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RESEARCH REPORT

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Xenon as an adjuvant to sevoflurane anesthesia in children younger than 4 years of age, undergoing interventional or diagnostic cardiac catheterization: A randomized controlled clinical trial

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Summary

Background: Xenon has repeatedly been demonstrated to have only minimal hemodynamic side effects when compared to other anesthetics. Moreover, in experimental models, xenon was found to be neuroprotective and devoid of developmental neurotoxicity. These properties could render xenon attractive for the anesthesia in neonates and infants with congenital heart disease. However, experience with xenon anesthesia in children is scarce.

Aims: We hypothesized that in children undergoing cardiac catheterization, general anesthesia with a combination of sevoflurane with xenon results in superior hemodynamic stability, compared to sevoflurane alone.

Methods: In this prospective, randomized, single-blinded, controlled clinical trial, children with a median age of 12 [IQR 3-36] months undergoing diagnostic/interventional cardiac catheterization were randomized to either general anesthesia with 50-65vol% xenon plus sevoflurane or sevoflurane alone. The primary outcome was the incidence of intraprocedural hemodynamic instability, defined as the occurrence of: (i) a heart rate change >20% from baseline; or (ii) a change in mean arterial blood pressure >20% from baseline; or (iii) the requirement of vasopressors, inotropes, chronotropes, or fluid boluses. Secondary endpoints included recovery characteristics, feasibility criteria, and safety (incidence of emergence agitation and postoperative vomiting.

Results: After inclusion of 40 children, the trial was stopped as an a priori planned blinded interim analysis revealed that the overall rate of hemodynamic instability did not differ between groups [100% in both the xenon-sevoflurane and the sevoflurane group. However, the adjuvant administration of xenon decreased vasopressor requirements, preserved better cerebral oxygen saturation, and resulted in a faster recovery. Xenon anesthesia was feasible (with no differences in the need for rescue anesthetics in both groups).

Conclusion: Our observations suggest that combining xenon with sevoflurane in preschool children is safe, feasible, and facilitates hemodynamic management. Larger

Trial registration: European Medicines Agency (EudraCT 2015-002329-20).

and adequately powered clinical trials are warranted to investigate the impact of xenon on short- and long-term outcomes in pediatric anesthesia.

KEYWORDS
anesthetics, child, emergence delirium, hemodynamics, inhalation, inhalation sevoflurane, neurotoxicity, preschool, xenon

1 | INTRODUCTION

Children with congenital heart disease (CHD) undergoing diagnostic and/or interventional cardiac catheterization are at increased risk for hemodynamic instability, intraprocedural cardiac arrest, and death.[1] Maintaining an intraprocedural stable blood pressure within the limits of cerebral autoregulation is mandatory in preventing cerebral hypoperfusion and probably also neurodevelopmental injury.[2] Moreover, the US Food and Drug Administration has recently published a drug safety communication approving label changes in which it is warned that the prolonged and/or multiple use of all commonly used general anesthetics in children younger than 3 years of age might affect brain development due to possible neurotoxicity.*

As a consequence, there is an urgent need to identify alternative anesthetic agents that provide hemodynamic stability and have the potential to dampen neurotoxic side effects. Xenon has been demonstrated to have only minimal hemodynamic side effects when compared to commonly used intravenous or inhalational anesthetics.[3,4] Moreover, xenon conveys neuroprotection in preclinical models of neonatal asphyxia and anesthesia-induced neurotoxicity.[5,6]

This favorable hemodynamic profile and the potential neuroprotective characteristics could render xenon an interesting alternative for children with CHD requiring repetitive and long-lasting procedures under general anesthesia (GA). Clinical experience with xenon in children is limited to neonates with peri-partal asphyxia.[7,8] There are, however, virtually no data available on the use of xenon in pediatric anesthesia, and the feasibility of xenon anesthesia in children has yet to be demonstrated.

The minimum alveolar concentration (MAC) of xenon has never been determined in children. Also in juvenile/neonatal animals, data on MAC are scarce. While in man, the MAC of xenon in adults is 63.1%, the MAC in children is expected to be higher, concurring with other anesthetics.[9] Based on a regression analysis of meta-analytic data, the MAC of xenon at the age of 1 year was fitted to be 92%.[9] To guarantee an inspiratory oxygen concentration of 30%, xenon can be used in children presumably only in subanesthetic concentrations, necessitating the adjuvant use of another anesthetic. In adults, the combination of xenon with sevoflurane allowed a significant dose-reduction of sevoflurane, resulting in improved hemodynamic stability.[10]

What is already known

- Xenon has only minimal hemodynamic side effects when compared to other anesthetics.
- Xenon conveys neuroprotective properties in experimental models mimicking neonatal neuronal injury, and protects against developmental neurotoxicity induced by other anesthetics.
- Experience with xenon anesthesia in children is scarce.

What this article adds

- Combining xenon with sevoflurane in preschool children is safe, feasible, and facilitates hemodynamic management.

We therefore hypothesized that in children with CHD undergoing anesthesia for cardiac catheterization, combining sevoflurane with 50%-65% xenon would result in superior hemodynamic stability, compared to equipotent mono-sevoflurane anesthesia. Furthermore, we aimed to prove safety and feasibility of xenon/sevoflurane anesthesia in this patient population.

2 | MATERIALS AND METHODS

2.1 | Study design and participants

This is a proof-of-concept, prospective, mono-center, single-blinded randomized controlled pilot trial, performed according to the principles of the International Declaration of Helsinki and the principles of good clinical practice. The study was approved by the local ethics committee (SR058078, Commissie Medische Ethiek, Universitaire Ziekenhuizen Leuven, July 22nd, 2015) and by the Federal Agency for Medicines and Health Products, Brussels, Belgium (AFMPS/R&D/CED/mm830076, August 10th 2015). It was registered at the European Medicines Agency (EudraCT 2015-002329-20), and reported according to the CONSORT statement† (supplementary data). After

*U.S. Food and Drug Administration, 2016. Safety Announcement: FDA Review Results in New Warnings About Using General Anesthetics and Sedation Drugs in Young Children And Pregnant Women. Available at: http://www.fda.gov/downloads/Drugs/DrugSafety/UCM533197.pdf (Accessed 13.07.2017)

†CONSORT statement (available at: http://www.consort-statement.org) (accessed 13.07.2017)

obtaining written informed parental consent, 40 children were enrolled in the trial and randomized to undergo GA maintained with either xenon as an adjuvant to sevoflurane (xenon group), or sevoflurane alone (sevoflurane group) at a 1:1 ratio. Randomization was performed using a software-generated allocation sequence (Sealed Envelope™, London, UK). Group assignments were ensured in sealed, nontransparent, serially numbered envelopes, only opened after the arrival of the patient in the intervention room. Two investigator types conducted the trial. Investigator I accomplished the enrollment (day prior to intervention) and all postoperative visits and was, similar to the patient and his parents, blinded to treatment allocation. Investigator II performed randomization and the GA and could not be blinded to the treatment due to the kind of intervention (administration and monitoring of either one or two inhalational anesthetics). Children were eligible if they were younger than 4 years of age and scheduled for an elective interventional or diagnostic cardiac catheterization. We excluded children if the intraprocedural oxygen requirement was expected to be above 40%, if the procedure was defined as high risk and complex by the pediatric cardiologist, or in the case of lack of written parental informed consent.

2.2 | Anesthesia, intervention, and postinterventional follow-up

Patients, fasted for 6 hours, received no premedication to avoid interaction with recovery characteristics. For anxiolysis, parents accompanied their children until the induction of anesthesia. Noninvasive cardiorespiratory monitoring was established according to institutional standards. Besides, the bispectral index (BIS) (pediatric sensor, Medtronic-Covidien, Minneapolis, MN, USA) and regional cerebral oxygen saturation ($rScO_2$) (CAS Medical Systems, Branford, CT, USA) were continuously monitored. Induction of anesthesia was performed with fentanyl (2 μg/kg), propofol (3 mg/kg), and rocuronium (0.3 mg/kg). Dexamethasone (0.15 mg/kg) was given to prevent postoperative nausea and vomiting. Exceptionally, there was no intravenous line available and anesthesia was induced by mask inhalation of sevoflurane. Subsequently, the randomization envelope was opened and GA was maintained with either 50%-65% xenon (LENOXe™; AirLiquide Santé International, Paris, France) in oxygen (FiO_2 = 0.25-0.4) as an adjuvant to sevoflurane (xenon group), or sevoflurane (Sevorane; AbbVie, Wavre, Belgium) alone (FiO_2 = 0.25-0.4) (sevoflurane group), using a closed-circuit respirator (FelixDual™; AirLiquide Medical Systems). To achieve a comparable depth of anesthesia, sevoflurane concentrations were titrated in both groups according to physiological signs indicative for an appropriate depth of anesthesia and to target BIS values of 40-60. Investigator II decided on the administration of additional fentanyl or rocuronium. All patients received paracetamol (15 mg/kg) for postoperative pain control. If available, according to the intervention, intracardiac, systemic, and pulmonary vascular pressures were measured postinduction and at the end of the procedure. Basic fluid replacement was performed according to the "4/2/1-rule" (mL/kg/h) using a balanced crystalloid solution. All patients were transferred to the postanesthesia care unit (PACU). Cardiopulmonary and safety parameters were reassessed 1 hour after discharge from the PACU and on the following morning.

2.3 | Outcome

The *primary outcome* of this clinical trial was the incidence of intraprocedural hemodynamic instability, defined by the occurrence of one of following events: (i) a heart rate (HR) change >20% from baseline (not caused by interventional manipulation); (ii) a change in mean arterial blood pressure (MAP) >20% change from baseline (this change has been recently demonstrated to be associated with cerebral desaturations in infants[11,12] and is frequently used as intervention trigger in pediatric studies[13]); or (iii) the requirement for an hemodynamic intervention performed by investigator II to treat hemodynamic instability as defined above (assessed as the composite of using either vasopressors, inotropes, chronotropes, or fluid boluses). Isolated blood pressure drops >20% from baseline were treated with phenylephrine (2-3 μg/kg) and/or a fluid bolus (crystalloid 10 mL/kg), isolated bradycardia with atropine (10-20 μg/kg), and the combination of bradycardia with hypotension with ephedrine (50-100 μg/kg).

2.4 | Secondary endpoints

- Hemodynamic parameters:
  - HR and MAP (noninvasively at the upper limb)
  - Blood pressure variability, assessed by the coefficient of variation of MAP [CV = standard deviation/mean MAP (in %)].[14]
  - Time-weighted number of hypotensive episodes, defined as the number of measurements with a MAP change >20% from baseline, normalized to the duration of anesthesia (n/min).
  - Incidence and duration of cerebral desaturation, defined as a decrease in $rScO_2$ of >20% from baseline.
  - Intraoperative fluid balance.
  - Intracardiac, systemic, and pulmonary vascular pressures, after induction and at the end of the procedure.

- Recovery parameters:
  - Time to extubation and to open eyes (measured from discontinuation of the investigational treatment).
  - Aldrete score, assessed at 5, 10, 15, 30, 45, and 60 minutes after extubation.
  - Recovery index:
    $$RI = \frac{1+\text{Aldrete score at T5}}{(2\times\text{time to extubation})+\text{time to open eyes}}$$ [15]
  - Time to readiness for discharge from the PACU (defined by the time to reach an Aldrete score of >9).
  - Length of PACU and hospital stay.
- Feasibility:
  - Depth of anesthesia, assessed by clinical signs (movements or sudden changes in HR or blood pressure) and BIS values.

- Intraoperative respiratory profile [measured by arterial oxygen saturation (SpO_2) and endtidal CO_2 concentrations in addition to blood gas analysis at the beginning and the end of the procedure].

- Intraoperative consumption of xenon, sevoflurane, and fentanyl.
- Safety:
  - The incidence of emergence delirium (ED) as assessed using the "Pediatric Anesthesia Emergence Delirium Scale" (PAED scale) and the "Four-point Agitation Scale" (Watcha scale), every 5 minutes by investigator I, blinded to the group allocation, from the moment of extubation until discharge from the PACU. ED was diagnosed if children had a score of ≥3 on the Four-point Agitation Scale or ≥10 on the PAED scale.[16]
  - The incidence of POV.
  - The incidence of (serious) adverse events [(S)AEs] at all study visits.
- Others:
  - Levels of serum protein 100β (neuroglial injury marker).

2.5 | Statistical analysis

Sample size estimation was based on data from 13 arbitrarily chosen children undergoing cardiac catheterization prior to the start of our study in which we found an incidence of hemodynamic instability (as defined above) of 70%. Using a two-sided Fisher's exact test for the detection of differences between proportions (with alpha = 5%), at least 37 patients per group were required to show a relative reduction of 50% in the incidence of hemodynamic instability with a power of 80%. To compensate for possible drop-outs, we planned to include 80 patients in total. As the needed sample size depended entirely on the assumed rate of perioperative hemodynamic instability, a sample size recalculation (SSR) was already planned prior to the start of the study. The SSR was scheduled to be performed after the inclusion of 40 patients. Stopping rules had not been defined beforehand. For this SSR, we used a blinded interim analysis of the overall rate of hemodynamic instability,[17] as defined by the above-mentioned criteria.

Details on the statistical analysis can be found in the supplementary document. All results were analyzed on an intention-to-treat basis. A $P < .05$ was considered statistically significant.

3 | RESULTS

3.1 | Study flow, baseline characteristics, type of procedure, and risk category

From September 2015 to April 2016, 69 children scheduled for elective heart catheterization were screened (Figure 1). A total of 40 were included and randomized to receive GA either with xenon plus sevoflurane or sevoflurane alone. All patients received the allocated intervention, but one patient of the xenon group did not require any administration of sevoflurane to maintain adequate depth of anesthesia and received mono-xenon anesthesia. There was no difference in the baseline characteristics between both groups, except for an imbalance in the primary type of CHD. Significantly more univentricular heart syndromes were randomly allocated to the xenon group. Groups did not differ with respect to the type of procedure (diagnostic or interventional), type of intervention, or the procedural risk category (as defined by the "Congenital Cardiac Catheterization Project on Outcomes") (Tables 1 and S1).[18]

3.2 | Primary outcome: Intraprocedural hemodynamic instability

After the enrollment of 40 patients, a blinded SSR was performed as planned prior to the start of the trial in the study protocol. According to the a priori established criteria, all patients fulfilled the definition of hemodynamic instability at least at 1 point during the study. Therefore, the study was stopped for futility,[19] ie, the probability to find a difference in hemodynamic instability at the end of the planned trial was so low that continuing the trial with this primary endpoint was not justified. Table 2 gives an overview of the results for the separate criteria of hemodynamic instability. The lack of difference for the primary outcome could also be found in a subgroup analysis in which cyanotic and univentricular conditions were assessed separately (data not shown).

3.3 | Secondary outcomes

3.3.1 | Hemodynamic parameters

Heart rate and MAP were comparable between both groups throughout the procedure (Figure 2). A further analysis of our data using absolute threshold values for the definition of hypotension (ie, <35 mm Hg in children <6 months; and <43 mm Hg in older children[20]) showed a lower incidence of hypotension in both groups, with however virtually no impact on the overall incidence of hemodynamic instability (see Table S3A). Likewise, no difference in the incidence in hypotension and the overall incidence of hemodynamic instability was found when taking into account only measurements starting 10 minutes after induction (when the hemodynamic effects of induction have probably waned) (see Table S3B). However, blood pressure variability (Figure S2) and the number of hypotensive episodes per minute of anesthesia (Table 3) were significantly lower in the xenon group. While there was no significant difference for the administration of ephedrine, atropine, or fluids, phenylephrine was required significantly less frequently and in significantly lower doses in the xenon group (Table 3, Figure S1). Significantly more children in the sevoflurane group showed cerebral desaturation compared to those in the xenon group (Table 3). Moreover, the duration below the threshold was longer.

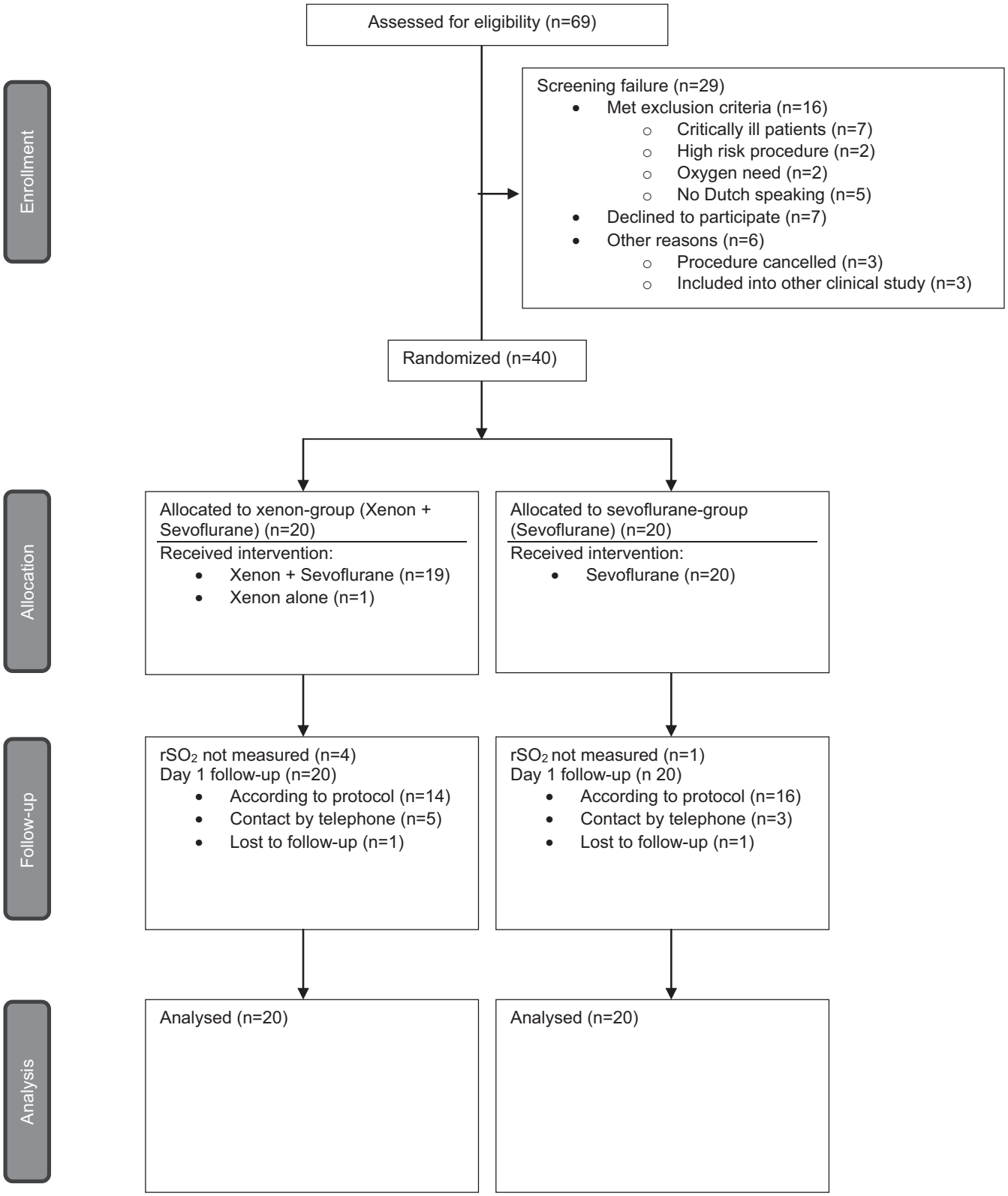

FIGURE 1 Flow diagram according to the CONSORT statement

3.3.2 | Recovery parameters

Recovery was faster in the xenon group than in the sevoflurane group as indicated by significantly shorter times to extubation and to open eyes, and a higher recovery index (Table 4). Time until readiness for discharge from the recovery room was shorter in the xenon group. This finding failed to translate into a significantly decreased length of PACU stay,

TABLE 1 Demographic and clinical characteristics at baseline

	Xenon + Sevoflurane (n = 20)	Sevoflurane (n = 20)
Age (months)	18 [2-39]	8 [3–26]
Height (cm)	77 [60-92]	68 [62-88]
Weight (kg)	10 [6-13]	8 [6-11]
Gender: male/female, n (%)	9/11 (45/55)	12/8 (60/40)
ASA score II/III/IV, n (%)	3/13/4 (15/65/20)	2/16/2 (10/80/10)
HR (bpm)	128 [109-145]	129 [103-141]
SpO_2 (%)	87 [80-99]	95 [89-100]
SpO_2 ≤95%, n (%)	11 (55)	8 (40)
Cerebral oxygenation (%)		
$SctO_2$ left side	72 [67-83]	76 [70-82]
$SctO_2$ right side	73 [65-82]	78 [68-81]
Classification of CHD, n (%)		
Acyanotic malformations	4 (20)	11 (55)
Isolated ASD type II	0 (0)	1 (5)
L-TGA	1 (5)	1 (5)
Coarctatio aortae	1 (5)	4 (20)
Dysplastic aortic valve	1 (5)	0 (0)
Dysplastic pulmonary valve	0 (0)	4 (20)
Persistent ductus Botalli	2 (10)	1 (5)
Cyanotic malformations	16 (80)	9 (45)
Tetralogy of Fallot	4 (20)	4 (20)
Univentricular heart	10 (50)	1 (5)
Hypoplastic right heart syndrome	8 (40)	1 (5)
Hypoplastic left heart syndrome	2 (15)	0 (0)
DORV	2 (10)	2 (10)
TAPVC	0 (0)	1 (5)
Ebstein malformation	0 (0)	1 (5)

Data are presented as median [interquartile range] and as absolute numbers [n, with the percentage (%) of the whole].
ASA, American Society of Anesthesiologists; ASD, atrial septum defect; bpm, beats per minute; CHD, congenital heart defect; DBP, diastolic blood pressure; DORV, double outlet right ventricle; HR, heart rate; L-TGA, levo-transposition of the great arteries; MAP, mean arterial pressure; SBP, systolic blood pressure; $SctO_2$, cerebral tissue oxygen saturation; SpO_2, peripheral oxygen saturation; TAPVC, total anomalous pulmonary venous connection.

most probably due to logistical reasons (lack of timely transfer capabilities).

3.3.3 | Feasibility

Three patients showed physical signs (movement) of an insufficient depth of anesthesia (xenon group, n = 1 and sevoflurane group, n = 2, $P = 1.0$), necessitating rescue fentanyl. Intraprocedural BIS values varied between 40 and 60, and did not differ between groups (Figure S3). The xenon group required significantly lower inspiratory sevoflurane concentrations than the sevoflurane group to achieve a comparable depth of anesthesia assessed by clinical signs and the BIS monitor, resulting in significantly lower intraprocedural end-expiratory sevoflurane concentrations (Table 3). Mean inspiratory xenon concentration was within the target range (50%-65%). Intraoperative opioid consumption was similar in both groups (Table 3). SpO_2 and endtidal CO_2 concentrations were continuously measured and within normal limits according to the patients' pathology.

3.3.4 | Safety

Based on the Four-point Agitation score, the incidence of ED was significantly lower in the xenon group than in the sevoflurane group (Table S2). No patients in the xenon group had a PAED score of ≥10 indicative for ED vs 24% in the sevoflurane group ($P = .1$). Neither incidence of POV nor use of anti-emetics was statistically different between both groups. The incidence of all other AEs was similar between the groups. One patient (sevoflurane group) suffered from a venous thrombosis at the puncture site, resulting in prolonged hospitalization.

3.3.5 | Laboratory results

Both groups showed an increase of postoperative serum protein S100β compared to baseline values (data not shown). This rise was not statistically different between both groups.

4 | DISCUSSION

In the present trial, we found that the use of 50-65vol% xenon as an adjuvant to sevoflurane was feasible in children younger than 4 years of age undergoing diagnostic/interventional heart catheterization. While xenon was unable to reduce the incidence of three a priori defined criteria of perioperative hemodynamic instability, it was associated with less vasopressor dependency, better maintained cerebral oxygen saturation, allowed faster recovery, and potentially decreased the incidence of ED.

To the best of our knowledge, this is the first trial on the use of xenon as an anesthetic in children. Our data suggest that the concept of supplementing sevoflurane with xenon is feasible and allows for an adequate depth of anesthesia in this patient population. As the MAC of xenon in children is currently unknown, we targeted a xenon concentration of 50%-65% (ie, 1 MAC in adults) and adjusted the sevoflurane concentration in order to achieve in both groups equipotent anesthetic concentrations as guided by clinical signs and the BIS monitoring. Both groups had similar BIS values between 40 and 60 throughout the procedure and required comparable doses of fentanyl. Endtidal sevoflurane concentrations were significantly reduced by xenon supplementation, confirming in children the decrease of the MAC of sevoflurane observed in adults when adding xenon.[21] In one child, a sufficient depth of anesthesia could be

TABLE 2 The incidence of hemodynamic instability

Predefined criteria	Xenon + Sevoflurane (n = 20)	Sevoflurane (n = 20)	Odds Ratio (95% CI)	*P*-value
HR, >20% change from BL, n (%)	15 (75)	13 (65)	1.62 (0.77-1.74)	.73
MAP, >20% change from BL, n (%)	19 (95)	20 (100)	0.32 (0.01-8.27)	1.00
Fluid bolus, n (%)	4 (20)	9 (45)	0.31 (0.07-1.25)	.18
Vasopressors/chronotropes/inotropes, n (%)	8 (40)	13 (65)	0.36 (0.10-1.30)	.21
Overall incidence of hemodynamic instability, n (%)	20 (100)	20 (100)	1.00 (0.02-52.90)	1.00

BL, baseline; HR, heart rate; MAP, mean arterial pressure.
Data are presented as absolute numbers [n, with the percentage (%) of the whole].

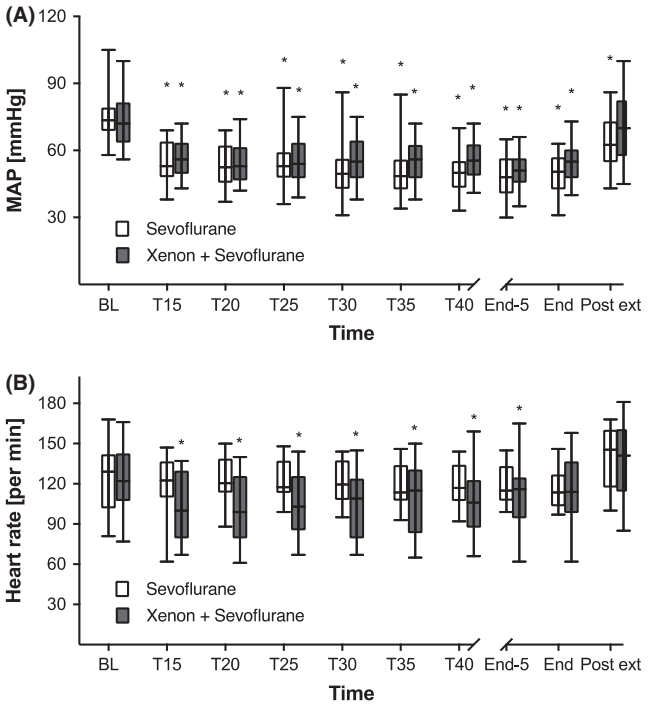

FIGURE 2 Intra-procedural time course of mean arterial pressure (MAP, A) and heart rate (HR, B). Data are presented as median (line within the box) and interquartile range (lower and upper boundary of the boxes). Whiskers indicate the minimum and maximum values. BL, Baseline; T15-40, 15–40 min after induction of anaesthesia; End-5, 5 min before the end of the procedure; End, end of the procedure; Post ext., 5 min after extubation. *$P < .05$ vs BL

achieved with mono-xenon anesthesia. Notably, the reliability of BIS monitoring in children is controversial and even unknown for children anesthetized with xenon. In adults, xenon was found to induce changes in the raw EEG comparable to those seen during propofol anesthesia.[22] Therefore, we endeavored to achieve comparable depth of anesthesia by the interpretation of clinical signs and the lack of movement, independently from the BIS monitoring.

Children with CHD undergoing cardiac catheterization are at particular risk for periprocedural hemodynamic instability due to the impact of the underlying disease, catheter-related arrhythmias, and procedural complications.[1] In fact, every participating child fulfilled at least one of the three a priori defined criteria of hemodynamic instability. Adding xenon to sevoflurane was unable to lower the occurrence of either criterion, even when using different definitions of hypotension. Unfortunately, the definition of hypotension in anesthetized infants is controversial with new recommendations having brought forward only recently.[2] Hypotension can be defined by the decrease of blood pressure relative to an awake baseline (as we did for our primary outcome) or beneath a predefined absolute threshold.[2]

Our findings suggest that supplementation with xenon may at least facilitate hemodynamic management by reducing the vasopressor support to preserve arterial normotension. This is in line with findings in adults undergoing cardiac surgery[3] and probably due to less sympathicolysis exerted by xenon.[23] Moreover, xenon decreased blood pressure variability which has been indicated as a novel predictor of perioperative adverse outcome.[24]

Last, patients in the xenon group showed a lower incidence and a shorter duration of decreases in cerebral oxygen saturation than patients in the sevoflurane group. The reasons for this may be related to the preservation of cerebral blood flow by xenon[25] and to the increased use of phenylephrine in children anesthetized with sevoflurane alone. Both hypotension and the use of phenylephrine have been associated with decreases in cerebral oxygen saturation.[11,26] Contrasting the majority of studies in adults,[4] HR in the xenon children was not lower than in children anesthetized with sevoflurane alone. This is an important finding for pediatric anesthesia and confirms observations in neonates receiving xenon-augmented cooling after birth asphyxia.[7]

In our study, children receiving xenon showed a shorter recovery as demonstrated by several parameters. This finding was expected from experience in adults[4] and can be attributed to the low blood/gas partition coefficient of xenon. Rapid emergence (in particular from sevoflurane anesthesia) has been implicated in the pathophysiology of ED.[16] Despite the faster emergence, children in the xenon group had a decreased incidence of ED as suggested by significant differences in the Four-point Agitation Scale. Of note, the differences in the PAED score failed to reach statistical significance. While the PAED scale is frequently used in pediatric anesthesia research, it should be noted that this measure was derived and validated in a cohort of children much older (mean age 3.7 years) than our study population (including 13 children <6 months).[27] In clinical practice, it

TABLE 3 Procedural data

	Xenon + Sevoflurane (n = 20)	Sevoflurane (n = 20)	Difference in median (95% CI)	OR (95% CI)	*P*-value
Procedural characteristics					
Type of procedure: diagnostic/interventional n (%)	5/15 (25/75)	5/15 (25/75)			
Risk category: 1/2/3/4[a], n (%)	4/6/8/2 (20/30/40/10)	3/11/5/1 (15/55/25/5)			
Duration of procedure, min	63 [43-95]	51 [40-69]	−12 (−27 to 5)		.25
Intraprocedural medication					
Total propofol, mg/kg	3.00 [2.90-3.06]	3.00 [2.77-3.12]	0 (−10 to 5)		.59
Total fentanyl, μg/kg	2.68 [1.99-3.57]	2.09 [1.96-2.72]	−0.6 (−15 to 3)		.25
Total rocuronium, mg/kg	**0.34 [0.30-0.57]**	**0.30 [0.29-0.34]**	**−0.04 (−2.20 to 0.15)**		**.04**
Phenylephrine					
n (%)	**5 (25)**	**13 (65)**			**.03**
μg/kg	**0 [0-2.49]**	**4.93 [0-15.37]**	**4.93 (0 to 60)**		**.01**
Ephedrine					
n (%)	2 (10)	3 (15)			1.00
mg/kg	0 [0-0]	0 [0-0]	0 (0 to 0)		.47
Atropine					
n (%)	2 (10)	1 (5)			1.00
μg/kg	0 [0-0]	0 [0-0]	0 (0 to 0)		.49
Mean inspiratory xenon concentration, %	57 [54-60]	-	-		-
Xenon consumption, l/h	10.1 [6.3-14.1]	-	-		-
Mean expiratory sevoflurane concentration, %	**0.87 [0.64-1.13]**	**2.08 [1.79-2.36]**	**1.21 (0.98 to 1.43)**		**<.001**
Fluid management					
Crystalloids, mL	188 [150-250]	195 [143-250]	7 (−30 to 90)		.70
Colloids, mL	-	0 [0-0]	0 (0 to 0)		1.00
Packed red blood cells, mL	0 [0-30]	0 [0-0]	0 (0 to 0)		.33
Intraprocedural regional cerebral oxygen saturation					
>20% decrease from BL, $SctO_2$					
Left side, n (%)	**2 (13)**	**10 (63)**		**0.13 (0.02-0.73)**	**.03**
Right side, n (%)	**3 (19)**	**11 (69)**		**0.17 (0.04-0.79)**	**.04**
Duration of 20% decrease					
Left side, min	**0 [0-0]**	**0.80 [0-3.70]**	**0.80 (0 to 2)**		**.03**
Right side, min	**0 [0-0]**	**0.80 [0-2.30]**	**0.80 (0 to 1.50)**		**.04**
Percentage of registration time under the threshold (>20% decrease from BL)					
Left side, % min	**0 [0-0]**	**0.74 [0-5.24]**	**0.74 (0 to 3.18)**		**.02**
Right side, % min	**0 [0-0]**	**1.41 [0-2.75]**	**1.41 (0 to 1.60)**		**.04**
Intraoperative hypotension					
Time-weighted number of hypotensive episodes, n/min	**0.14 [0.03 - 0.19]**	**0.17 [0.14 - 0.21]**	**0.04 (0.01 to 0.09)**		**.028**

BL, baseline; PDB, persistent ductus Botalli; RVOT, right ventricular outflow tract; $SctO_2$, cerebral tissue oxygen saturation.
[a]Risk of intervention assessed according to the "Congenital Cardiac Catheterization Project on Outcomes"[18].
Data are presented as median [interquartile range] and as absolute numbers [n, with the percentage (%) of the whole].
Bold values indicate *P*-values of <.05

TABLE 4 Recovery characteristics

	Xenon + Sevoflurane (n = 20)	Sevoflurane (n = 20)	Difference in median (95% CI)	*P*-value
Time to extubation (min)	**6 [3-7]**	**9 [6-13]**	**3 (1.83 to 6.50)**	**<.001**
Time to open eyes (min)	**8 [5-11]**	**14 [11-20]**	**6 (3.50 to 9.73)**	**<.001**
Recovery index (/min)	**0.44 [0.39-0.69]**	**0.27 [0.19-0.40]**	**−0.17 (−0.36 to −0.13)**	**<.001**
Time to be ready for discharge from PACU (min)	**68 [58-79]**	**83 [60-98]**	**15 (0 to 28)**	**.048**
Duration PACU stay (min)	83 [71-97]	94 [77-114]	11 (−5 to 26)	.12

PACU, postanesthesia care unit.
Data are presented as median [IQR] or as absolute numbers [n, with the percentage (%) of the whole].
Bold values indicate *P*-values of <.05

appears, at least in neonates, very difficult to reliably assess several items of the PAED (eg, eye contact with the caregiver or awareness of the surrounding). Moreover, in a direct comparison of different scaling systems, the Four-point Agitation Scale was found to have the highest overall sensitivity and specificity and to be a more practical tool to assess ED following anesthesia in children.[16] In any case, given the small sample size and the secondary nature of this endpoint, the finding of a reduced EA incidence in the xenon group does not prove any causal relationship. The reduced doses of sevoflurane in the xenon group could be responsible for this decrease, but it is tempting to speculate that the reduction in ED is related to the lack of effect of xenon on gamma-aminobutyric acid type A receptors.[28] An adequately powered clinical trial with ED as primary outcome parameter is warranted to confirm our current results. More xenon children appeared to suffer from POV, as expected from the adult literature.[4] This difference was not statistically significant and the study was not powered for this complication.

We acknowledge that our study is subject to several limitations. First, retrospectively, the definition of the primary outcome was probably too ambitious and relied entirely on baseline values. We opted for this endpoint as hypotension is increasingly recognized as major risk factor in pediatric anesthesia.[2] We avoided any sedative premedication in order not to confound recovery characteristics but this likely resulted in baseline hemodynamics being affected by fear and higher than normal. In fact, the subjects upon whom the sample size estimation was based had received midazolam premedication. Consequently, the occurrence of the three criteria of hemodynamic instability was much lower in these children than in the definite trial. Moreover, a binary comparison with the baseline parameters is probably too simplistic to describe hemodynamic instability. Second, hemodynamic stability could be most unambiguously assessed by directly comparing the number/degree of hypotensive episodes in both groups. However, such a direct quantification is unwarranted, as this would require tolerating instead of treating hypotensive episodes. Third, it can be discussed whether a reduction in vasopressor requirements can be considered an important outcome improvement. It has to be noted though that phenylephrine use has been linked to cerebral desaturations.[29] Fourth, the attending anesthetist could not be blinded for the interventional treatment. While hemodynamic interventions were at his discretion, these had to be triggered by the decrease of MAP or HR >20% from the baseline to minimize treatment bias. Note that the different options for hemodynamic treatment were assessed as a single composite endpoint, in order to lessen the significance of subjective therapeutic preferences. A strict treatment algorithm to standardize hemodynamic treatment is nearly impossible to define in children with CHD, especially as there is even no consensus on a "normal" blood pressure in healthy children. Fifth, feasibility of xenon anesthesia was demonstrated for cardiac catheterization. It is at present not justified to extrapolate our results to settings with severe surgical stimuli. Sixth, despite strict randomization, significantly more children in the xenon group suffered from cyanotic or univentricular conditions which may present a significant bias as these patients are more prone to hemodynamic alterations and adverse events.[1] Last, the study was prematurely stopped for futility. Note that an unplanned termination for futility (as opposed to stopping for efficacy) does not inflate the type-I error,[19] but tends to reduce the overall power of the trial. Therefore, all secondary measures should be interpreted with caution.

In conclusion, this study shows for the first time that the use of xenon as an adjuvant to sevoflurane anesthesia in preschool children suffering from CHD and undergoing elective heart catheterization is safe and feasible. Although in our study, xenon did not reduce the incidence of three a priori defined criteria of perioperative hemodynamic instability, the adjuvant administration of xenon might decrease vasopressor requirements, preserve better cerebral oxygen saturation, result in a faster recovery, and decrease the incidence of ED. Further trials exploring the putative neuroprotective effects of xenon in children are warranted.

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SUPPORTING INFORMATION

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