hour 4 the bispectral index values were reassuring and the hydromorphone infusion was decreased to 12.5 mcg/kg/hr. Eventually an increase in the propofol infusion to 175 mcg/kg/min was required at hour 9. The propofol remained at 175 mcg/kg/min, the hydromorphone remained at 12.5 mcg/kg/hr, and the dexmedetomidine at 1 mcg/kg/hr for the remainder of the washout.

Hemodynamics remained stable during the entirety of the washout and the child had been on low-dose milrinone and low-dose dopamine, neither of which required titration. The child did not require a fluid bolus during the washout. Arterial blood gases were monitored every 4 hours during the washout and lactates remained below 1 mmol/L. As the 24-hour period elapsed, it was felt that the child was ready for extubation as she had good lung compliance and was triggering her own breaths in a continuous positive airway pressure/pressure support mode of ventilation. At hour 27 of the washout the propofol was discontinued from 175 mcg/kg/min, the hydromorphone was discontinued from 12.5 mcg/kg/hr and the patient was successfully extubated to noninvasive pressure control and was quickly weaned to high flow nasal cannula.

Figure 1 demonstrates the various infusion doses at each hour of the washout.



After extubation, the dexmedetomidine was continued at 1.0 mcg/kg/hr and the patient was started on morphine 1 mg every 4 hours, thus giving her a daily dose of morphine of 6 mg. She remained on quetiapine for delirium, although this was discontinued for a period of 36 hours due to the development of extrapyramidal symptoms. The quetiapine was then restarted at a lower dose once these symptoms improved. Cornell Assessment of Pediatric Delirium Scores were in the high teens and decreased over the course of a week after the washout. Withdrawal Assessment Tool-1 scores ranged from 4-8 after the washout and also decreased over the week following the washout.

The dexmedetomidine and morphine were slowly weaned over the course of the remainder of the admission without issue.

## Discussion

We present the case of a young child with congenital heart disease who had a high analgesic and sedative requirement postoperatively. She completed a 24-hour washout in which propofol was initiated and titrated to allow for rapid weaning of opiate. This facilitated the discontinuation of several infusions and a proportionally low dose of opiate to be continued afterwards. This case is novel as it demonstrates that a propofol infusion can be used to very rapidly wean sedating agents and opioids in a child and tempers the subsequent withdrawal. Additionally, this case demonstrates that propofol can be safely used in children after surgery for congenital heart disease, even in the presence of significant residual lesions. Also, of note, is that hemodynamics were not significantly affected and lactates remained normal.

Propofol is a sedating agent that has multiple mechanisms of action. It is a GABA<sub>A</sub> receptor modulator at lower doses and a frank GABA<sub>A</sub> agonist at higher doses. Additionally, propofol has been shown to be an NMDA-receptor agonist [4,5]. Propofol has also shown to be a sodium channel antagonist and perhaps an endocannabinoid system agonist. Propofol is highly protein-bound and is mostly bound to

albumin [6]. Once administered, propofol has a quick onset of action with effect starting within 10 to 25 seconds of administration. Propofol quickly distributes into the tissues and is also quickly metabolized by the liver. Duration of effect is approximately 3 to 10 minutes with a terminal half-life that ranges from 1.5 to 11 hours. Once an infusion is discontinued, patients will often start to awaken within 10 to 15 minutes.

Studies have also demonstrated that propofol may have an effect on the  $\mu$ -opioid receptors, as it appears to upregulate the expression of these receptors and may also enhance the activity of the endogenous  $\mu$ -opioid system [7]. The precise clinical implications of this are not entirely understood but may help facilitate a lower opioid requirement in those who undergo a propofol washout as more receptors may be available for opioid binding. The effects on the  $\mu$ -opioid system may be what facilitates rapid opiate wean as has been described in the literature [3,8,9].

Propofol has effects on the cardiovascular system. Hypotension has been noted in pediatrics although this appears to be more associated with bolus doses of propofol rather than continuous infusion [10]. A decrease in cardiac output has also been demonstrated in some studies, some of which demonstrate a decrease of up to 30% in cardiac output. Pulmonary arterial and pulmonary capillary wedge pressure have also been shown to decrease with propofol [11].

Propofol also has effects on the respiratory system. Respiratory drive decreases with propofol as can minute ventilation. These effects are dose-dependent and can be seen with both bolus doses and continuous infusions [12,13].

Propofol related infusion syndrome is perhaps one of the most feared adverse effects associated with propofol. Formal diagnosis criteria for propofol related infusion syndrome do exist and consist of refractory bradycardia associated with one of the following conditions: 1) hepatomegaly or fatty liver; 2) lipemic plasma; 3) metabolic acidosis; 4) skeletal muscle breakdown [14]. Propofol related infusion syndrome appears to be dose dependent and duration dependent with higher doses and longer infusions making propofol related infusion syndrome more likely. Pediatric studies have noted an incidence of propofol related infusion syndrome of 1% to 4%. The risk of propofol related infusion syndrome makes mitochondrial disease a contraindication for the use of propofol [2,15-17].

While there is a large amount of data regarding the use of propofol for general anesthesia in children and for procedural sedation, little has been published regarding longer term propofol infusions in pediatric intensive care units. Most studies have reported infusion rates of 100 mcg/kg/min or less with most infusions lasting 24 hours or less [1,18-22]. The dose and duration of propofol infusion used in the currently presented case is higher and longer than the average reported. Nonetheless, like reported in most case series there were no significant hemodynamic effects or elevation in lactate. Also, of note, is that the patient in this presented case had residual congenital heart disease consisting of severe mitral regurgitation. Even in light of this, propofol was hemodynamically well tolerated.

The particular benefits of this strategy were as follows: 1) allowed for rapid wean of opioids and sedating agents and 2) facilitated prompt extubation after rapid wean. This strategy of a propofol washout can prove to be particularly helpful in critically ill children requiring high-doses of sedating agents and opioids as it allows for rapid weaning as described. Since propofol is not without its adverse effects this must be done in a controlled fashion. It should be noted that in the intensive care unit there is routine monitoring of patients that helps facilitate the use of propofol. A patient who is already intubated and mechanically ventilated and has an arterial line or central venous line in place can be adequately monitored for longer term infusions. This allows for control of ventilation and monitoring of the partial pressure of carbon dioxide. End-tidal carbon dioxide monitoring can also provide more continuous monitoring of the partial pressure of carbon dioxide. Having an arterial line or central venous line also allows for routine blood gases to trend serum lactate. An arterial line also allows for continuous blood pressure monitoring.

Anecdotally, some cardiac intensive care units have firmly opposed the use of propofol infusion in patients. This strategy is not supported by the current published data and, in fact, ignores published data of the benefits of propofol infusion in some children. What is perhaps a better strategy, is to identify patients in whom propofol may be particularly helpful, identify specific goals that are hoped to be accomplished by the propofol infusion, and then develop a monitoring strategy to employ while a propofol infusion is being utilized.

This unique case demonstrates the utility of propofol infusion in a child with congenital heart disease and residual heart disease.

## **Conclusion**

We present a case of a 16-month old girl who underwent mitral valve repair and had residual moderate to severe mitral valve regurgitation and required high doses of sedating agents and opioids postoperatively. Use of a propofol infusion allowed for rapid weaning of these sedation agents and opioids and also facilitated prompt extubation after the rapid wean. This was done safely without hemodynamic compromise or increase in serum lactate.

## **Clinical Significance**

This case report is the first pediatric case to be presented in which propofol infusion was used to rapidly wean from high dose opioid and sedative agents in a child after cardiac surgery with significant residual cardiac lesions without hemodynamic compromise. This case also demonstrates that the opioid requirement to account for residual withdrawal after such a wean is relatively minimal.

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