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Key Words:	Newborn, Sevoflurane, Peripherally inserted catheter, procedural pain, neonatal intensive care, sedation

Sevoflurane for central catheter placement in neonatal intensive care: A randomized trial

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Conflict of interest: none

ABSTRACT

Objective: To compare the efficacy and safety of sevoflurane **deep sedation** with glucose and non-nutritive sucking (GNNS) in reducing the duration of the procedure and in preventing pain-related effects during peripheral inserted central catheter (PICC) placement.

Background: PICC placement in neonatal intensive care is a delicate and stressful procedure that requires pain prevention. GNNS have been recommended in this situation but remain often inefficient.

Methods: We designed a randomized controlled study in a sixteen-bed paediatric and neonatal unit in a tertiary hospital. Fifty-nine neonates at >28 weeks of gestation with CPAP or invasive mechanical ventilation and requiring PICC placement were included. Patients were randomized to receive inhaled sevoflurane (IS) or glucose and non-nutritive sucking (GNNS). Procedural duration and conditions, hemodynamic and respiratory parameters, occurrence of movements and complications were compared (<http://clinicaltrials.gov> trial register no. NCT00420693).

Results: The 2 groups had similar demographics. There were no between group differences in procedural duration ($p=0.84$) despite **greater immobility in IS group ($p=0.017$)**. IS was also associated with fewer episodes of hypertension ($p=0.003$), tachycardia ($p<0.001$) and bradycardia ($p=0.02$). Occurrences of hypotension were not different between groups ($p=0.06$). The GNNS group showed more desaturation during the 4 hours after the procedure ($p=0.03$). Complications during intensive care stay did not differ between groups.

Conclusion: Inhaled sevoflurane does not make easier catheters **placement** but prevent pain-related symptoms. Since sevoflurane is responsible for hypotension, it requires careful monitoring and treatment adaptation.

Introduction

Despite expert recommendations, pain-control measures in neonates, especially in preterm neonates undergoing invasive procedures are limited in most neonatal intensive care units (NICUs) (1).

Peripherally-inserted central catheters (PICCs) are widely used in NICUs, however, placement of these very thin catheters is a delicate and stressful procedure, often requiring several punctures and prolonged handling. Topical anaesthesia and non-nutritive sucking, recognized as efficient in routine procedures (2), are frequently insufficient for line placements, particularly because most of these procedures do not result in successful placement on the first attempt (3). The pharmacokinetic and pharmacodynamic properties of opioids (4) and benzodiazepines in neonates make them unpredictable, both in regard to their effectiveness in reducing pain and in terms of their side effects (3). In ventilated patients, these medications can prolong mechanical ventilation.

Sevoflurane enables rapid induction and recovery and is easily titratable with predictable results. The results of a prospective randomized trial for intubation in neonates (6) and for sedation, conserving spontaneous breathing, in children undergoing MRI, suggest that sevoflurane may be helpful to reduce pain manifestation during PICC placement in neonates (7).

In a preliminary study, we showed the feasibility and efficiency of inhaled sevoflurane for central venous catheterization in spontaneously breathing term and preterm neonates in the NICU (8). Based on these findings, we designed a randomized controlled study comparing sevoflurane inhalation with glucose and non-nutritive sucking in preventing pain-related effects during PICC placement in neonates. The primary outcome was the ease in performing PICC placement, determined by duration of the procedure. Secondary outcomes included the efficacy and tolerance of treatments.

Methods

This prospective randomized study was performed in a French tertiary center care and was approved by our ethics committee. Written informed consent was obtained from the parents of all children. (<http://Clinicaltrials.gov> trial register no. NCT00420693).

Patients and groups

Neonates between 28 to 41 weeks of gestational age, requiring PICC were included in this study. Patients were excluded if they had received analgesic treatment; if they had a neurological disorder; if they had hemodynamic instability, defined as hypotension requiring treatment; and if they had contraindications to sevoflurane administration. Ventilated neonates were also excluded except if extubation was programmed in the 6 hours after PICC placement. All the mechanically ventilated patients were intubated nasally, according to our practice.

Patients were randomly assigned, using sealed envelopes, to receive inhaled sevoflurane (IS) or glucose and non-nutritive sucking (GNNS). Groups were stratified according to ventilation support: nasal CPAP (infant-flow®) or invasive ventilation (synchronized intermittent mechanical ventilation (Evita 4; Dräger; Germany)). Neonates were not sedated during mechanical ventilation.

All neonates received local anaesthesia with a lidocaine and prilocaine (Emla cream 5%) dressing 45 min before PICC.

Treatment administration

Glucose 30% (0.2 ml) was administered through a pacifier used for non-nutritive sucking, before the puncture and during all procedures according to clinical evaluation.

Sevoflurane was administered in a ventilated room (6 total air changes/h), using equipment and facilities suitable for general anaesthesia. Three hours before the beginning of the procedure, enteral nutrition was stopped and the stomach was emptied by aspiration of the

gastric tube and compensate by an increase of parenteral alimentation for the time of procedure. Pulse oximetry (SpO₂), heart rate (HR), cutaneous temperature, respiratory rate (RR) and transcutaneous carbon dioxide (tcCO₂) were monitored continuously. Non-invasive arterial pressure was measured every 3 minutes. The sevoflurane evaporator was installed on an external fresh gas delivery system. This fresh gas was added to the gas of either the CPAP or the respirator, via the heater, with a flow rate of 4 to 8 L.min⁻¹. Fresh gas flow of the Infant CPAP was decreased to maintain the expiratory pressure between 3 and 5 cmH₂O. The Infant Flow system allowed gas administration with very low nasal leak and the installation of an anaesthetics gas scavenging filter to trap waste gases at the site of overflow from the breathing circuit. When children had invasive mechanical ventilation, the flowmeter was recalibrated after external flow connection. The gas scavenging filter was installed on the expiratory circuit. Sevoflurane inhaled concentration and FiO₂ were monitored (Phillips M1026B, Boeblingen, Germany) on output of the heater. Insufflation started with 1% sevoflurane, and was progressively increased by 0.5% steps until the patient was asleep, as determined by closed eyes, absence of motor response to gentle handling and lost of tonus. Throughout the procedure, sevoflurane concentration was increased by 0.5% if movement complicating the procedure and due to stimulation occurred. Inversely, sevoflurane was decreased by 0.5% if MAP decrease of 30% of baseline value or if apnea (>30s and SpO₂<85%) occurred.

PICC placement

Twenty-four gauge silastic catheters (Epicutaneo – cava – katheter, Vygon, Germany) were used for all babies. The procedure was performed by a junior or senior neonatal intensivist; if placement failed after 4 attempts, a second operator (senior intensivist) was called in. The procedure was considered successful when the catheter was introduced in the vein and advanced to the expected distance.

Data collection

Data were reported by an independent observer (senior intensivist). Duration of the procedure was recorded as the time between the first skin puncture and the end of dressing placement. FiO_2 , SpO_2 , HR, RR, tcCO_2 and MAP were prospectively recorded before (basal measurements) and during the procedure. All data were printed and analyzed under blinded conditions, to determine maximal and minimal values (max and min), occurrence of tachycardia ($\text{HR} > 20\%$ of basal value or $> 180/\text{min}$), hypotension ($\text{MAP} < \text{gestational age in weeks}$), hypertension ($\text{MAP} > 30\%$ of basal value), apnea ($> 30 \text{ sec}$), and bradycardia ($\text{HR} < 100/\text{min}$).

Movements during the procedure were recorded as little or none (0 or 1 movement, regarded as not complicating the procedure), moderate (2 to 5 occurrences, which complicated the procedure), or frequent (> 5 occurrences which complicated the procedure). We also recorded sevoflurane concentration during the procedure; the experience of the operator; the total number of punctures; and the number of punctures outside the locally anaesthetized zone; clonic movements, laryngospasm and other adverse events. At the end of each procedure, the operator scored the ease in carrying out that procedure as “easy”, “intermediate” or “difficult”. Glycemia by hemoglucotest (Accu-Chek Performa, Roche Diagnostics) was measured immediately after the end of each procedure, SpO_2 , HR and MAP were continuously monitored for 4 hours after the end of each procedure. Serious complications (death, cerebral hemorrhage, bacteremia, bronchopulmonary dysplasia, enterocolitis, and persistent ductus arteriosus) during the stay in the NICU were also recorded.

Statistical analysis

The number of patients was calculated to show a decrease in the mean duration of the procedure from 60 to 45 min in the sevoflurane group with standard deviation of 20 min, risk $\alpha=0.05$ and risk $\beta=0.8$. A minimum of 29 patients per group was required.

The data are expressed as the mean $\pm$ SD for normally distributed data and median with interquartile range (IQR) for non-normally distributed data. Differences between and within the 2 groups were assessed using t-test for the continuous variables and chi square tests for categorical variables. Fisher exact tests were used when previous tests were not applicable. For repeated measures, differences between groups and within-groups were assessed by one-way repeated measures ANOVA using general linear model.

Results

Thirty children were included in each group between September 2006 and May 2008. One child in the GNNS group was excluded due to a severe congenital encephalopathy. The baseline demographic and clinical characteristics of the two groups were similar. The operator was a junior in most cases (table 1). Mean maximal and minimal inhaled sevoflurane concentrations used in the IS group were 2.7 ± 0.8 and 1.0 ± 0.7 respectively.

PICC placement data (Table 2)

There were no differences between groups in mean duration ($p=0.83$) of procedure, total number of punctures and number of punctures outside the locally anaesthetized zone. A second operator was required in the same proportion in each group. Evaluation of the ease in performing the procedure showed no significant difference between two groups (Table 2). Success rate of PICC placement was similar in the 2 groups ($p=0.3$). In one case in the GNNS group and none in the IS group the catheter was inserted in the vein but not advanced to the expected distance.

Efficacy and tolerance of treatments (Table 3 and 4)

Occurrence of movements complicating the procedure were significantly different between groups ($p=0.024$). Immobility during the procedure was significantly more frequent in IS group ($p=0.017$) (Fig. 1). Mean HRmax was significantly higher in children with movements that complicated the procedure ($p=0.003$). For 2 children in the GNNS group and 1 in the IS group, arterial pressure measures were lost. MAP and HR increased significantly in the GNNS and the maximum values were significantly higher in the GNNS than in the IS group. MAPmin was lower in the IS group (Table 3) but hypotension occurrence was not significantly different. Tachycardia, bradycardia and hypertension were more frequent in the GNNS group (Table 4).

The occurrence of apnea and desaturation was not different (Table 4). Apneas in the IS group were always rapidly reversible with diminution of sevoflurane concentration.

Two neonates in the IS group experienced punctual clonic movements which stopped with decrease of sevoflurane. In one child, sevoflurane had to be stopped because repeated clonic movements occurred. Clinical evolution was normal for this child.

Patent ductus arteriosus was diagnosed in 4 neonates in each group. Only one in the GNNS group and none in the IS group developed hypotension. Inversely, one in the IS group and none in the GNNS group developed hypertension. None of these eight children developed tachycardia. One of them in the IS group developed desaturation requiring to increase FiO₂ to 28%.

Post procedure survey

Glycemia at the end of the procedure did not differ between the IS (8.7 mmol/L) and GNNS (7.5 mmol/l) groups (ns). One infant in the IS group died at 21 days of life. The death

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was due to septic shock. Two other infants in the IS group developed intra ventricular hemorrhage (Grade I). Among them, one had not developed hypotension during the procedure. Neither of these complications occurred in the GNNS group. Occurrence of others complications were similar in the 2 groups.

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Discussion

We compare for the first time, sevoflurane to GNNS to decrease movements, facilitate the procedure and prevent procedural pain effects in neonates during PICC placement. In this study we failed to difference in the duration of the procedure and in the success placement rate. These findings are in agreement with previous results of studies that evaluated pain treatments during PICC placement (3,5,9). Probably that others factors than limbs movements explain the difficulty to insert and advance the catheters. It could be visibility and fragility of veins, presence of oedema in the first days of life or experience of operators. Furthermore, according to the site of puncture, it can be difficult to thread the catheter in the vein. This last situation occurred one time in our study.

We found however that sevoflurane deep sedation strongly decreased hemodynamic pain manifestations and movements during the procedure. We choose GNNS as referent treatment because they are widely used and have been described as effective in avoiding procedural pain in neonates (10). We found that this non-pharmacological treatment failed to prevent pain-related hemodynamic modifications in more than half the patients. Topical analgesia has been shown effective in preventing pain caused by skin puncture (9,11), but as we observed, punctures outside the anaesthetized zone are frequent. In addition, topical analgesia remains inactive during stressful parts of the procedure, and a recent study showed few differences in pain score between topical analgesia and no treatment (3). As highlighted in this study, duration of procedure and success placement rate are not improved by sedation and immobility.

Intravenous opioids, have also been used to prevent pain due to PICC placement. Morphine with topical tetracaine was more effective than tetracaine alone or than no treatment in preventing pain (3). Morphine, however, has been associated with increased ventilatory

requirements, and boluses of morphine have been responsible for hypotension. One important drawback of morphine is its non-controlled and prolonged action (4). Remifentanyl, which has a much shorter contextual half life, has been found to decrease pain score compared with sucrose and non-nutritive sucking, without hemodynamic or respiratory adverse effects (5). Nevertheless, the remifentanyl dose in this study was low and mean NIPS scores >3. Use of higher doses of opioids could lead to respiratory complications.

Sévoflurane is an anaesthetic drug and induces deep sedation such that infants could not feel the discomfort associated with handling. Moreover, halogenated anaesthetics, by acting on neurotransmission in the spinal cord, can decrease synaptic transmission and contribute to provide immobility (12) and central analgesia (13).

Although we used <1 MAC concentrations of sevoflurane, we observed that half the children develop hypotension in the IS group vs one third in the GNNS group. The difference was not significant but MAPmin was significantly lower in the IS group. The definition of hypotension in previous studies was based on clinician practice and defined by need of treatment. Since there are no recommendations regarding ideal blood pressure during general anaesthesia, we used a disputable but objective definition, daily applied in clinical practice in NICU. It may have increased the apparent rate of hypotension compared with previous studies. Careful hemodynamic monitoring by trained and attentive clinicians is required to titrate sevoflurane concentration according to its clinical effects.

We observed clonic movements in 4 neonates. Sevoflurane is known to induce epileptiform cerebral activity particularly with high inhaled concentrations (14). Despite the low sevoflurane concentrations used, clonic movements could be linked to sevoflurane administration. Nevertheless, interpretation of clonic movements in neonates is difficult and do not correspond to epilepsy in many cases (15). Because for 3 neonates clonic movements stopped rapidly sevoflurane was continued. In 1 case repeated episodes require to stop

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3 sevoflurane. Long term neurotoxicity of general anesthetics is an other concern for
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5 sevoflurane use. Recent works had shown neurotoxicity of general anaesthetics on animals
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7 developing brain, with impairment of cognitive functions and behavioural troubles (16). More
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9 worrying, two recent studies suggest that repeated anaesthesia or anaesthesia in young
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11 children and infants could be associated with learning disabilities and/or disturbed
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13 neurobehavioral development (17,18). Despite important limitations, these studies would
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15 lead anaesthetists to find solutions to avoid anaesthetics' use in this population. On the other
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17 hand, repetitive untreated pain is responsible for neuronal cell death in animals. In human
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19 babies, sensitization and hyperalgesia phenomenon had been proved and recently, pain in
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21 preterm neonates has been associated with poorer cognitive and motor development at 8 and
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23 18 month (19). As debated (20), clinicians are confronted to an awful choice between pain
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25 and analgesia.
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32 Sevoflurane administration to avoid pain manifestation could be called “anaesthesia”
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34 rather than “deep sedation”. We chose “deep sedation” in this situation because sevoflurane is
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36 titrated to limit occurrence of movement and avoid adverse effects. Maximum concentration
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38 of sevoflurane was 2.7 (2 – 3) %. Nevertheless because we have measured inhaled
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40 concentrations, and because nasal CPAP administration is associated with gas leak, exhaled
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42 concentrations were probably much lower. According to the American Society of
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44 Anesthesiologists, the state procured in this case is a “deep sedation” (21). Nevertheless, the
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46 difference between anaesthesia and deep sedation remains very thin (22) and inhaled
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48 sevoflurane with spontaneously breathing requires the same equipments, facilities and skills
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50 than general anesthesia.
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56 Furthermore this study had several limitations. Treatment could not be blinded, since
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58 sevoflurane has a specific odour. Lack of blinding may have affected time measurements,
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60 number of operators or number of punctures. Hemodynamic data were analyzed under blinded

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conditions using recorded and printed data. The occurrence of movements and the conditions required to perform PICC placement are the most sensitive to this methodological problem. Nevertheless, despite a lack of blinding, operators did not consider conditions better with sevoflurane, in agreement with treatment duration.

Another important limitation was the lack of pain score measurement. The premature infant pain profile score (23) or douleur aigue du nouveau-né (24) could be used. However, these measurements are difficult to make under aseptic conditions and when the child is covered by a sterile sheet. Taped video could have been used but this study was not initially designed to compare efficacy of treatments on pain because in our experience, efficacy was clinically evident. Despite the lack of validated score, we evaluated pain by indirect means, including HR, MAP and movements, with HR modification showing the highest correlation with pain score (25).

Finally, environmental pollution and potential personnel exposure to sevoflurane require ventilated rooms and scavenging gas system on the output of breathing circuit. Despite the precautions and the low concentration used, operators could sometimes smell sevoflurane vapors near of the child; we have to work, to resolve this inconvenient.

In conclusion, IS do not improve conditions for PICC placement compared with GNNS in >28 weeks of gestational age, but is effective in preventing pain-related effects during PICC placement. **In our daily practice, inhaled sevoflurane maintaining spontaneous breathing is now a very useful mean to prevent pain and its consequences in neonates.** However, sevoflurane is associated with decrease of MAP and require careful hemodynamic monitoring. Moreover, it is essential to keep in mind its potential neurotoxicity and potential long terms clinical effects.

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Figure 1: Occurrence of movements during the procedure

*: $p=0.017$ compared with other group
ns: non significant
Abbreviations: GNNS, glucose and non-nutritive sucking; IS, inhaled sevoflurane

Table 1: Patient characteristics

Population	GNNS	IS	p
n	29	30	
Gestational Age (weeks), mean $\pm$ SD	29.9 $\pm$ 1,6	29.7 $\pm$ 3.1	0.77
Age (d), mean $\pm$ SD	1.7 $\pm$ 0.8	2.0 $\pm$ 0.8	0.11
Gender F/M (n)	15/14	17/13	0.70
Weight (g), mean $\pm$ SD	1267 $\pm$ 330	1338 $\pm$ 451	0.50
CRIB2 score, mean $\pm$ SD	3.6 $\pm$ 2.7	3.8 $\pm$ 2.7	0.81
CPAP (n/%)	24/82.7	27/90.0	0.25
IMV (n/%)	5/17.3	3/10.0	0.71

Abbreviations: GNNS, Glucose and non-nutritive sucking; IS, inhaled sevoflurane; IMV, invasive mechanical ventilation

Table 2: Characteristics of the procedure

	IS	GNNS	p
Trained operator (n/%)	7/23.3	11/37.9	0.22
Second operator required (n/%)	11/36.6	11/37.9	0.92
Successful placement (n/%)	27/90	24/82.7	0.25
Number of punctures / child			
Total (mean±sd)	3.8±2.9	3.7±2.7	0.84
Outside of anaesthetized zone (mean±sd)	1.0±1.1	1.3±1.5	0.52
Duration of procedure (min)	45 (33-68)	50 (25-71)	0.84
Ease to carry out the procedure			
Easy (n/%)	21/70.0	14/48.2	0.13
Intermediate (n/%)	6/20.0	13/44.8	
Difficult (n/%)	3/10.0	2/6.9	

Abbreviations; GNNS, glucose and non-nutritive sucking; IS, inhaled sevoflurane

Table 3: Hemodynamic and respiratory parameters before analgesia (basal) and during the procedure (maximal and minimal values)

MAP	Basal	Minimal	Maximal
IS	44 (39-51)	27 (23-32) ^a	41 (38-47)
GNNS	43 (36-46)	34 (28-42) ^{a, e}	55 (49-66) ^{a, d}
HR	Basal	Minimal	Maximal
IS	143 (136-154)	126 (118-140) ^a	151 (138-157)
GNNS	146 (136-154)	135 (110-142) ^a	175 (168-180) ^{a, d}
TcCO₂	Basal	Minimal	Maximal
IS	43 (39-47)	45 (42-48)	49 (45-52)
GNNS	43 (38-47)	40 (34-44) ^b	46 (43-52) ^c
FR	Basal	Minimal	Maximal
IS	44 (37-51)	36 (29-45) ^c	75 (56-80) ^a
GNNS	48 (41-55)	35 (26-40) ^b	69 (60-80) ^a
SpO₂	Basal	Minimal	Maximal
IS	98 (96-100)	92 (85-95) ^b	99 (98-100) ^c
GNNS	98 (96-99)	87 (82-91) ^a	100 (98-100) ^c
FiO₂	Basal	Minimal	Maximal
IS	21 (21-21)	21 (21-21)	21 (21-24)
GNNS	21 (21-21)	21 (21-21)	21 (21-30)

All data reported as median (range).

Abbreviations: GNNS, glucose and non-nutritive sucking; IS, inhaled sevoflurane.

a: p<0.001; b: p<0.01; c: p<0.05 vs basal
d: p<0.001; e: p<0.01 vs IS group

Table 4: Neonates with hemodynamic and respiratory difficulties during PICC placement

	IS	GNNS	
Hypertension n/%	2/6.9	15/55.5	$p=0.003$
Hypotension n/%	16/55.5	9/33.3	$p=0.06$
Tachycardia n/%	0/0.0	15/51.7	$p<0.001$
Bradycardia n/%	1/3.3	7/24.1	$p=0.02$
Desaturation n/%	6/20.7	12/41.4	$p=0.08$
Apnea n/%	4/13.3	1/3.4	$p=0.17$

Abbreviations: GNNS, glucose and non-nutritive sucking; IS, inhaled sevoflurane

Flow of patients

CONSORT Statement 2001 - Checklist

Items to include when reporting a randomized trial

PAPER SECTION And topic	Item	Descriptor	Reported on Page #
TITLE & ABSTRACT	1	<u>How participants were allocated to interventions</u> (e.g., "random allocation", "randomized", or "randomly assigned").	1-2
INTRODUCTION Background	2	<u>Scientific background and explanation of rationale.</u>	3-4
METHODS Participants	3	<u>Eligibility criteria for participants</u> and the <u>settings and locations where the data were collected.</u>	4
Interventions	4	<u>Precise details of the interventions intended for each group and how and when they were actually administered.</u>	4-5
Objectives	5	<u>Specific objectives and hypotheses.</u>	
Outcomes	6	<u>Clearly defined primary and secondary outcome measures</u> and, when applicable, any <u>methods used to enhance the quality of measurements</u> (e.g., multiple observations, training of assessors).	3
Sample size	7	<u>How sample size was determined</u> and, when applicable, <u>explanation of any interim analyses and stopping rules.</u>	6
Randomization -- Sequence generation	8	<u>Method used to generate the random allocation sequence, including details of any restrictions</u> (e.g., blocking, stratification)	4
Randomization -- Allocation concealment	9	<u>Method used to implement the random allocation sequence</u> (e.g., numbered containers or central telephone), clarifying whether the sequence was concealed until interventions were assigned.	4
Randomization -- Implementation	10	<u>Who generated the allocation sequence, who enrolled participants, and who assigned participants to their groups.</u>	4
Blinding (masking)	11	<u>Whether or not participants, those administering the interventions, and those assessing the outcomes were blinded to group assignment.</u> If done, <u>how the success of blinding was evaluated.</u>	-
Statistical methods	12	<u>Statistical methods used to compare groups for primary outcome(s); Methods for additional analyses</u> , such as subgroup analyses and adjusted analyses.	6
RESULTS Participant flow	13	<u>Flow of participants through each stage</u> (a diagram is strongly recommended). Specifically, for each group report the numbers of participants randomly assigned, receiving intended treatment, completing the study protocol, and analyzed for the primary outcome. <u>Describe protocol deviations from study as planned, together with reasons.</u>	7
Recruitment	14	<u>Dates defining the periods of recruitment and follow-up.</u>	7
Baseline data	15	<u>Baseline demographic and clinical characteristics of each group.</u>	7 – Table1
Numbers analyzed	16	<u>Number of participants (denominator) in each group included in each analysis and whether the analysis was by "intention-to-treat".</u> State the results in absolute numbers when feasible (e.g., 10/20, not 50%).	7
Outcomes and estimation	17	<u>For each primary and secondary outcome, a summary of results for each group, and the estimated effect size and its precision</u> (e.g., 95% confidence interval).	7-8
Ancillary analyses	18	<u>Address multiplicity by reporting any other analyses performed</u> , including subgroup analyses and adjusted analyses, indicating those pre-specified and those exploratory.	7-8
Adverse events	19	<u>All important adverse events or side effects in each intervention group.</u>	8
DISCUSSION Interpretation	20	<u>Interpretation of the results</u> , taking into account study hypotheses, sources of potential bias or imprecision and the dangers associated with multiplicity of analyses and outcomes.	9-10-11
Generalizability	21	<u>Generalizability (external validity) of the trial findings.</u>	-
Overall evidence	22	<u>General interpretation of the results in the context of current evidence.</u>	9-10-11