Effect of etomidate on systemic and regional cerebral perfusion in neonates and infants with congenital heart disease: A prospective observational study

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Abstract

Background: Neonates and infants with congenital heart disease undergoing general anesthesia have an increased risk for critical cardiovascular events. Etomidate produces very minimal changes in hemodynamic parameters in older children with congenital heart disease. There is a lack of studies evaluating the effect of etomidate on systemic and regional cerebral perfusion in neonates and infants with congenital heart disease.

Aim: The aim of this prospective observational study was to evaluate the effect of etomidate on systemic and regional cerebral perfusion in neonates and infants with congenital heart disease.

Methods: In fifty infants aged 0-11 months (24% neonates n = 12) with congenital heart disease, mean arterial blood pressure, cardiac index using electrical cardiology, and regional cerebral oxygen saturation using near-infrared spectroscopy were measured at baseline and 1, 3, 5, and 10 minutes after induction by 0.4 mg kg\(^{-1}\) etomidate. Hypotension was defined as a mean arterial blood pressure under 35 mm Hg and cerebral desaturation as a regional cerebral oxygen saturation of less than 80% of baseline.

Results: Mean arterial blood pressure, cardiac index, and regional cerebral oxygen saturation remained stable above the predefined limits. Mean arterial blood pressure decreased slightly within a physiological range after 3 minutes (\(P = .005\), 95% CI: -5.9 to -1.0). No significant change in cardiac index could be observed.

Conclusion: Etomidate 0.4 mg kg\(^{-1}\) does not impair systemic or regional cerebral perfusion in neonates or infants with congenital heart disease.

KEYWORDS

blood pressure, cardiac index, congenital heart disease, etomidate, infants, neonates, perfusion
1 | INTRODUCTION

Infants undergoing general anesthesia have an increased risk for severe cardiovascular critical events. Especially in newborns or infants with limited hemodynamic reserve, induction of anesthesia has to be performed very carefully, including a critical, rational choice of the induction agent to be used. Propofol has a rapid onset of sedation and relaxes the oropharyngeal musculature, an effect that facilitates laryngoscopy and tracheal intubation. It remains the induction drug of choice for many older infants in daily routine, but may lead to hypotension. Thiopental has fewer cardiovascular effects in neonates and small infants, and is therefore a good alternative for these patient groups, but was recently temporarily not available on the European market. As it is not associated with clinically significant hypotension, etomidate is often used in children with head injury, and in the emergency department setting and for induction of children with severe congenital heart disease.

It is important to realize that, especially in neonates and small infants, normal blood pressure does not automatically reflect normal perfusion. After administration of etomidate, cardiac catheterization studies demonstrated only minimal hemodynamic responses in pediatric patients, but these data were collected on sedated children during the catheterization procedure and may not reflect the routine induction situation. Furthermore, these studies did not include neonates and infants.

Modern non-invasive techniques for measurement of regional cerebral oxygenation (Near-infrared spectroscopy, NIRS) and cardiac index (electrical cardiometry) can report online on cerebral and systemic perfusion during induction of anesthesia. At our clinic, etomidate is routinely used for induction of neonates and infants with CHD undergoing cardiac surgery. Therefore, we conducted a prospective non-interventional observational study to evaluate the effect of etomidate on blood pressure, regional cerebral oxygen saturation, and cardiac index during a routine induction procedure. We hypothesized that all three parameters would not change significantly and would remain stable above the predefined lower limits.

2 | METHODS

This study was conducted according to standards set forth by the Declaration of Helsinki and Good Clinical Practice guidelines. Following the local ethics committee’s approval (Ethics Committee of Hannover Medical School, Germany, Chairperson Prof. Dr S. Engeli, No. 8473 dated June 25, 2019), 50 infants with CHD ranging from 0 to 11 months of age scheduled for cardiac surgery were included in this prospective observational study. Neonates and infants who were already receiving ventilator support or were on inotropic or vasoactive drugs were excluded. The study was conducted from June to December 2019 at the Clinic for Anesthesiology and Intensive Care Medicine, Hannover Medical School, Germany.

After positioning on the operating table, standard monitoring for all children included electrocardiography, pulse oximetry, non-invasive blood pressure measurement, and capnography (Carescape B850, GE Healthcare, General Electric Company, Boston, USA). Regional cerebral oxygenation was measured by a near-infrared spectroscopy (NIRS) sensor on the forehead (INVOS™, Medtronic, Dublin, Ireland). Additionally, four adhesive electrodes were placed on the forehead, left neck, left chest, and left thigh for non-invasive measurement of cardiac index with electrical cardiometry (ICON™, Osypka Medical, Berlin, Germany).

A warm air blanket was used to maintain normothermia (Moeck Warming System, Moeck, Hamburg, Germany). If necessary, the infants were calmed with oral glucose-40% on a dummy to establish the monitoring, to obtain baseline values and for pre-oxygenation. Anesthesia was induced by injection of 0.4 mg kg⁻¹ etomidate, 0.5 µg kg⁻¹ sufentanil, and 0.5 mg kg⁻¹ atracurium followed by tracheal intubation. Subsequently, the infants were normoventilated and anesthesia was maintained with sevoflurane adjusted according to the attending anesthetist’s discretion. Decisions about anesthetic management continued as per the usual practice during data collection. Mean arterial blood pressure (MAP), cardiac index, and regional cerebral oxygen saturation (S₅O₂) were documented at baseline and 1, 3, 5, and 10 minutes after administration of etomidate. The cerebral fractional oxygen extraction was calculated by (S₅O₂−rS₅O₂)/S₅O₂.

Hypotension was defined as MAP lower than 35 mm Hg and cerebral desaturation as regional cerebral oxygen saturation lower than 80% of baseline. In accordance with Hsu et al., a cardiac index above 2.5 L min⁻¹m⁻² was assumed as normal.

Our sample size considerations were based on the rate of desaturation in infants during general anesthesia (6.1%) published by Michelet et al. and the R-function binom.test that performs an exact test of a simple null hypothesis about the probability of success in a Bernoulli experiment: 49 infants without cerebral desaturation are sufficient to state with 95% probability that this complication would occur in <6.1%.
All recorded data were analyzed using MS Excel (Excel 2010; Microsoft, Seattle, USA), GraphPad Prism (Prism 7; Graph Pad Software Inc, San Diego, USA), and MedCalc (MedCalc Statistical Software version 17.4; MedCalc Software bvba, Ostend, Belgium) software tools. Normal distribution was checked with D’Agostino-Pearson test. Patient characteristics are presented as mean ± SD (range). Mean arterial blood pressure, cardiac index, and regional cerebral oxygenation are presented as median [IQR] (range). To compare parameters at baseline with parameters after induction of anesthesia, Wilcoxon test was used with a predefined significance level of $\alpha = 0.05$.

3 | RESULTS

A total of 50 infants with CHD were included, 12 (24%) of whom were neonates. One infant was excluded because of established inotropic support (Milrinone) prior to induction. Four infants had to be excluded because of artifact interference in the electrical cardiometry (Figure 1). Patient characteristics are summarized in Table 1.

The median MAP was 57.5 [IQR 52-61] (range 45-70) mmHg at baseline and decreased during the observation time within a physiological range above the predefined lower limit to 54 [IQR49-58] (range 40-68) mmHg after 3 minutes ($P = .005$, 95% CI: -5.9 to -1.0; compared to baseline) and to 51 [IQR 47-55] (range 40-65) after 10 minutes ($P = .0001$, 95% CI: -8.5 to -4.0; compared to baseline). Median cardiac index was $3.9 \pm 0.3$ (range 2.7-4.9) L min$^{-1}$ m$^{-2}$ at baseline, remained stable and had not changed significantly after 10 minutes ($P = .13$, 95% CI: -0.4 to 0.1). Median regional cerebral oxygen saturation at baseline was 66 [IQR 59-71] (range 50-87)%, increased significantly after one minute ($P = .0003$, 95% CI: 3.3 to 10.5) and remained above the predefined lower limit (Figure 2). No episodes of hypotension or cerebral desaturation could be observed. No neonate or infant received inotropic or vasoactive drugs or got an additional fluid bolus during the induction and observation phase. Two neonates (one with hypoplastic left heart, one with double outlet right ventricle) and three infants (one with hypoplastic left heart, one with ventricular septal defect, one with isthmus stenosis) had decreases of >20% in MAP compared to baseline, but remained above the threshold of 35 mm Hg. In one neonate (with ventricular septal defect) and in four infants (two with ventricular septal defect, one with hypoplastic left heart, one with atrial septal defect), cardiac index decreased >20% from baseline, but remained above 2.5 L min$^{-1}$ m$^{-2}$.

Median cerebral fractional tissue oxygen extraction at baseline was 0.30 [IQR 0.23-0.34] (range 0.08-0.48) and decreased significantly after three minutes ($P = .035$, 95% CI: -0.077 to 0.003). Median endtidal CO$_2$ one minute after induction of anesthesia was 38 [IQR 36-40] (range 34-45) mmHg and had not changed significantly after 10 minutes ($P = .59$, 95% CI: -0.6 to 1.1). Sevoflurane was first applied in some patients after three minutes. Median exhaled sevoflurane was 0.0 [IQR 0.0-0.2] (range 0.0-0.5) vol% after 3 minutes and increased slightly up to 1.35 [IQR 1.1-1.5] (range 0.1-2.5) vol% after 10 minutes (Figure 3). The applied dose of sevoflurane did not correlate with MAP (after 3 minutes: $R^2 = 0.01$, $P = .47$, 95% CI: -8.2 to 16.9; after 5 minutes: $R^2 = 0.07$, $P = .06$, 95% CI: 10.0 to 0.3; after 10 minutes: $R^2 = 0.02$, $P = .30$, 95% CI: -6.2 to 1.9), neither with cardiac index (after 3 minutes: $R^2 < 0.01$, $P = .89$, 95% CI: -0.9 to 1.1; after 5 minutes: $R^2 = 0.04$, $P = .18$, 95% CI: -0.7 to 0.2; after 10 minutes: $R^2 < 0.01$, $P = .91$, 95% CI: -0.4 to 0.4) or with $rS_{O_2}$ (after 3 minutes: $R^2 = 0.03$, $P = .19$, 95% CI: -0.9 to 32.6; after 5 minutes: $R^2 < 0.01$, $P = .79$, 95% CI: -7.1 to 9.2; after 10 minutes: $R^2 < 0.01$, $P = .96$, 95% CI: 7.2 to 7.5).

| TABLE 1 | Patient characteristics (n = 50). Data are presented as mean ± standard deviation (range) or numbers. ASA, American Society of Anesthesiologists; VSD, ventricular septal defect; TOF, tetralogy of Fallot; AVSD, atrio-ventricular septal defect; DORV, double outlet right ventricle; HLHS, hypoplastic left heart syndrome; ISTA, isthmus stenosis of aorta; TGA, transposition of great arteries; TA, tricuspid valve atresia |
| Age (months) | 3.4 ± 3.1 (0-11) |
| Weight (kg) | 5.1 ± 1.7 (2.5-10.7) |
| Height (cm) | 60.0 ± 8.0 (44-78) |
| Sex (M/F) (n) | 28/22 |
| ASA physical status II/III/IV (n) | 5/41/4 |
| Cyanotic (n) | 21 (42%) |
| Neonate (n) | 12 (24%) |
| Kind of congenital heart disease (n) |
| VSD | 12 |
| TOF | 7 |
| AVSD | 5 |
| DORV | 5 |
| HLHS | 4 |
| ISTA | 6 |
| TGA | 3 |
| TA | 3 |
| other | 5 |
DISCUSSION

In line with our hypothesis, the key findings of this prospective observational study were stable systemic and regional cerebral perfusion with no episodes of hypotension or cerebral desaturation after administration of 0.4 mg kg\(^{-1}\) etomidate in neonates and infants with CHD.

Performing anesthesia in neonates or small infants (even without CHD) is often a challenge, and the risk for severe cardiovascular critical events is high.\(^1\) Avoiding hypotension should always be a major goal in pediatric anesthesia. Michelet et al demonstrated in 60 infants younger than three months that systolic blood pressure variation should be maintained <20% to avoid possible cerebral desaturation.\(^13\) This threshold can easily be exceeded if propofol is used in this age group, and the drug of choice for neonatal intubation remains controversial.\(^14\) Thiopental seems to be more convenient,\(^4\) but, as mentioned in the introduction, it was temporarily not available in Europe.

Infants with CHD have an increased risk for anesthesia-related morbidity and mortality.\(^15-17\) Especially in infants with aortic
stenosis or cardiomyopathy, a drop in blood pressure can easily compromise coronary perfusion, resulting in high risk for cardiac arrest. In case of cyanotic heart disease, a decrease in vascular resistance can increase right-to-left shunt volume and may lead to desaturation. Infants with heart insufficiency and limited cardiac reserve due to high left-to-right shunt volume or cardiomyopathy may be compromised by negative inotropic effects of the chosen induction drug.

Based on these considerations, children with higher ASA classes, CHD of more severity, and expected limited hemodynamic reserve tend to be induced with etomidate, ketamine, or midazolam/fentanyl. Etomidate is a steroid-based carboxylated imidazole derivative that rapidly induces hypnosis following intravenous injection. Offset after a short duration of action is by redistribution. Similar to propofol, younger children require a larger bolus dose of etomidate than older children to achieve equivalent plasma concentrations. In neonates and infants with CHD, the clearance is lower as compared to values for older children without CHD. Sarkar et al. studied twelve children (age 2 to 16 years) undergoing cardiac catheterization for device closure of atrial septal defect or radiofrequency catheter ablation procedures. They found no significant changes in right atrial, aortic, or pulmonary artery pressure, oxygen saturations, calculated Qp:Qs ratio or pulmonary or systemic vascular resistance after an intravenous bolus of 0.3 mg kg⁻¹ etomidate. In a study of 30 children (age 3 to 7 years) with CHD undergoing cardiac catheterization, Dhawan et al. demonstrated no changes in heart rate, systemic mean arterial pressure, systemic mean blood flow, Qp:Qs ratio, and SVRI after an intravenous bolus of 0.3 mg kg⁻¹ etomidate. In both studies, the children were sedated with midazolam and morphine prior to administration of etomidate.

In our study, MAP remained stable far above the predefined lower limit for hypotension in all neonates and infants. Although statistically significant, the decreases in MAP starting after 3 minutes were not clinically relevant. The reason for the slight decreases may be the initiation of the administration of sevoflurane to maintain the infants’ anesthesia after redistribution of etomidate, but we could not demonstrate a statistically significant correlation between the applied dose of sevoflurane and MAP. Cardiac index and regional cerebral oxygen saturation remained stable, with no statistically significant change in cardiac index and no decrease in regional cerebral oxygenation. For measurement of cardiac index, electrical cardiometry was used. Animal studies as well as clinical studies in preterm neonates and children with CHD found an acceptable degree of compliance with the results from transpulmonary thermodilution, echocardiography, and the Fick principle. Near-infrared spectroscopy (NIRS) for measurement of regional cerebral oxygenation was used to detect a possible decrease in cerebral perfusion. In a recent clinical study, an acceptable agreement with a weighted average from arterial und jugular bulb oxygenation saturation could be demonstrated. The increase in regional cerebral oxygenation after induction is common in hemodynamically stable patients and reflects pre-oxygenation and the reduced oxygen consumption during general anesthesia. Both techniques (electrical cardiometry and NIRS) are non-invasive and can therefore be easily administered during induction of anesthesia. The results of the presented study, in accordance with the results of the above-mentioned cardiac catheterization studies, support the clinical practice of using etomidate as a beneficial induction agent in infants with CHD or expected limited hemodynamic reserve.

Etomidate inhibits cortisol production in the adrenal gland primarily through the inhibition of 11β-hydroxylase and should therefore not be used for repeated bolus dosing or continuous infusion. In a study investigating the effect of a single induction dose of etomidate on plasma cortisol and adrenocorticotropic hormone levels in children with CHD, plasma cortisol levels decreased with anesthesia induction and remained low during cardiopulmonary bypass and at the end of surgery. However, cortisol levels did not fall below the lower normal limit, and adrenocortical suppressive effects diminished after 24 h. Most infants (like all participants of this observational study) receive high doses of corticosteroids during cardiopulmonary bypass to suppress the inflammatory response, which may mitigate the effect of etomidate on adrenal gland function. This should be kept in mind if considering the use of etomidate. We did not measure adrenocortical hormone levels in the presented study, but found no clinically obvious outcome of adrenocortical suppression in the infants during their hospital stay. New etomidate formulations that are not associated with adrenal suppression are in development, but have not yet been investigated in clinical trials.

The presented study has some limitations. At our hospital, etomidate has for more than 20 years been the standard induction drug for all children with CHD scheduled for cardiac surgery, resulting in hemodynamically stable situations in nearly all cases. Therefore, the Ethics Committee advised that we would for ethical reasons be unable to randomize the patients into groups of different induction drugs. The number of investigated infants was too small to calculate the risk of hypotension or desaturation. In the four infants excluded because of artifact interference in the electrical cardiometry, we did not record the other hemodynamic parameters; this may be an inadvertent selection bias. Measuring cerebral oxygenation by NIRS is limited to the area beneath the sensor; cerebral desaturation in deeper parts of the infant’s brain might not have been detected. Cardiac Index measured by electrical cardiometry should be seen as a trend parameter with limitations in low and high cardiac output states. The results of validation studies on electrical cardiometry are conflicting, which emphasize the need for definitive validation of accuracy and precision. In a recent published review and meta-analysis on accuracy and precision of non-invasive cardiac output monitoring by electrical cardiometry, Sanders et al. demonstrate low bias for both adults and pediatrics, but the mean percentage error was not clinically acceptable. They concluded that electrical cardiometry cannot replace thermodilution and transthoracic echocardiography for the measurement of absolute cardiac output values, but that electrical cardiometry might still be applicable as a trend monitor to measure acute changes in cardiac output, which is relevant for clinical decision-making.
In conclusion, a single bolus of etomidate 0.4 mg kg\(^{-1}\) does not impair systemic or regional cerebral perfusion in neonates or infants with CHD.

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CONFLICT OF INTEREST
The authors declare no conflict of interest.

ETHICAL APPROVAL
This observational study was approved by the local ethics committee (Ethisches Committee of Hannover Medical School, Germany, Chairperson Prof. Dr S. Engeli, No. 8473 dated June 25, 2019).

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