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ORIGINAL ARTICLE

Propofol Formulation Affects Myocardial Function in Newborn Infants

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Abstract

This study aimed to evaluate the effects of propofol in diluted and undiluted formulations on cardiac function in infants. Infants > 30 days received propofol sedation for central line insertion. Cases were divided into two groups: those who received undiluted 1% propofol (P1%); and those who received a diluted formulation (Pd) of equal volumes propofol 1% and 0.9% NaCl. Echocardiograms were performed pre (t_0)-, immediately post (t_1)-, and 1-h post (t_2) propofol administration. Myocardial deformation was assessed with tissue Doppler imaging (TDI) analysis and peak longitudinal strain (LS). 18 cases were included: nine (50%) P1% and nine (50%) Pd. In the P1% group, TDI velocities and LS were significantly reduced at t_1 and t_2. In the Pd Group, only TDI velocities in the left ventricle were reduced at t_1, but not at t_2. Dilution of propofol may minimize myocardial dysfunction while maintaining adequate sedation in infants. Further comparative studies are needed to investigate the safety and efficacy of this approach.

Keywords Myocardial strain · Tissue doppler · Cardiac function · Propofol · Formulation · Hemodynamics

Abbreviations

BP	Blood pressure
CL	Central line
DBP	Diastolic blood pressure
TDI E'	Diastolic velocity
ECMO	Extra corporeal membrane oxygenation
FLACC	Face, legs, activity, cry, and consolability scale
HR	Heart rate
LV	Left ventricle
LS	Longitudinal strain
P1%	Propofol 1%
Pd	Propofol diluted
PP	Pulse pressure
RV	Right ventricle
SR	Sarcoplasmatic reticulum
STE	Speckle tracking echocardiography
SBP	Systolic blood pressure
TDI S'	Systolic velocity
TDI	Tissue doppler imaging
SpO_2	Transcutaneous oxygen saturation

Introduction

Newborn infants receiving intensive care frequently require short invasive procedures, including intubation, surfactant administration, or central line insertion [1]. Use of anesthetic agents during these procedures may reduce distress and pain, and the risk of technical failure [2].

Propofol, chemically described as 2,6-diisopropylphenol [3], is a lipid-soluble anesthetic agent with very rapid onset and fast recovery time, making it potentially well suited for short invasive procedures in neonates [4, 5]. In preterm infants undergoing intubation, propofol may be associated with shorter procedure time and faster recovery [6]. There has been additional interest in propofol for minimally invasive surfactant administration [7]. However, propofol use

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for intubation and surfactant administration in newborn infants has also been associated with systemic hypotension and transient reduction in cerebral oxygenation particularly when used at higher doses [8, 9]. In older children, adverse hemodynamic effects also include hypotension, and in severe cases, fatal metabolic acidosis and myocardial failure [6–10]. Mechanisms of propofol-associated hypotension may include reduction in vascular resistance, vagal effects, and impaired myocardial function [11–13]. The effect of propofol in neonates may be dose dependent, but also potentially affected by adapting the formulation to a microemulsion [14–16].

Modern echocardiographic techniques of cardiac deformation analysis provide new insights into cardiac function in neonatal health and disease [17, 18]. Better understanding of the effects of propofol on the neonatal circulation may guide improved use with minimization of hemodynamic side-effects. This study aimed to explore the formulation-dependent effects of propofol on neonatal myocardial function using tissue doppler imaging (TDI) and speckle tracking echocardiography (STE).

Materials and Methods

Study Design and Setting

This retrospective observational pilot cohort study was conducted at the Bambino Gesù Children's Hospital, a neonatal surgical center and the national Extra Corporeal Membrane Oxygenation (ECMO) center. Study ethical approval was provided by the institutional Information Governance and Research Office.

In our department ultrasound-guided central line (CL) positioning is usually performed after sedation with propofol bolus 1 mg/kg followed by NaCl 0.9% 1 mL/kg flush over 10 s. Echocardiography was performed pre-propofol (t_0) to visualize the vein and assess cardiac function before line insertion. A second scan (t_1) was performed immediately post-CL insertion to check the correct line positioning and reassess cardiac function, typically within 15 min. Patients who required re-positioning of the CL had a third scan performed up to 1-h postprocedure (t_2). Neonates were included between March 2018 and October 2018 if they had a gestational age at birth > 27 weeks, a corrected age of 40 weeks or more, and were more than 30 days old at the time of the procedure. Neonates with significant structural cardiac disease, severe prematurity (< 27 weeks gestation), hepatic dysfunction, preexisting hypotension or cardiac dysfunction were excluded.

Participants were divided into two consecutive subgroups based on time (March to June, and June to October 2018). Neonates included prior to June 2018 received propofol at 1% (1–2 mg/mL), P1% Group. From June 2018 onward, infants received propofol diluted to produce a more dilute solution for administration (Pd Group), by dilution of 1% solution with 0.9% NaCl in equal volumes. Diluted propofol was prepared sterile, immediately before procedure by a registered nurse. Although, propofol is an alkylphenol derivative, it is an oil-in-water lipid emulsion characterized by an extreme lipophilicity and limited aqueous solubility [15]. Propofol molecules are predominantly incorporated into the droplet core so that only very small quantities are present in the aqueous phase. The maximal dose of propofol administered to neonates in each group was 1–2 mg/kg, in accordance with dosing recommendations [7]. Face, legs, activity, cry, and consolability (FLACC) scale was used bedside to quantitate the level of sedation, and results < 2 were considered as adequate [19]. All cases received 1 mg/kg of propofol. To achieve adequate clinical levels of sedation, three cases in the P1% Group required a second bolus at the same dosage (one infant had an omphalocele; two had severe laryngomalacia). In the diluted propofol (Pd) Group, four cases received a second bolus at the same dosage of 1 mg/kg (one case had a repaired gastroschisis; one had retinopathy of prematurity treatment; and two had bowel obstruction). Weights were similar in the cases who received a second dose of propofol compared to those who did not in both groups (P1% Group: 2600 ± 1200 g; 2700 ± 1260 g, respectively, and Pd Group: 3230 ± 1810 g; 3039 ± 1210 g, respectively).

Hemodynamic Monitoring

Blood pressure (BP), heart rate (HR), and transcutaneous oxygen saturation (SpO_2) were continuously monitored during this procedure. Blood gas analysis was performed immediately pre (t_0)-, 15-min post (t_1)-, and one hour post-propofol administration (t_2). Hypotension during propofol administration was defined as a reduction in mean blood pressure < [gestational age in weeks]. Hypotension was treated by a standard protocol of initial fluid bolus of 10 mL/kg of 0.9% NaCl.

Myocardial Function Evaluation

Echocardiographic data were collected by the study researcher (ACM) using a Philipps Epiq 5 with an 8–12 MHz probe, and analyzed using IntelliSpace CardioVascular software incorporating QLab V.10. Post-acquisition analysis was performed by a nonblinded single observer (ACM).

To examine right ventricle (RV) and left ventricle (LV) functions, we performed pulsed wave tissue Doppler imaging (TDI) and myocardial strain derived from speckle tracking echocardiography (STE). Both techniques are highly reproducible [20].

TDI velocities in systole (S′) and diastole (E′) were measured in the basal myocardium of the LV and RV lateral walls and the interventricular septum from an apical 4-chamber view [21]. For longitudinal strain (LS), we acquired a 4-chamber apical view and assessed systolic strain (myocardial shortening) using STE. Images with an optimized frame rate: heart rate ratio were selected [17]. To optimize tissue-tracking, regions of interest were traced within the endocardial border and adjusted manually. Measurements of peak longitudinal strain (LS, in the LV and RV) were collected.

Statistical Analysis

Group demographics were summarized as median (range), hemodynamic parameters, LS and TDI at t_0 versus t_1 and t_0 versus t_2 were reported as mean (standard deviation) and compared using unpaired *T* testing. Chi-square or Fisher's exact tests were used to compare categorical data. Analysis was performed using Prism 7 (GraphPad Software, La Jolla, CA, USA). A p value < 0.05 was considered significant and reported in bold in each Table. Statistical analysis was provided by an experienced statistician.

Results

Demographic and Treatment Data

One hundred and sixty-nine cases were eligible for this study. 151 cases were excluded due to no paired data. Of the 18 included cases, there were nine (50%) in the P1% Group and nine (50%) in the Pd Group. There were no significant differences in baseline demographic data between P1% and Pd Groups, except for weight at the time of the administration (Table 1).

Main diagnoses in the P1% Group were severe laryngomalacia ($n=2$), esophageal atresia ($n=2$), sepsis ($n=2$), omphalocele ($n=1$), bowel obstruction ($n=1$), and prematurity ($n=1$, GA at birth 27 weeks, term corrected as term at time of procedure).

Main diagnoses in the Pd Group were anorectal malformation ($n=1$), severe gastro-esophageal reflux ($n=1$), bowel obstruction ($n=2$), sepsis ($n=2$), esophageal atresia ($n=1$), repaired gastroschisis ($n=1$), rand etinopathy of prematurity ($n=1$, GA at birth 27 weeks, term corrected as term at time of procedure). Indications for CL in both groups were parenteral nutrition and antibiotic administration.

In the P1% Group, four patients were mechanically ventilated, five were receiving noninvasive ventilation or no respiratory support and were in room air. In the Pd Group, three patients were mechanically ventilated, four were receiving noninvasive ventilation, and two were breathing spontaneously in room air.

Hemodynamic Assessment

In the P1% Group, systolic BP (SBP), diastolic BP (DBP), and pulse pressure (PP) were significantly reduced at t_1 compared to t_0 (Table 2). Three of these cases developed clinically significant hypotension requiring fluid administration. In the Pd Group, SBP and DBP were significantly reduced at t_1 compared to t_0 (Table 2). No cases in the Pd Group developed hypotension. A significant reduction was observed in heart rate in P1% patients at t_1, but not in the Pd Group. Blood gas analysis was available in all patients at t_0, t_1, and t_2 for P1% cases and only at t_0 and t_1 for the Pd group. In the P1% Group, a significant reduction was observed in pH although no significant differences were found for pCO_2, base excess, bicarbonate, or lactate (Table 2).

Myocardial Function Evaluation

TDI and LV LS were performed in all 18 cases at all time points. RV LS was obtained in 16 cases. There were no statistical differences in cardiac functional measures between P1% Group and Pd Group at t_0 (Table 3). All cardiac function parameters in the P1% Group were significantly reduced at t_1 in P1% Group when compared to t_0. Also, RV LS and

Table 1 Patient demographics

Demographics data	Propofol 1% group ($n=9$)	Propofol dilution group ($n=9$)	p value
GA at birth (weeks), median (range)	36 (27–40)	35 (27–40)	0.6
Days of life at propofol administration	57 (32–210)	54 (35–179)	0.8
Weight at birth (g), median (range)	2165 (1130–4760)	2195 (730–4000)	0.9
Weight at propofol administration	2615 (1130–4760)	2820 (1200–5870)	**0.002**
Male/female (n)	7/2	6/3	NS
Number of neonates intubated	4	3	NS
Noninvasive ventilation	4	4	NS
Spontaneously breathing in room air	1	2	NS

Bold value is statistically significant ($p < 0.05$)

Table 2 Hemodynamic parameters in the propofol 1% group and the propofol diluted group

	Time 0 (t_0)	Time 1 (t_1)	Time 2 (t_2)	p value (t_0 vs. t_1)	p value (t_0 vs. t_2)
Propofol 1% group					
SBP mmHg	73 (18)	60 (19)	77 (15)	**0.02**	0.2
DBP mmHg	50 (19)	36 (19)	45 (21)	**0.04**	0.6
PP mmHg	57 (18)	42 (18)	51 (22)	**0.03**	0.6
pH	7.39 (0.06)	7.32 (0.08)	7.39 (0.09)	**0.02**	0.8
pCO_2 mmHg	41 (0.7)	47 (7.6)	43 (5)	0.1	0.8
BE	0.4 (5.1)	− 0.2 (6.7)	2 (7.3)	0.3	0.6
Bicarbonate	24.4 (3.7)	23.6 (3.2)	NS	0.4	–
Lactate	1.58 (0.7)	2 (0.5)	1.7 (0.6)	0.7	0.9
Heart rate	140 (12.6)	130 (19)	139 (21)	**0.02**	0.8
Propofol diluted (Pd) group					
SBP mmHg	74 (7)	64 (8)	70 (12)	**0.02**	0.5
DBP mmHg	42 (9)	36 (6)	46 (20)	0.08	0.5
PP mmH	53 (9)	45 (6)	53 (17)	**0.02**	0.8
pH	7.4 (0.05)	7.39 (0.1)	NS	0.08	–
pCO_2 mmHg	39 (5)	35 (10)	NS	0.2	–
BE	− 0.5 (4.4)	− 3.5 (7)	NS	0.4	–
Bicarbonate	22.3 (4.6)	21.8 (2.7)		0.7	
Lactate	1.75 (0.4)	1.3 (0.3)	NS	0.3	–
Heart rate	147 (30)	124 (23)	131 (21)	0.05	0.1

Bold values are statistically significant ($p < 0.05$)

Mean (standard deviation)

BE base excess, *SBP* systolic blood pressure, *DBP* diastolic blood pressure, *PP* pulse pressure

LV S′ remained significantly reduced at t_2 compared to t_0. In the Pd Group, there were no significant differences in RV LS or LV LS pre- and post-administration of propofol. TDI LV S′ was reduced at t_1 compared to t_0, but normalized at t_2 suggesting a transient systolic function reduction. TDI RV S′ was significantly reduced at t_2 compared to t_1. Follow-up echocardiograms, performed in all cases with myocardial dysfunction from 24 h after propofol administration, demonstrated normalization of function.

Discussion

We investigated the effects of propofol on myocardial function in neonates and observed impairment of systolic and diastolic functions in the right and left ventricles. Dysfunction as reflected by reductions in LS and TDI velocities, was the greatest in infants who received undiluted 1% propofol, compared to those who received a diluted formulation at similar total dose, suggesting a formulation-dependent effect.

There is clinical interest in the use of propofol for procedural sedation in infants and children undergoing line placement, intubation, and surfactant administration [6]. However, propofol is also associated with adverse hemodynamic effects, including hypotension and bradycardia in infants [6, 8, 9]. The mechanisms of propofol-induced hypotension in infants are not fully understood. We used novel echocardiographic techniques to assess cardiac function in response to propofol. Speckle tracking echocardiography and tissue Doppler imaging are feasible in newborn infants and permit global assessment of deformation indices, including strain (myocardial shortening), which may be more sensitive and less load dependent than the traditional geometric measures of cardiac function [17, 21-24].

Myocardial Function and Propofol

Propofol 1% administration was associated with reduced systolic and diastolic functions in both the RV and LV, as demonstrated by means of both STE-derived strain and TDI. Similarly, Yang et al. observed a reduction in LV longitudinal strain, systolic and diastolic TDI velocities, at 1, 3, and 5 min after propofol administration in female adults undergoing noncardiac surgery [25]. Our findings suggest that the mechanism of propofol-induced hypotension may be, at least in part, secondary to impaired myocardial function. The negative inotropic and lusitropic effects of propofol may be due to a direct effect on the myocardium. In vitro studies using mammalian cardiac muscle have observed reduced intracellular Ca^{2+} availability after propofol administration. Release and reuptake of calcium, through the sarcoplasmatic reticulum (SR), were seen to be affected, leading to both myocardial contraction and relaxation impairments [10, 26, 27].

Propofol may also have a direct action on the systemic vasculature, consistent with the reduced diastolic BP in our cohort. Reduced systemic vascular resistance after propofol administration may be due to Ca2þ-channel blockade, endothelial nitric oxide release, and protein kinase C-activation [9, 11]. These combined effects, on the myocardium and the vascular endothelium, may produce a global loss of hemodynamic autoregulation mechanisms. Reduced preload,

Table 3 Myocardial evaluation with longitudinal strain and tissue Doppler velocities between two groups (propofol 1% and propofol diluted)

$Time_0$ compared to $time_1$						
	Propofol 1%			Propofol diluted		
	Time 0 (t_0)	Time 1 (t_1)	p value (t_0 vs. t_1)	Time 0 (t_0)	Time 1 (t_1)	p value (t_0 vs. t_1)
Longitudinal systolic strain %, mean (SD)						
RV-LS	− 17.5 (2.3)	− 14.6 (4.2)	**0.02**	− 19 (3.8)	− 17.6 (3.3)	0.25
LV-LS	− 19.1 (3.3)	− 15.6 (4.05)	**0.01**	− 19.2 (3.4)	− 16.5 (4.8)	0.07
TDI velocities cm/s, mean (SD)						
RV S'	6 (1.1)	4.7 (0.8)	**0.001**	6.3 (1.2)	5.5 (0.9)	0.16
RV E'	7.7 (3.4)	5.8 (2.06)	**0.01**	6.7 (2)	6.8 (1.8)	0.9
RV A'	9.1 (4)	5.8 (1.3)	**0.02**	7.4 (1.2)	7.7 (1.5)	0.8
IVS S'	3.8 (0.7)	3.2 (0.6)	0.08	4.1 (0.7)	4 (0.6)	0.07
IVS E'	3.9 (1.1)	3.6 (0.9)	0.3	4.9 (1)	5.4 (1.3)	0.4
IVS A'	5.1 (1.5)	4.3 (1.1)	0.2	5.8 (1.2)	5.3 (1.8)	0.4
LV S'	4.4 (1.5)	3.4 (1.1)	**0.04**	5 (1.2)	4.5 (0.8)	**0.04**
LV E'	4.7 (1)	3.6 (0.7)	**0.02**	6.3 (1.8)	5.9 (2.4)	0.5
LV A'	6.01 (1.9)	4.4 (1.5)	**0.004**	6.6 (2.3)	7.1 (3)	0.6
$Time_0$ compared to $time_2$						
	Propofol 1%			Propofol diluted		
	Time 0 (t_0)	Time 2 (t_2)	p value (t_0 vs. t_2)	Time 0 (t_0)	Time 2 (t_2)	p value (t_0 vs. t_2)
Longitudinal systolic strain %, mean (SD)						
RV-LS	− 17.5 (2.3)	− 15.6 (2.5)	**0.02**	− 18.4 (2.7)	− 19 (3.8)	0.6
LV-LS	− 19.1 (3.3)	− 18.4 (3.2)	0.6	− 18.8 (3.2)	− 19.2 (3.4)	0.9
TDI velocities cm/s, mean (SD)						
RV S'	6 (1.1)	5.6 (0.9)	0.3	6.3 (1.2)	5.4 (1)	**0.02**
RV E'	7.7 (3.4)	6.8 (3.8)	0.2	6.7 (2)	6.6 (1.9)	0.6
RV A'	9.1 (4)	7.4 (2.7)	0.2	7.4 (1.2)	7.6 (1.6)	0.5
IVS S'	3.8 (0.7)	3.8 (0.7)	0.7	4.1 (0.7)	4.2 (0.5)	0.6
IVS E'	3.9 (1.1)	4.3 (1.6)	0.4	4.9 (1)	5.8 (0.8)	0.1
IVS A'	5.1 (1.5)	4.9 (1.7)	0.7	5.8 (1.2)	5.5 (1.2)	0.9
LV S'	4.4 (1.5)	3.5 (0.9)	**0.04**	5 (1.2)	4.6 (0.9)	0.08
LV E'	4.7 (1)	4.8 (1.5)	0.8	6.3 (1.8)	6 (1.2)	0.9
LV A'	6.01 (1.9)	5.3 (2.1)	0.2	6.6 (2.3)	5.6 (1.4)	0.5

Bold values are statistically significant ($p < 0.05$)

Mean (standard deviation)

LV left ventricle, *LS* longitudinal strain, *IVS* interventricular septum, *RV* right ventricle, *TDI* tissue Doppler imaging

reduced cardiac function, and systemic vasodilatation may result in global circulatory compromise [25].

Of note, in the P1% group, administration of propofol was associated with a significant reduction in pH, associated with a combined trend of increasing PCO_2, rising lactate, and reduced base excess. It is unclear, however, whether this observed change in acid–base status is a primary contributor to cardiac dysfunction, or a secondary effect of reduced systemic perfusion following Propofol administration.

Myocardial Function and Propofol Formulation

Oh et al. observed that in adults, the adverse effects of propofol on cardiac function appear to be dose dependent, within the normal recommended dosing range [28]. We now observed that dilution of propofol and reformulation, by mixing equal volumes with normal saline, altered the hemodynamic response. Administration of diluted propofol (Pd Group) was not associated with a change in myocardial function parameters, despite the total dose of propofol being unchanged. The differential effect of diluted and undiluted

1% propofol may be explained by factors relating to timing of drug action and final blood concentration. Dilution of 1% propofol with normal saline may alter the lipophilicity of the compound and its pharmacokinetics potentially reducing the rate of passage into cells. Similarly, diluted propofol is administered in a larger volume of fluid which may alter pharmacokinetics and subsequent pharmacodynamics (rate, extent and/or duration of action). The larger volume of administration may also result in an increase in the volume of distribution within the intravascular space, leading to a lower final blood concentration.

Clinical Significance of Our Findings

These findings may be relevant to future safe use of propofol in infants. Administration of diluted propofol solution may minimize the risk of hemodynamic compromise, while maintaining adequate sedation. Future comparative studies are needed to investigate the safety and efficacy of different propofol formulation to find the optimal balance between effects and side-effects.

Limitations

This study was limited by use of retrospective data and sample size. There was significant difference in weights between P1% and Pd groups, but total dose of propofol/body weight was the same. STE and TDI allow direct assessment of myocardial deformation, but have a degree of load-dependency; as such, it could not be known if the observed changes reflect exclusively direct effects on the myocardium, or secondary responses to change in load.

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Compliance With Ethical Standards

Conflict of interest All authors declare that there are no known financial or conflicts of interest.

Ethical Approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. The study was approved by our Institutional Review Board and as a retrospective analysis with no patient identifiable information, and therefore was approved without need for written consent.

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