

Preliminary Experience With a Combination of Dexmedetomidine and Propofol Infusions for Diagnostic Cardiac Catheterization in Children

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No specific regimen has been universally accepted as ideal for procedural sedation during cardiac catheterization in infants and children. In this paper, we retrospectively describe our preliminary experience with a continuous infusion of dexmedetomidine and propofol for sedation during cardiac catheterization in children with congenital heart disease. The short-half life of these two drugs creates a potential for easier titration, quicker recovery and less prolonged sedation-related adverse effects. This combination was not only able to limit the dose of either drugs, but was also very stable from cardio-respiratory standpoint. There were no adverse effects noted in our two patients. This initial experience showed that the combination of propofol and dexmedetomidine as a continuous infusion may be a suitable alternative for sedation in spontaneously breathing children undergoing cardiac catheterization.

KEYWORDS cardiac catheterization, dexmedetomidine, procedural sedation, propofol,

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INTRODUCTION

The goals of sedation for children undergoing diagnostic or therapeutic cardiac catheterization include the provision of adequate sedation and immobility with limited effects on hemodynamic and respiratory function. As there remains no consensus on the optimal agent, several different pharmacologic agents or combinations have been reported.^{1,2} The pharmacologic choices are limited, and controversy exists regarding whether such procedures should be accomplished with general anesthesia and endotracheal intubation, or procedural sedation techniques. The general consensus among the cardiac anesthesiologists appears to be procedural sedation as the depth

of sedation preserves not only the myocardial contractility, but also respiratory mechanics.³ The most common agent used in this setting is pro-

ABBREVIATIONS ASA, American Society of Anesthesiology; BP, blood pressure; DSST, DANTES Subject Standardized Tests; HR, heart rate; RR, respiratory rate

propofol although there is increasing interest with the potential applications of dexmedetomidine in this setting. Either of these drugs when used alone is associated with dose-related adverse effects as hemodynamic instability, respiratory depression and metabolic acidosis.^{4,7} We report our preliminary experience detailing the combination of continuous infusions of propofol and dexmedetomidine for sedation in children undergoing cardiac catheterization. To our knowledge, this is the first report of the use of combined propofol and dexmedetomidine continuous infusions in children undergoing cardiac catheterization. However, there are reports demonstrating the use

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of this combination during esophagoduodenoscopy, laryngoscopy, bronchoscopy, and tracheal extubation following tracheal reconstruction.⁸⁻⁹

METHODS

IRB approval was deferred for this review and publication, as such approval is not required for retrospective case reports per the regulations of the Massachusetts General Hospital.

Patient 1

A 17-year-old girl with a history of severe pulmonary hypertension due to probable chronic thromboembolic disease presented for diagnostic cardiac catheterization for the evaluation of pulmonary artery pressures. Pertinent physical examination findings included body weight of 49 kg, elevated jugular venous pressures of approximately 11-12 mmHg, brisk carotid upstrokes with no bruits, and split S2 with a loud pulmonic component. Echocardiography revealed dilated pulmonary arteries and elevated right ventricular systolic pressures with no structural defects. Previous cardiac catheterization revealed an elevated right pulmonary artery pressure of 72/40 mmHg and elevated left pulmonary artery pressure of 69/19 mmHg with a pulmonary capillary wedge pressure of 13 mm Hg. The cardiac index was 3 L/min/M², the Q_p/Q_s was 1, and pulmonary vascular resistance was 13.3 Wood units. The patient was held *nil per os* for 4 hours and routine American Society of Anesthesiologists (ASA) monitors were placed. Sedation was initiated with propofol (Diprivan, AstraZeneca, Willingham, Delaware) at 10 µg/kg/min and dexmedetomidine (Hospira, Inc, Lake Forrest, Illinois) at 0.7 µg/kg/hour. The initial vital signs were blood pressure (BP) 127/84 mmHg with a mean arterial pressure of 96 mmHg, heart rate (HR) 91 beats/min, respiratory rate (RR) 8 breaths/min, and oxygen saturation measured by pulse oximetry 100% on 2 L/min of oxygen delivered via nasal cannula. Sedation was maintained with dexmedetomidine at 0.7 µg/kg/hour and propofol at 10-25 µg/kg/min. Prior to the initiation of the procedure and placement of femoral arterial and venous cannulae, the groin was infiltrated with 3 mL of 1% lidocaine (Hospira, Inc, Lake Forrest, Illinois). There was no patient movement in response to the infiltration. The duration of the procedure was 216 minutes.

The total amount of propofol used was 110 mg (2.2 mg/kg) and dexmedetomidine was 87.06 µg (1.8 µg/kg). At the conclusion of the procedure, the drips were discontinued. Vital signs were stable throughout the procedure with the heart rate ranging from 63-91 beats/minute, mean arterial blood pressure ranging from 60 to 104 mmHg, respiratory rate ranging from 8-19/minute and oxygen saturations ranging from 94%-100%. There were no arrhythmias or metabolic acidosis noted. Arterial blood gas analysis at the completion of the procedure revealed a pH of 7.33, PaCO₂ of 36 mm Hg and a base excess of -4.5. The oxygen saturation was 100% on 2 L/min of oxygen delivered via nasal cannula. The patient was awakened at the conclusion of the procedure without any difficulty. The time for initial eye opening was about 10 minutes, and the time to full responsiveness was about 30 minutes. The times for wakefulness were determined by the anesthesiologist taking care of the patient. There was no mention of any sedation scores used for this purpose. The post-procedure course was uncomplicated and the patient did not receive any analgesics after the completion of the procedure. The patient was discharged home on the second post-procedure day without complications.

Patient 2

An 8 ½ year-old girl status post an intracardiac fenestrated Fontan procedure for tricuspid atresia, ventricular septal defect and severe pulmonic stenosis presented for diagnostic cardiac catheterization. Her baseline ECG revealed right ventricular hypertrophy via voltage criteria and a prolonged QTc of 437 milliseconds. The cardiopulmonary examination was normal. Pertinent physical examination findings included body weight of 30 kg, strong femoral pulses, brisk capillary refill and no brachial-femoral pulse delays. Her abdominal examination was unremarkable. The review of systems was negative with no history of syncope or chest pain. The patient was held *nil per os* for 4 hours and routine American Society of Anesthesiologists (ASA) monitors were placed. Following premedication with 0.3 mg/kg of oral midazolam (Versed, NovaPlus, Irving, Texas), an intravenous cannula was placed. This was followed by a loading dose of dexmedetomidine, (0.5 µg/kg over 10 minutes) and then a continuous infusion of propofol, at 10 µg/kg/

min and dexmedetomidine at 0.7 µg/kg/min. The initial vital signs included a BP of 119/57 mmHg with a mean arterial pressures 77 mmHg, HR 81 beats/min, RR 8 breaths/min, and oxygen saturation 94 % on room air. Sedation was maintained with dexmedetomidine at 0.7 µg/kg/minute and propofol at 25-50 µg/kg/min. Prior to the initiation of the procedure and placement of femoral arterial and venous cannulae, the groin was infiltrated with 3 mL of 1% lidocaine. There was no patient movement in response to the infiltration. The duration of the procedure was 210 minutes. The total amount of propofol used was 146 mg (4.9 mg/kg) and dexmedetomidine was 87.7 µg (2.9 µg/kg). At the conclusion of the procedure, the drips were discontinued. The patient's vital signs were stable throughout the procedure with the heart rate ranging from 81-98 beats/min, mean arterial blood pressure ranging from 64-78 mmHg, respiratory rate ranging from 8-22/min and oxygen saturations ranging from 87%-100%. There were no arrhythmias noted during the procedure. Arterial blood gas analysis at the completion of the procedure revealed a pH of 7.34, PaCO₂ of 39 mm Hg and a base excess of -5.2. The oxygen saturation was 91% on room air. The patient was awakened at the conclusion of the procedure without any difficulty. The time for initial eye opening was about 15 minutes and time for full responsiveness was about 35 minutes. The times for wakefulness were determined by the anesthesiologist taking care of the patient. There was no mention of any sedation scores used for this purpose. The post-procedure course was uncomplicated and the patient did not receive any analgesics after the completion of the procedure. The patient was discharged home on the second post-procedure day without complications.

DISCUSSION

Several different agents and combinations of agents have been used to provide procedural sedation of children undergoing diagnostic or interventional cardiac catheterization. The lists of agents used in this setting have included opioids, barbiturates, benzodiazepines, chloral hydrate, the lytic cocktail (i.e., meperidine, promethazine, and chlorpromazine), propofol, and in recent times dexmedetomidine. As this procedure requires not only adequate immobility but

also hemodynamic stability with no respiratory compromise and the maintenance of spontaneous ventilation, the majority of these agents have proved, at best, to be moderately successful. Furthermore, caution should be exercised in using any of these agents as the monotherapy, as the individual use of these drugs may be associated with higher doses which in turn may lead to dose-related adverse effects including hemodynamic instability and respiratory depression.⁴⁻⁷ Therefore, in many settings, a combination of two short-acting drugs, such as propofol and dexmedetomidine as a continuous infusions may be the optimal regimen for such procedures. The short-half lives of propofol and dexmedetomidine could potentially allow for easier titration, quicker recovery, and less prolonged sedation-related side effects. Recent pharmacokinetic data in children indicated that the elimination half-life of dexmedetomidine is two hours,¹⁰ and that of propofol is approximately 25 minutes.^{11,12} Furthermore, their short half-lives allows rapid titration with the use of continuous intravenous infusions rather than bolus dosing which may be associated with either hemodynamic or respiratory compromise.

Since its introduction into clinical practice, there is increasing interest in the potential applications of dexmedetomidine in the arena of procedural sedation for infants and children. Dexmedetomidine is an α_2 -adrenoreceptor agonist that possesses sedative, analgesic, and anxiolytic properties with no limited effects on respiratory function when administered within clinical dosing guidelines.^{13,14} Dexmedetomidine also modulates the release of catecholamines from the sympathetic nervous system, which makes this drug an ideal for use in this setting.¹⁵ The literature on the interaction of concomitant administration of dexmedetomidine with other drugs, including propofol, is not only limited, but also complex. Hammer et al. used a combination of dexmedetomidine (1 µg/kg given over 10 minutes) and propofol infusion during esophagogastroduodenoscopy and reported no change in median effective concentration (EC₅₀) of propofol required to produce adequate anesthesia.⁸ There was no significant shift in the propofol concentration-response curve in the presence of dexmedetomidine.⁸ Heard et al used dexmedetomidine infusion in combination with midazolam (0.1 mg/kg) and found that this combination

provides adequate sedation for MRI although the recovery is prolonged when compared with propofol infusion.¹⁶ Tokuhira et al demonstrated the successful use of dexmedetomidine infusion (at 0.3-0.4 µg/kg/hr) with propofol boluses in the management of post-Fontan surgical pediatric patients with the exception of significant bradycardia requiring frequent use of cardiac pacemaker.¹⁷

There have been multiple studies using dexmedetomidine either alone or in combination with other drugs for pediatric cardiac catheterization. Munro et al. were the first to use dexmedetomidine for sedation during cardiac catheterization in children.³ Following premedication with midazolam and inhalational induction with sevoflurane, an intravenous cannula was placed. Following this, the inhalational anesthetic agent, sevoflurane, was discontinued and dexmedetomidine administered as a loading dose of 1 µg/kg over 10 minutes followed by an infusion of 1 µg/kg/hr titrated up to 2 µg/kg/hr as needed. The average maintenance infusion rate was 0.6-2.0 µg/kg/hr. Five patients (25%) moved during local infiltration of the groin, which did not require treatment or interfere with cannulae placement. Twelve (60%) of patients received a propofol bolus during the procedure for movement, an increasing BIS number, or anticipation of a stimulus. No adverse hemodynamic or respiratory effects were noted. The report of Munro et al demonstrates that dexmedetomidine may not be effective as the sole agent for a painful invasive procedure such as cardiac catheterization, as 25% of the patients moved during attainment of vascular access and 60% of the patients required supplemental propofol. Two other groups of investigators have used a combination of dexmedetomidine and ketamine for pediatric cardiac catheterization. Tosun et al. compared a dexmedetomidine-ketamine combination with a propofol-ketamine combination in 44 children (4 months to 16 years) with acyanotic congenital heart disease undergoing cardiac catheterization.¹ Although sedation was managed effectively with both regimens, patients sedated with ketamine-dexmedetomidine required more ketamine (2.03 ± 1.33 vs. 1.25 ± 0.67 mg/kg/hr, $p < 0.01$), more supplemental doses of ketamine (10/22 vs. 4/22), and had longer recovery times (median time of 45 vs. 20 minutes, $p = 0.01$) than patients sedated with a

propofol-ketamine combination. No clinically significant differences were noted in hemodynamic and respiratory parameters. Mester et al. present the successful use of a combination of a bolus dose of ketamine and dexmedetomidine followed by a dexmedetomidine infusion.² The study cohort included 16 infants and children undergoing either diagnostic or therapeutic cardiac catheterization. Sedation was initiated with a bolus dose of ketamine (2 mg/kg) and dexmedetomidine (1 µg/kg) administered over 3 minutes followed by a continuous infusion of dexmedetomidine (2 µg/kg/hr for the initial 30 minutes followed by 1 µg/kg/hr for the duration of the case). Supplemental analgesia/sedation was provided by ketamine (1 mg/kg) as needed. No clinically significant changes in BP or RR were noted. No patient responded to local infiltration of the groin and placement of the arterial and venous cannulae.

Although a majority of studies demonstrate a favorable pattern of hemodynamic stability of dexmedetomidine in pediatrics, dexmedetomidine has the potential to produce dose-dependent decreases in BP and heart rate.⁴ One of our patients (Patient 1) had a decrease in the heart rate and BP of more than 20% of the baseline values, though the patient was clinically stable throughout the procedure. Rarely, dexmedetomidine has also been reported to cause life threatening complications including sinus arrhythmias, left ventricular dysfunction, refractory cardiogenic shock, and cardiac arrest in adults and children.^{13,18-20} Dexmedetomidine has also been shown to depress sinus and atrioventricular nodal function in pediatric patients, and may be associated with adverse effects in patients at risk for bradycardia and atrioventricular nodal block.²¹ For these reasons, it may be beneficial to combine dexmedetomidine with an agent such as propofol to limit the dosing requirements of both agents and thereby minimize dose related adverse effects. However, there is still some controversy regarding the use of a dexmedetomidine bolus prior to start of infusion in these patients.^{1,2} Based on the clinician preference, one of our patients (Patient 2) received a dexmedetomidine bolus prior to the start of infusion. However, there was no clinically significant hemodynamic shift, which is consistent with the available literature in pediatrics.²²⁻²⁴ This finding is different in adults, as hemodynamic shifts have been reported with

a dexmedetomidine bolus in adults.²⁵ When used as a sole agent for MRI sedation (which has procedure times comparable to pediatric cardiac catheterization), Mason et al. reported that the doses of dexmedetomidine required to establish adequate sedation were high (3 µg/kg of bolus followed by 1.5-2 µg/kg/hr infusion) and greater than the doses approved by the Food and Drug Administration (FDA) for use in the adult population.²³ FDA does not approve dexmedetomidine for procedural sedation in pediatrics. The recommended dose for this purpose in adults is a bolus of one mcg/kg over 10 minutes followed by a maintenance infusion initiated at 0.6 mcg/kg/hr and titrated to achieve desired clinical effect with doses ranging from 0.2 to 1 mcg/kg/hr.²⁶ These doses resulted in decreases in HR and BP outside the established 'awake' norms.²³ About 16% of the patients had HR below the age specific norms but within 20% of age adjusted normal range. The same was true for mean arterial pressures for these patients, which were, in fact, outside the age-specific normal range but within 20% of normal boundaries in either direction. Although these hemodynamic changes may be tolerated by patients without co-morbid cardiac disease, such may not be the case in patients presenting for cardiac catheterization. Moreover, depression of cardiovascular function may not allow the cardiologist to obtain the hemodynamic information needed in these patients during cardiac catheterization.

Similarly, despite its efficacy, dose-related adverse effects may occur with propofol including prolonged awakening times, lipemia, and alteration of platelet function.⁵⁻⁷ Especially in the ICU literature, there has been increased interest and concern regarding the potential adverse effects of propofol.²⁷ Although the majority of such reports have involved its long term administration in the ICU setting,^{25,28,29} recent evidence has also suggested the potential for intraoperative complications even with short-term infusions.²⁹⁻³¹ Cravens et al. noted metabolic acidosis, defined as a base deficit of -2 or greater, in 13 of 55 patients (24%) anesthetized with propofol during radiofrequency ablation, compared with 22 of 267 patients (8.2%, $p < 0.01$) who received inhalational anesthesia for carotid endarterectomy.⁷ *In vivo* and *in vitro* studies suggest that propofol may also negatively impact platelet function.^{5,32,33} More importantly, the effect may be dose depen-

dant. Hiroshi et al. evaluated platelet aggregation following propofol infusion in 10 adults.³³ Platelet aggregation induced by adenosine diphosphate was inhibited by propofol, but not by the lipid carrier. *In vivo*, the effect was dose related, occurring at 5.81 ± 2.73 µg/mL, but not at 2.08 ± 1.14 µg/mL. An additional concern with the long term administration of propofol is that one of its primary advantages, a rapid recovery, may be lost.

In contrast, our two patients were not only well sedated but also hemodynamically stable with no issues of oversedation. The blood gas repeated in both patients at the end of the procedures demonstrated no metabolic acidosis. We were not only able to limit the dose of dexmedetomidine (0.7 µg/kg/min), but also the amount of propofol used during the entire procedure. The doses of propofol described in literature (when used alone or in combination with other drugs) range from 100-300 mcg/kg/min which is in sharp contrast to the doses used in our two patients (10-50 mcg/kg/min).^{1,9,16} Though individual use of dexmedetomidine and propofol have been reported with arrhythmias in high doses, there were no arrhythmias reported in our patients.^{13,18-20,34} In addition to the above mentioned advantages, we also propose the following advantages of this combination. Dexmedetomidine when used alone is associated with slower onset of action (~10 minutes),²² which can be mitigated by the use of a combination with propofol, a rapid acting agent with onset of action of less than 30 seconds.²⁷ For the same rationale, the recovery can be quicker if dexmedetomidine and propofol continuous infusions are used as a combination. The time for initial eye opening in our study patients was much less (10 and 15 minutes) when compared to available literature with the individual use of propofol (26.9 ± 12.6 minutes) and dexmedetomidine (34.0 ± 18.9 minutes).¹⁶ Propofol, when used alone, is associated with increased post-operative need of analgesics, which can be mitigated with the combined use of dexmedetomidine. This is due to the fact that dexmedetomidine has a half-life of two hours, and likely its analgesic-sparing properties persist in the recovery period also.³⁵ This was very well demonstrated in our two patients who did not require any analgesics in the post-catheterization period. Though our subjects were well sedated in the post-catheterization period, their performance was not impaired and they were awake

enough to perform psychomotor testing as DANTES Subject Standardized Tests (DSST).

This paper reports no side effects or complications attributed to either anesthetic. Nausea and vomiting did not occur after either treatment during the hospital stay or after discharge. The limitations of this study are the retrospective nature of the publication, with only two patients and adolescent age of one patient (which can make many of her physiological attributes closer to that of an adult rather than a child) and the need for larger, randomized, controlled prospective studies to confirm the efficacy of this combination. One of the patients (Patient 2) also received midazolam prior to the start of the procedure. This variable may limit the value of the combination of continuous infusion of propofol and dexmedetomidine in this setting.

CONCLUSION

This initial experience showed that the combination of propofol and dexmedetomidine as a continuous infusion may be a suitable alternative for sedation in spontaneously breathing children undergoing cardiac catheterization. This combination may also be suitable for procedural sedation requiring long procedure times such as MRI sedation and minor surgical procedures like laryngoscopy, bronchoscopy, and esophagogastroduodenoscopy. However, until larger prospective control studies confirm the safety of this combination, full monitoring in these patients is recommended.

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