Cardiology in the Young

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Intranasal dexmedetomidine for transthoracic echocardiography in infants with shunt-dependent single ventricle heart disease

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Abstract

Objectives: We investigated the efficacy and complication profile of intranasal dexmedetomidine for transthoracic echocardiography sedation in patients with single ventricle physiology and shunt-dependent pulmonary blood flow during the high-risk interstage period. *Methods:* A single-centre, retrospective review identified interstage infants who received dexmedetomidine for echocardiography sedation. Baseline and procedural vitals were reported. Significant adverse events related to sedation were defined as an escalation in care or need for any additional/increased inotropic support to maintain pre-procedural haemodynamics. Minor adverse events were defined as changes from baseline haemodynamics that resolved without intervention. To assess whether sedation was adequate, echocardiogram reports were reviewed for completeness. *Results:* From September to December 2020, five interstage patients (age 29–69 days) were sedated with 3 mcg/kg intranasal dexmedetomidine. The median sedation onset time and duration time was 24 minutes (range 12–43 minutes) and 60 minutes (range 33–60 minutes), respectively. Sedation was deemed adequate in all patients as complete echocardiograms were accomplished without a rescue dose. When compared to baseline, three (60%) patients had a >10% reduction in heart rate, one (20%) patient had a >10% reduction in oxygen saturations, and one (20%) patient had a >30% decrease in blood pressure. Amongst all patients, no significant complications occurred and haemodynamic changes from baseline did not result in need for intervention or interruption of study. *Conclusions:* Intranasal dexmedetomidine may be a reasonable option for echocardiography sedation in infants with shunt-dependent single ventricle heart disease, and further investigation is warranted to ensure efficacy and safety in an outpatient setting.

Introduction

Dexmedetomidine is a central acting alpha-2 agonist with sedative hypnotic properties commonly used intravenously as a continuous infusion in the operative and ICU settings, or as a bolus or continuous infusion for diagnostic imaging. Due to a low rate of serious adverse events, dexmedetomidine has been used with increasing frequency in paediatrics and in patients with CHD.[1–4] Dexmedetomidine is available as an intranasal formulation delivered via an atomiser with a relatively short half-life and minimal effects on respiratory drive.[5–7] Intranasal dexmedetomidine has been described as part of a single agent or multimodal sedation regimen for the successful completion of diagnostic imaging procedures.[8]

As sedation is often administered for complete anatomic and haemodynamic evaluation by transthoracic echocardiogram in uncooperative infants and young children, a procedural sedation approach avoiding general anaesthesia, intravenous access, and drugs with an unpleasant taste is an attractive option. Additionally, the procedural sedation approach should avoid drugs with a higher risk profile considering some anaesthetic and sedative drugs that can alter the haemodynamic status dramatically in children with CHD. In fact, several reports have already described intranasal dexmedetomidine, intranasal ketamine, oral chloral hydrate, and intranasal midazolam use as suitable options for this purpose.[9–12] Intranasal dexmedetomidine use for echocardiographic sedation has emerged as perhaps the most attractive option as it is widely available, easy to administer, safe and efficacious with minimal adverse events.[4,9–16] Despite its potential utility in paediatric procedural sedation, no published reviews have examined intranasal dexmedetomidine administration in patients with shunt-dependent single ventricle heart disease who may be more vulnerable to changes in afterload and heart rate. A determination of a safe and effective sedation regimen in this patient population would be most beneficial as the haemodynamic effects of a procedural sedation regimen would be most pronounced.[17]

This case series describes our initial experience with the use of intranasal dexmedetomidine for transthoracic echocardiography sedation in patients with single ventricle physiology and shunt-dependent pulmonary blood flow during the interstage period. The purpose is to report the efficacy and complication profile of intranasal dexmedetomidine in this high-risk infant population.

Methods

This is a single-centre, retrospective case series of infants with shunt-dependent single ventricle CHD after Stage 1 palliation (S1P) who underwent inpatient transthoracic echocardiography with intranasal dexmedetomidine sedation. As per institutional practice, patients with acyanotic and cyanotic CHD undergoing echocardiography between 1 month and 2 years of age are routinely sedated under supervision of a paediatric cardiologist in the outpatient echo lab at Children's Wisconsin with intranasal dexmedetomidine. Prior to October 2018, chloral hydrate was the drug of choice for routine sedation as it was still commercially available. Patients with shunt-dependent single ventricle heart disease are not sedation candidates in the outpatient echo lab at Children's Hospital of Wisconsin based on institutional practice. Informed parental consent was waived due the retrospective nature of the review. Chart review was performed to collect demographic data, baseline, and procedural sedation vitals, establish efficacy (ability to obtain a complete study) and sedation related complications. Concurrent medications at the time of procedural sedation were also reviewed.

Dosing for intranasal dexmedetomidine was 3 mcg/kg administered using an atomisation device (100 mcg/ml via MAD Nasal^{TM}). An adjunct dose of 1 mcg/kg dose was available if not sedated after 25 minutes per institutional practice. Standard monitoring was used in all cases and procedural sedation was performed in the cardiac ICU where a dedicated nurse or anaesthesiologist monitored all patients during sedation and recovery, given inexperience prior to this time with sedation of interstage infants with intranasal dexmedetomidine in the outpatient echocardiography lab. Level of sedation was assessed based on nursing and anaesthesia assessment of behaviour. The onset time of sedation was defined as the time from drug administration to successful sedation. Duration time was defined as the time from successful sedation to arousal and recovery. During the review period, haemodynamic variables (blood pressure, heart rate, pulse oxygen saturation were reported at baseline (prior to administration of medication) and while sedated. Near-infrared spectroscopy-derived somatic/renal regional saturations as a non-invasive measure of systemic venous oxygen delivery were not available in all patients due to the retrospective nature of this study but is reported when available. Quantitative data are presented as medians with minimum and maximum values (ranges).

Significant adverse events related to sedation were defined as escalation in care (such as administration or increases in supplemental oxygen) or the need for any additional/increased vasoactive medications to maintain pre-procedural haemodynamics. Minor adverse events were defined as changes from baseline values that resolved without intervention (heart rate and pulse oxygen saturation decreases > 10% and > 30% drop in blood pressure). For all sedated echocardiograms, the clinical report indicates whether complete imaging was interrupted due to the patient waking during the exam. To assess whether sedation was adequate, echocardiogram reports were reviewed to determine if a complete echo was obtained during sedation.

Results

Five interstage infants with shunt-dependent pulmonary blood flow underwent sedation with intranasal dexmedetomidine for transthoracic echocardiography between September and December 2020. Baseline characteristics are listed for patient cases 1–5 in Table 1. Four patients had hypoplastic left heart syndrome and had undergone a Norwood procedure with a modified Blalock-Taussig shunt for pulmonary blood flow. One infant had double inlet left ventricle, normally related great vessels and severe pulmonary stenosis palliated with a Blalock-Taussig shunt for pulmonary blood flow. Concomitant medications for all patients are listed along with demographics in Table 1. Cases 1, 3, and 5 were on supplemental oxygen via nasal cannula at baseline. At the time of procedural sedation, cases 2, 3, and 5 were on continuous vasoactive support at baseline (0.25 mcg/kg/minute of milrinone). Additionally, all patients except case 4 were on scheduled clonidine and all patients except case 3 were on angiotensin-converting enzyme inhibitor therapy at baseline. No patients were receiving a continuous dexmedetomidine infusion.

At the time of sedation, patient age was 29–69 days and patients were post-operative day 15–36 from S1P. The sedation times for onset and duration were variable with each case. The median sedation onset time and duration time was 24 minutes (range 12–43 minutes) and 60 minutes (range 33–60 minutes), respectively. Two (40%) patients woke during sedation, interrupting the exam, but sedation was deemed adequate in all 5 patients as complete echocardiograms with adequate images were accomplished. No patients required an additional intranasal dexmedetomidine rescue medication dose to obtain a complete study.

For the entire cohort of patients, baseline and procedural vitals varied as demonstrated in Table 1. When compared to baseline, three (60%) patients had a > 10% reduction in heart rate and one (20%) patient had a > 10% reduction in pulse oxygen saturation. The latter scenario was case 5 who had a transient 23% pulse oxygen saturation decrease from baseline to 61% pulse oxygen saturation; however, this was with a simultaneous elevation in heart rate to 151beats per minute and may not be a sedation related effect. All changes in heart rate and pulse oxygen saturation self-resolved and did not require intervention. One (20%) patient (case 1) had documented hypotension during sedation and recovered without intervention. This patient was not on milrinone and the available near-infrared spectroscopy documentation demonstrated no significant (>10%) reduction in near-infrared spectroscopy throughout the entire procedural duration. Temporal trends in baseline/pre-sedation and procedural vitals during sedation for all cases are shown graphically in Figure 1 where onset of intranasal dexmedetomidine administration is indicated at zero minutes.

There were no significant major adverse events or complications. Specifically, there were no escalations in respiratory or circulatory support. There were no episodes of post-procedure nausea or vomiting and all patients awoke without agitation.

Discussion

In this case series, sedative effectiveness and safety of intranasal dexmedetomidine for echocardiography sedation in the most haemodynamically vulnerable group of complex cyanotic CHD patients was demonstrated. A one-time dose of 3 mcg/kg intranasal dexmedetomidine resulted in successful study completion for all five infants with shunt-dependent pulmonary blood flow. While the majority of patients (80%) demonstrated changes in procedural

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Table 1. Patient characteristics at baseline and procedural data during sedation

Case	Age (day)/ Sex	Diagnosis	S1P	POD from S1P	Medications	Baseline HR (per minute)	Baseline O_2 flow rate (lpm)/FiO_2 (%)	Baseline SpO_2 (%)	Procedural vitals	
									HR range (per minute)	SpO_2 range (%)
1	46/F	HLHS	Norwood, BTS	36	Clonidine, captopril	146	1/25	82	146-170	79-94
2	69/M	HLHS	Norwood, BTS	27	Milrinone, clonidine, enalapril	143	RA	77	138-149	87-92
3	69/F	HLHS	Norwood, BTS	17	Milrinone, clonidine	138	1/25	78	128-160	68-91
4	59/M	DILV, PS	BTS	15	Enalapril	174	RA	92	127-158	86-94
5	29/M	HLHS	Norwood, BTS	21	Milrinone, clonidine, captopril	164	1.5/35	79	108-151	61-86

BTS = modified Blalock-Taussig shunt; DILV = double inlet left ventricle; F = female; FiO_2 = fraction of inspired oxygen; HLHS = hypoplastic left heart syndrome; HR = heart rate; lpm= L/minute; M = male; POD = post-operative day; PS = pulmonary stenosis; RA = room air; S1P = stage 1 palliation; SpO_2 = pulse oxygen saturation.

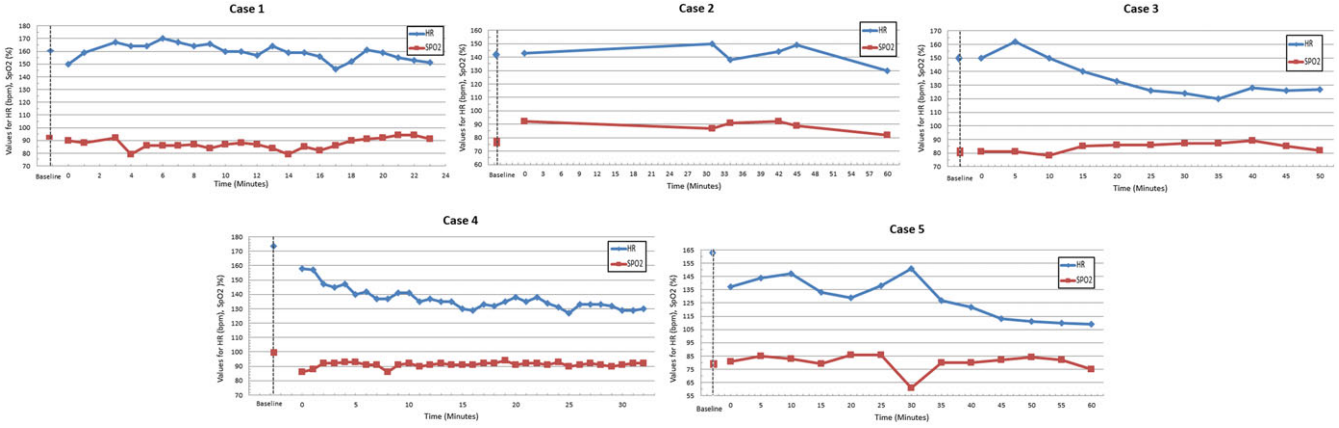

Figure 1. Temporal trends in baseline and procedural vitals during sedation for all cases. BPM = beats/minute; HR = heart rate; SpO_2 = pulse oxygen saturation.

vitals, there were no significant haemodynamic or major adverse events.

Transthoracic echocardiography is one of the most commonly performed diagnostic procedures requiring sedation in uncooperative children. The optimal regimen has not been established, leading to wide institutional variation in not only the choice of sedative agent but also the dose and route of administration. Drugs like pentobarbital, propofol or some combination of narcotics, benzodiazepines, inhaled anaesthetics, and etomidate have demonstrated improved image quality without serious adverse events; however, they are not easily administered.[17–18] Intranasal dexmedetomidine, intranasal ketamine, oral chloral hydrate, and intranasal midazolam have been described as perhaps more suitable options.[9,12,14–16,18]

Dexmedetomidine is a highly selective alpha-2 agonist that provides anxiolysis, mild analgesia, and cooperative sedation without respiratory depression.[19] It decreases central nervous system sympathetic outflow in a dose-dependent manner and can be administered intranasally for procedural sedation which is ideal when attempts to minimise traumatic administration via intravenous or intramuscular routes are taken into consideration.[19–23] Oral chloral hydrate has previously been the drug of choice for moderate sedation in uncooperative infants and toddlers requiring complete echocardiogram for decades.[24–26] However, chloral hydrate is no longer commercially available in the United States.[2] Prior studies have established good sedative features of intranasal dexmedetomidine with short half-life, faster recovery time, and effective sedation.[1,3]

intranasal dexmedetomidine has been safely and effectively used for sedation in children undergoing transthoracic echocardiography, but little has been published on its use in infants with complex and/or cyanotic heart disease.[10–13,18] Our institutional experience has documented tolerance of intranasal dexmedetomidine in patients with significant complex heart disease and cyanotic heart disease; however, this had previously excluded single ventricle heart disease.[14] Virtually no published data exist regarding intranasal dexmedetomidine use in infants with single ventricle physiology and shunt-dependent pulmonary blood flow who are more at risk for complications related to changes in afterload and heart rate. While intranasal dexmedetomidine has emerged as an attractive option for procedural sedation in paediatrics, the downside to intranasal dexmedetomidine use includes dose-dependent hypotension and bradycardia that may limit its use amongst interstage infants who have a potentially unstable circulation.[20–21]

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Doses of 1.5–4 mcg/kg/dose intranasal dexmedetomidine have been described for procedural sedation with higher doses resulting in longer duration of adequate sedation.[20–21,27] Based on institutional experience, our practice was to administer 3 mcg/kg as an initial dose of intranasal dexmedetomidine with an adjunct 1 mcg/kg/dose if not sedated after 25 minutes. As previously published, the initial dose of 3 mcg/kg intranasal dexmedetomidine resulted in high rates of echocardiogram completion with over 98% study completion without need for adjunct dose at our institution's echo lab.[14] This same initial intranasal dexmedetomidine dose resulted in adequate sedation defined as successful study completion in all five inpatient interstage patients without the administration of a rescue adjunct dose. Two patients (40%) briefly awoke during the echocardiogram but were able to fall back asleep without additional sedation.

There were no significant adverse events. Procedural vitals showed reductions in heart rate, pulse oxygen saturation and blood pressure when compared to baseline in all but one patient, however these haemodynamic trends were considered minor as they did not require escalation in care or interruption of echo and ultimately, self-resolved. Consistent with its mechanism of action, most patients receiving intranasal dexmedetomidine had a transient lower heart rate during sedation, but this did not cause circulatory compromise. We detected no concomitant hypoperfusion or decreased contractility on echocardiogram in any of these patients. There were no episodes of haemodynamic instability, and importantly, there was no requirement for any additional inotropy to maintain haemodynamic stability.

Our institutional practice has favoured intranasal dexmedetomidine for echocardiographic sedation as it has several advantages over other commonly used and comparable agents by avoiding unpleasant side effects while maintaining ease of administration, good efficacy, and low-risk profile. Midazolam, a benzodiazepine, is the most commonly studied procedural sedation drug and can be administered either intranasally or orally; however, it provides no analgesia and is associated with adverse events such as post-operative behavioural changes, cognitive impairment, paradoxical reactions, and respiratory depression.[9,16] Additionally, intranasal midazolam is known to provide nasal irritation and burning.[28] On the contrary, intranasal ketamine is used for its pain controlling aspect and may provide less bradycardia than dexmedetomidine but is not devoid of adverse events such as gastrointestinal tract stimulation, excessive salivation, nystagmus, an increased incidence of emergence agitation, and an unpleasant bitter taste.[4–5,9,12,15] Finally, an important factor when choosing a sedative medication in children is their potential effect on the developing brain.[4,6,17] Neurotoxic effects of GABAergic agonists, such as midazolam, and NMDA receptor antagonists, such as ketamine, have been established in animal studies, whereas dexmedetomidine has demonstrated neuroprotective effects in rodent models and primates.[29–31]

This study did have several limitations. The sample size of our study was small, and further study in a larger cohort is needed to truly evaluate both efficacy and safety. Although comprehensive echo studies were completed in all subjects using a one-time dose of 3 mcg/kg intranasal dexmedetomidine, while adequate sedation was achieved, uninterrupted sedation was not achieved. Prior investigations do suggest that when selecting intranasal dexmedetomidine dose for echo sedation, consideration for cyanotic CHD is important as the effective dose for sedation is higher in children with cyanotic CHD.[18,20–21] Our study did not investigate different dosing strategies for sedation in interstage infants nor the intranasal dexmedetomidine dose-response relationship since our target was achieving sedation. Also, our study did not establish an objective sedation scale which is a consideration for future studies. Future investigation should consider the haemodynamic risk of a higher intranasal dexmedetomidine dose balanced with the potential benefits of longer depth and duration of sedation. Finally, it has been well-established that circulatory compromise during the interstage period can be reflected using near-infrared spectroscopy-derived somatic/renal regional saturations as a non-invasive measure of systemic venous oxygen delivery and can allow for earlier identification of low cardiac output early after initial palliation of hypoplastic left heart syndrome.[32] Due to the retrospective nature of this study, complete near-infrared spectroscopy data on all patients were not available. Additional study in patients with single ventricle physiology and shunt-dependent pulmonary blood flow during the interstage period using regional oximetry to fully describe the haemodynamic effects of intranasal dexmedetomidine is warranted.

Conclusions

In this preliminary case series, intranasal dexmedetomidine use in interstage infants with shunt-dependent pulmonary blood flow provided safe, adequate echocardiography sedation. No patients required any intervention or interruption of the echocardiogram study due to adverse events. These initial findings are encouraging but larger-scale studies are needed with formal sedation scores in order to definitively demonstrate intranasal dexmedetomidine safety and efficacy in the high-risk CHD population.

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Conflicts of interest. None

Ethical standards. The authors assert that all procedures contributing to this work comply with the ethical standards of the Institutional Review Board guidelines on human experimentation and with the Helsinki Declaration of 1975, as revised in 2008, and has been approved by the institutional review board approval by the Children's Hospital of Wisconsin.

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