Premedication with fentanyl for less invasive surfactant administration (LISA): A Randomized Controlled Trial

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Abstract

Currently, there is no consensus regarding analgesic premedication before the LISA procedure. In this randomized controlled trial, we compared the level of comfort of preterm infants receiving fentanyl as analgesic versus no fentanyl during LISA procedure. We randomized 34 preterm infants of 28⁺⁰ – 33⁺⁶ weeks of gestation with RDS within 6 h of birth to receive either fentanyl (1 µg /kg intravenous) or no premedication during LISA procedure. Primary objective was to assess the proportion of infants to be comfortable during the procedure (R-PIPP score < 10) and secondarily complications occurring during the procedure, hemodynamically significant patent ductus arteriosus (hsPDA), intraventricular hemorrhage (IVH) (≥ grade 3), bronchopulmonary dysplasia (BPD) and composite outcome of BPD/mortality. Proportion of infants with a R-PIPP score < 10 during LISA was significantly higher in the fentanyl group (13/17 (76.5%) vs 6/17 (35.3%); p value 0.036). There were no differences in secondary outcome parameters.

Conclusion: Low dose fentanyl during LISA procedure resulted in more comfort in preterm infants and without increased complication of both the LISA procedure and fentanyl administration. Further studies are needed to determine the safest and most effective pharmacologic measures to prevent pain and discomfort during LISA.

Trial registration: www.ctri.nic.in id CTRI/2020/08/027144, registration date August 14, 2020

What Is Known?

Less invasive surfactant administration (LISA) is being increasingly used in spontaneously breathing premature infants with RDS, but trials of premedication for LISA are fewer.

What is new?

Low dose fentanyl can be used for premedication before LISA to increase comfort in preterm infants with acceptable tolerance for the LISA procedure.

Introduction

Respiratory distress syndrome (RDS) in neonates is associated with prematurity, and surfactant administration is essential for its management [1, 2, 3]. Various methods have been successively proposed over time to deliver surfactant, including intubation at birth and prophylactic surfactant administration, intubation surfactant administration extubation (INSURE), surfactant instillation through a thin intratracheal catheter in spontaneously breathing infants with nasal continuous positive airway pressure (nCPAP) [4, 5, 6]. This last technique often referred to as less invasive surfactant administration (LISA). The aim of LISA technique is to effectively provide an adequate dose of surfactant, while allowing spontaneous respiration to continue, and with the support of noninvasive ventilation. European consensus guidelines on the management of respiratory distress syndrome–2019 Update state that

“LISA is the preferred mode of surfactant administration for spontaneously breathing babies on CPAP, provided that clinicians are experienced with this technique” [3]. LISA has been associated with the decreased use of invasive ventilation and reduced bronchopulmonary dysplasia [7, 8]. However, there is still a wide variation regarding many aspects of the LISA method particularly standardization of sedation and analgesia use [9, 10]. In fact, most studies were performed without sedation or with sedation at the discretion of the clinicians [11].

For all nonemergent neonatal intubations, analgesia, sedation, or a combination of both is recommended by the American Academy of Pediatrics and by a consensus of European neonatologists [12, 13]. Awake laryngoscopy causes acute cardiovascular effects such as increased catecholamine release, systemic and pulmonary hypertension, tachycardia, arrhythmias, apnea and in some cases, increased intracranial and intraocular pressures [14, 15, 16]. Resistance against laryngoscope and attempts to cry during the procedure can cause an increase in intracranial pressure when it is performed without sedation [17, 18]. Even this can increase the risk of intraventricular hemorrhage especially in preterm babies [17]. LISA procedure becomes smooth and successful with sedation, but it might compromise the infant’s respiratory drive which is a prerequisite for LISA [19].

Thus an ideal drug for this context should provide a good level of comfort with little impact on respiratory drive. Till date, there is no consensus concerning premedication prior to the LISA procedure. Propofol, ketamine, atropine, morphine, lidocaine spray, and fentanyl have been reported in the literature as premedication for the LISA procedure [19, 20, 21].

Fentanyl is a highly lipophilic, a short acting potent opioid analgesic, rapidly crosses the blood brain barrier. The levels in plasma and CSF decline rapidly owing to redistribution of fentanyl from highly perfused tissue groups to other tissues, such as muscle and fat. The duration of effect of fentanyl approaches the length of their elimination $t_{1/2}$, 3–4 hr.

Fentanyl dose used across studies for intubation/INSURE varies between 0.5 µg /kg and 3 µg/kg [22, 23]. It was found that prescription of 1 µg /kg of fentanyl effectively reduces all physiological discomfort parameters in preterm without compromise the infant’s respiratory drive [24].

As of now, there is a definite lack of evidence with regard to the analgesia protocol during LISA procedure especially in low and middle income countries, and there is a dire need to find an optimum analgesic agent that is safe and efficacious in premature infants without compromise the infant’s respiratory drive.

Therefore, we hypothesized that low-dose fentanyl as an analgesic would increase the comfort of preterm infants during the LISA procedure with good respiratory and cardiovascular tolerance.

Material And Methods

Trial design, settings and participants

This randomized controlled trial was conducted in a level III neonatal intensive care unit (NICU) in a tertiary care hospital in East India from June 2020 to June 2021. Infants with gestation age of 28⁺⁰ to 33⁺⁶ weeks diagnosed with RDS were enrolled in the study. Infants with major congenital anomalies or known/suspected chromosomal anomalies, perinatal asphyxia (cord blood pH<7.20), and those who required intubation in labour room were excluded.

Intervention

After infant's eligibility was verified, parent's informed consent was obtained before the infants enrollment. Noninvasive positive pressure ventilation (NIPPV) was started in all the infants with initial settings of peak inspiratory pressure (PIP) of 12–15 cm of H₂O, positive end expiratory pressure (PEEP) of 5–6 cm of H₂O, respiratory rate of 40/min and fraction of oxygen in inspired air (FiO₂) adjusted to achieve a target saturation of 90 to 95% by using the Drager babylog 8000 plus ventilator (Lübeck, Germany). Short binasal mask along with nasal tubing was used as an interface for NIPPV. RDS was diagnosed by treating physician both by clinically based on the need of supplemental oxygen, clinical signs of tachypnea, retraction and grunting, and by chest x-ray. Infants who required FiO₂ more than 30% on NIPPV to SpO₂ between 90 and 95% in the first 6 h of life were randomized to receive surfactant by LISA technique either by analgesia with fentanyl or not. All infants received caffeine at admission to NICU.

For endotracheal intubation, intravenous fentanyl 2 µg /kg is routinely used for analgesia in our unit. However, to reduce all physiological discomfort parameters in preterm without compromise the infant's respiratory drive, a reduced dose of intravenous fentanyl (1 µg /kg infused slowly over 2 minutes) was administered before LISA.

LISA procedure

The procedure was performed by two trained neonatologists and two staff nurses for video recording and assistance. The interface was changed to Ram's nasal cannula for delivering NIPPV prior to LISA procedure. Heart rate, SpO₂, and mean arterial blood pressure were monitored throughout the procedure. Injection fentanyl (1µg /kg) was infused over 2 minutes just before the LISA. Direct laryngoscopy was performed and a 5 Fr feeding tube was inserted to the desired depth with Magill forceps. The required tip to lip length was calculated as weight in kilograms plus 7 cm [25].

After feeding tube placement, the laryngoscope was removed. Poractant alpha (Curosurf, ChiesiFarmaceutici Group, Parma, Italy) at the dose of 200 mg/kg was used for surfactant replacement therapy. The surfactant was drawn up in a 10 ml syringe and given in 1-ml aliquot in stages with each stage lasting for 10-20 s. After a complete dose of surfactant administration, the feeding tube was withdrawn. Following the LISA procedure, the nasal interface was changed again to standard nasal mask and nasal tubing for NIPPV. If infants had SpO₂< 85% during the procedure, FiO₂ was escalated in

increment of 5%. The second dose of surfactant was administered if the infant continued to require $\text{FiO}_2 > 30\%$ after 6 h of initial surfactant therapy.

Infants were intubated in the presence of persistent respiratory acidosis ($\text{pH} < 7.2$ and $\text{pCO}_2 > 60$ mm Hg) or recurrent apnea requiring positive pressure ventilation or requiring NIPPV setting of $\text{FiO}_2 > 60\%$, PIP > 25 cm of H_2O , and PEEP > 6 cm of H_2O .

Infants were weaned to CPAP when showed minimal or no signs of respiratory distress and apnea free for the last 24 hours with NIPPV setting PIP 12-14 cm of H_2O , PEEP 4-5 cm of H_2O , and FiO_2 25-30%.

Infants were weaned from CPAP to either HHHFNC or room air as per unit protocol.

The procedure was video recorded, where both the face and extremities of the infant could be observed. The video recordings were coded and reviewed by three independent NICU doctors who were blinded for the allocation and measured the level of comfort using the Revised-PIPP score.

Outcomes

- Primary outcome: Proportion of infants with a R-PIPP (Revised Premature Infant Pain Profile) score ≤ 10 during the LISA procedure.

- Secondary outcome parameters

- i. Need for intubation during the procedure and within 72 h
- ii. Complication occurring during the procedure ($\text{SpO}_2 < 80\%$, bradycardia < 100 bpm, increased FiO_2 need during the procedure)
- iii. Incidence of hsPDA (26)
- iv. Intraventricular hemorrhage $\geq$ grade 3 (27)
- v. Necrotizing enterocolitis $\geq$ Stage 2 (28)
- vi. Bronchopulmonary dysplasia (29)
- vii. Retinopathy of prematurity

Sample size

Earlier study had shown that almost 88% of the baby who did not receive any sedation during the LISA procedure had pain more than moderate to severe degree [19]. We, therefore, chose to study 17 infants in each group in order to have 80% power to reduce the severe pain from this baseline rate of 88% to 44% with a significance level of 0.05% (two-tailed), using an uncorrected chi-square test to evaluate the null hypothesis. The sample size was calculated using PS: Power and Sample Size Calculation (Version 3.1.6, Department of Biostatistics, Vanderbilt University School of Medicine, Nashville, USA).

Randomization

We used computer generated random numbers with variable block sizes (2 and 4) to allocate the infants into the two groups. Infants were stratified according to gestational age (28-31⁺⁶ weeks and 32-33⁺⁶ weeks). Infants born from multiple gestations were assigned by individual randomization. The allocation ratio was 1:1 and concealment was done by using a sequentially numbered opaque sealed envelope. An investigator, who did not participate in collecting baseline data, applying the intervention or measurement of outcomes, prepared the randomization sequence. Due to the lack of pharmacy facility, blinding with a placebo could not be done with the clinical staff that was looking after the infants during LISA procedure. However, data collecting staff and members of the trial who analyzed the data were blinded.

Statistical analysis

Analysis was done using Statistical version 8 (Tulsa, Oklahoma: StatSoft Inc., 2007), MedCalc version 15.8 (Mariakerke, Belgium: MedCalc Software bvba, 2015). Data were summarized by routine descriptive statistics, median and interquartile range for numerical variables, and counts and percentages for categorical variables. Numerical variables were compared between subgroups by Student's independent samples t-test if normally distributed, or by Mann-Whitney U test if otherwise. Fisher's exact test was employed along with the calculation of relative risk (RR) and 95% confidence interval (CI) for inter-group comparison of categorical variables. All analyses were 2-sided and P value less than 0.05 were considered statistically significant. The intraclass correlation coefficient was used to assess inter-rater agreement.

Ethics

The study was conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki, and that was consistent with GCP. The trial was approved by the institutional ethics committee of the Institute of Post Graduate Medical Education and Research, Kolkata, India (IPGME&R/IEC/2020/593). Written informed consent was obtained from all legal guardians before participation in the study. This trial was registered in the clinical trial registry of India (CTRI/2020/08/027144).

Result

Population

A total of 143 preterm live births during the study period, 65 infants were assessed for eligibility. After exclusion of 31, a total of 34 infants were subjected to stratified randomization into one of the two groups of fentanyl and non-fentanyl, stratification done based on gestational age in two subgroups 28-31⁺⁶ weeks and 32-33⁺⁶ weeks. The flow of participants in the study is summarized in Fig. 1. Baseline demographic variables between the two groups were comparable (Table 1). The median gestation age of the infants was 31.5 weeks with a median birth weight of 1336 g.

LISA and R-PIPP score

The results of primary and secondary outcomes are depicted in Table 3 and Table 4. There was no difference in time point after birth when LISA procedure was performed (fentanyl vs placebo group: median (IQR) of 60 (50-80) vs 60 (50-80) minutes; p 0.971). Percentage of infants with a R-PIPP score <10 during LISA was significantly higher in the fentanyl group compared with the placebo group (13/17 (76.5%) vs 6/17 (35.3%); p value 0.036). The R-PIPP score during LISA was significantly lower in the fentanyl group compared with the placebo group (fentanyl vs placebo group: median (IQR) 9 (7-10) vs 12 (9-13); p 0.004).

All the recorded videos were evaluated by three fellows in the neonatology department, blinded to the group allocation, and measured the level of comfort using the R-PIPP scale. Inter-rater reliability between these fellows were assessed and strong agreement was present (Intraclass correlation 0.964, 95% Confidence Interval 0.937 to 0.980) (Fig 2).

Efficacy and tolerance

Efficacy and tolerance of the premedication are described in Table 2. There was no difference in FiO_2 requirement, SpO_2 , heart rate, mean blood pressure between two groups at three time points (1 minute, 5 minutes and 60 minutes). The incidence of desaturation ($\text{SpO}_2 < 80\%$ for more than one minute during LISA) and increased FiO_2 need during LISA occurred in more infants in fentanyl groups, but these were not significantly different between the groups.

Only one infant in the fentanyl group was intubated during LISA, while none of the infants were intubated in the non-fentanyl group (1/17 (5.9%) vs 0/17 (0%), p=1.00). Overall, the rate of intubation in the first 72 hours after LISA was similar in the two groups (2/17 (11.8%) vs 1/17 (5.9%); p value 1.00). No differences were observed between the two groups for hemodynamically significant patent ductus arteriosus, intraventricular hemorrhage $\geq$ grade 3, necrotizing enterocolitis $\geq$ Stage 2, composite duration of noninvasive ventilation days.

Outcome at discharge

There were no differences in rate of retinopathy of prematurity, bronchopulmonary dysplasia, composite outcome of bronchopulmonary dysplasia, and mortality before discharge. Infants in the fentanyl group stayed in the hospital for more days in comparison with the non-fentanyl group (fentanyl vs non-fentanyl group: mean (SD) 36.94 (24.16) vs 29.82 (23.55); p 0.391).

Discussion

In this randomized controlled trial, we found that infants receiving fentanyl had a higher level of comfort compared to the infants receiving no analgesia before LISA procedure. This finding is in consistent with the results of the previous studies that were mostly conducted in high-resource settings. [19, 20, 21]. The incidence of desaturation, increased FiO_2 need during LISA, and days of hospitalization occurred in more infants in fentanyl groups, although this did not reach statistical significance. No differences were

observed in other complications of the procedure or the use of fentanyl. In many European countries, LISA has been accepted as standard of care in a selected group of premature infants on noninvasive ventilation. However, there is still a wide variation regarding many aspects of the LISA method especially standardization of sedation before the procedure [9, 30]. Trials of premedication for LISA have been fewer. To the best of our knowledge, this is the first randomized controlled study in low and middle income countries that has compared the efficacy of fentanyl vs non-fentanyl in reducing pain during LISA procedure.

It is believed that early neonatal pain experiences shape the somatosensory scaffolding of later perceptual, cognitive, and social development. Such risks of neurosensory impairment appear to be aggravated by prematurity [31]. On the other hand, adverse effects in the brain can occur with the use of analgesia [32]. A high level of analgesia correlates strongly with reduced cerebellar volume and poorer cognitive and motor outcomes in infancy [33, 34]. However, in our study we used a single low dose of fentanyl, which reduced the stress of a painful stimulus in these vulnerable infants and thereby might have influenced later neurodevelopment outcomes positively.

Premedication has been shown to increase the success rate of intubation [35]. De Kort et al. reported that there was a low success rate on the first attempt of LISA without sedation [36]. In the current trial, more infants in the non-fentanyl group required more than one attempt laryngoscopies than the fentanyl group.

In a randomized controlled trial by Dekker et al. showed that low-dose sedation was accompanied by a greater risk of desaturation ($\text{SpO}_2 < 85\%$) events during the procedure in the sedation group (91% vs 69%, $P = .023$) [20]. The present study demonstrated that more infants in the fentanyl group had desaturation and bradycardia but this did not reach statistical significance. The rate of intubation during or within 72 hours after the procedure also did not differ between the groups, thereby indicating that the desaturation and bradycardia were transient. Brotelande C et al. suggested in a recent study that ketamine or propofol can be used safely as premedication before LISA with comparable efficacy and tolerance [37].

Jourdain et al reported that relevant airflow limitation occurred during LISA, which might cause carbon dioxide retention [38]. But no data on carbon dioxide values during LISA are available. We had found no differences in pCO_2 value after LISA between the groups, yet this trial was not powered on this outcome.

A variety of drugs have been studied for the purpose of analgesia/ sedation during the LISA procedure, with fentanyl, ketamine, and propofol being the most frequently used medications [39, 40]. The ideal drug for this context should have a rapid onset, short action, fast offset, and provide adequate sedation, and analgesia with minimal adverse effects and especially little impact on respiratory drive [41]. Though peak activity is optimal but half-life of fentanyl is not ideal for this type of technique. But there is considerable experience with its use in neonatology, alone or in combination with other drugs [24]. Fentanyl as premedication is routinely used before endotracheal intubation in our unit.

One of the most noted side effects of fentanyl is the occurrence of chest wall rigidity and laryngospasm, although the incidence varies in studies [42]. None were reported in the present study with this low dose

of fentanyl.

The strength of our study is that to the best of our knowledge, this is the first randomized controlled study in low and middle income countries that has compared the efficacy, safety, tolerance of fentanyl vs non-fentanyl in reducing pain during LISA in spontaneously breathing preterm infants with good sample size. Our study is a well conducted RCT with sound methodology. R-PIPP score was assessed by an independent clinician not involved in the study and blinded to the group allocation, thus minimizing bias.

The major limitation of the study was that blinding could not be done. And another limitation is the insufficient sample size to perform subanalyses based on different gestational age strata. Though there was a significant difference in comfort score in this small group, but it is possible that differences in complications would have reached significance in a larger group.

Our study was not powered for the need for invasive ventilation shortly after LISA and also for clinically significant other outcomes like mortality or BPD. These outcomes are multifactorial and require larger populations. Therefore, we cannot draw any conclusions on these important clinical outcomes. To investigate this, we are conducting another trial at our NICU which is powered for the need for mechanical ventilation following LISA procedure with fentanyl as premedication.

Finally, the validity of many assessment tools has been questioned because of interobserver variability and subjectivity. Preterm infants also consistently demonstrate muted responses to pain measured by these assessment tools [43]. So, neuroimaging or neurophysiologic approaches are preferred over subjective assessment methods. Strong agreement between the three observers was present in our study. But the validity of R-PIPP in the preterm infant was not adequately studied.

Further studies are warranted to determine the safest and most effective pharmacologic and nonpharmacologic measures to prevent pain and discomfort during LISA. Two trials on this matter are currently ongoing. The first is being assessed in the PROLISA study, which is investigating the need for mechanical ventilation within 72 h of life following premedication with propofol or placebo before the LISA procedure in preterm infants (NCT04016246) [44]. This trial might provide robust data on premedication use before a routine LISA and the neurodevelopmental outcome at 2 years of age.

To date, no study has investigated the hormonal and physiological effects of INSURE or LISA procedure. However, STRASS (STressAssessment with and without analgesia during surfactant therapy in preterm infants; NCT04073173), is ongoing and will hopefully provide data on this matter.

To provide comfort and pain management of infants during the LISA procedure without hampering the spontaneous breath is very challenging. So far, LISA without premedication has proven its ability to reduce mechanical ventilation and bronchopulmonary dysplasia in preterm infants, but the pain induced by the procedure has not been sufficiently studied. The present study has demonstrated that low dose (1 mcg/kg/dose) fentanyl is effective in reducing pain and also safe during LISA. Additional studies are needed to determine the safest and most effective pharmacologic and nonpharmacologic measures to

prevent pain and discomfort during LISA. There is a need for large adequately powered randomized control trial to answer issues related to mechanical ventilation, BPD, and long term neurodevelopmental outcome.

Declarations

Funding

none

Conflicts of interest/Competing interests

The authors declare no competing interests.

Availability of data and material Available for viewing at

https://docs.google.com/spreadsheets/d/1_s0YmqIS2PpW07EUz-eH527sdcFxH9Qp/edit#gid=838154668

Authors' contributions

Dr. Md Habibullah Sk conceptualized and designed the study, developed the protocol, patient management and prepared the first draft. Dr. Bijan Saha helped in protocol development, coordinated, supervised data collection, reviewed and revised the manuscript at all stages of its production. Dr. Suchandra Mukherjee helped in protocol development and critically reviewed the manuscript for improving the content. Dr. Avijit Hazra performed the statistical analysis of the data. All the authors approved the final manuscript as submitted and agree to be accountable for all aspect of the work.

Ethics approval & Consent to participate

Informed consent was obtained from the legal guardian of all included participants.

Consent for publication

Informed consent was obtained from the legal guardian of all included participants.

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Abbreviations

LISA Less invasive surfactant administration

NIPPV	nasal intermittent positive pressure ventilation
nCPAP	nasal continuous positive airway pressure
HHFNC	heated high flow nasal cannula
NEC	necrotizing enterocolitis
hsPDA	hemodynamically significant patent ductus arteriosus
IVH	intraventricular haemorrhage
ROP	retinopathy of prematurity
BPD	bronchopulmonary dysplasia
CI	confidence interval
RR	relative risk
RDS	respiratory distress syndrome
NICU	neonatal intensive care unit
FiO ₂	fraction of inspired oxygen
SpO ₂	oxygen saturation
PIP	peak inspiratory pressure
PEEP	positive end expiratory pressure
MAP	mean arterial pressure
HR	heart rate
IQR	interquartile range

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Tables

Table 1. Baseline variables of enrolled neonates

Variable	Fentanyl (n=17)	Non-Fentanyl (n=17)	p Value
Age of mother, years [†]	27.59 (6.97)	27.41 (6.27)	0.939
Gestation, weeks [†]	30.76 (2.05)	31.6 (2.19)	0.689
Number of fetuses (single/twin)*	13 (76.5) / 4(23.5)	13 (76.5)/4(23.5)	1.000
Antenatal steroids (complete/incomplete)*	1 (5.9) / 9 (52.9)	2 (11.8) / 14 (82.3)	0.107
Caesarean section delivery*	9 (52.9)	11 (64.7)	0.388
Birth weight, grams [†]	1330.6 (379.86)	1476.18 (417.27)	0.296
Male*	11 (64.7)	9 (52.9)	0.728
APGAR score at 5 min [†]	8.18 (0.81)	8.12 (1.1)	0.856
Positive pressure ventilation*	1 (5.9)	4 (23.5)	0.335
SNAPPE 2 scores [†]	9.41 (10.38)	7.71 (9.95)	0.628
Silverman Anderson score [‡]	5 (5 to 6)	5 (5 to 6)	0.854
Surfactant administration time after birth, minute [†]	66.76 (21.86)	67.06 (25.19)	0.971

Data are presented as *n (%), [†]Mean (SD), [‡]Median (IQR)

Table 2. Comparison of Fio2, SpO2, heart rate and mean blood pressure between two groups at four time points

Timing	Parameters	Fentanyl (n=17)	Non-Fentanyl (n=17)	p Value
Pre-Surfactant				
	FiO ₂	39.41(7.47)	38.53 (5.52)	0.698
	SpO ₂	89.94 (4.36)	90.24 (2.01)	0.803
	HR	149.71 (14.82)	149.47 (22.08)	0.971
	MAP	31.24 (6.54)	31.47 (4.96)	0.907
Post-Surfactant				
1 minute	FiO ₂	43.53 (9.48)	41.18 (7.18)	0.421
	SpO ₂	80.41 (5.91)	81.47 (7.16)	0.642
	HR	135.12 (23.62)	135.35 (24.83)	0.977
	MAP	36.53 (6.16)	37.41 (7.00)	0.699
5 minute	FiO ₂	36.18 (6.73)	35.29 (5.98)	0.689
	SpO ₂	90.47 (1.41)	90.65 (1.76)	0.750
	HR	137.06 (12.55)	139.35 (18.28)	0.673
	MAP	35.06 (3.75)	34.47 (5.51)	0.718
60 minute	FiO ₂	26.94 (5.05)	27.24 (4.76)	0.863
	SpO ₂	94.47 (1.90)	94.24 (1.88)	0.720
	HR	142.24 (14.13)	145.82 (15.27)	0.482
	MAP	35.82 (4.72)	34.29 (3.68)	0.300

Data are expressed as mean (SD). FiO₂, Fraction of inspired oxygen; SpO₂, Oxygen saturation; HR, Heart Rate; MAP, Mean Arterial Pressure.

Table 3. Primary Outcome measure

Variable	Fentanyl (n=17)	Non-Fentanyl(n=17)	Relative risk (95% confidence interval)	p Value
Revised -PIPP score ≤ 10 *	13 (76.5)	6 (35.3)	2.17 (1.08 to 4.34)	0.036

Data are presented as *n (%), †Mean (SD)

Table 4. Secondary outcome measure

Variable	Fentanyl (n=17)	Non- Fentanyl(n=17)	Relative risk (95% confidence interval)	p Value
Revised- PIPP Score [†]	9 (2.37)	11.59 ((2.5)		0.004
Laryngoscopy attempt >1*	1(5.9)	5(29.4)	0.20 (0.02 to 1.53)	0.174
SpO2< 80% for more than one minute during LISA*	7 (41.2)	5 (29.4)	1.40 (0.55 to 3.54)	0.721
Bradycardia (<100bpm) during LISA*	2 (11.8)	2 (11.8)	1.00 (0.15 to 6.30)	1.000
Increased FiO2 need during LISA*	8 (47)	6 (35.3)	1.33 (0.58 to 3.02)	0.728
pCO2 value after LISA [†]	48.11(6.47)	48.05(7.45)		0.981
Intubation during LISA*	1 (5.9)	0	3.00 (0.13 to 68.84)	1.000
Invasive ventilation in the first 72hr of life*	2 (11.8)	1 (5.9)	2.00 (0.19 to 20.03)	1.000
Hemodynamically significant patent ductus arteriosus*	6 (35.3)	4 (23.5)	1.50 (0.51 to 4.38)	0.708
Intraventricular haemorrhage ≥ grade 3*	1 (5.9)	1 (5.9)	1.00 (0.06S to 14.71)	1.000
Necrotising enterocolitis ≥ Stage 2*	3 (17.6)	4 (23.5)	0.75 (0.19 to 2.85)	1.000
Retinopathy of prematurity required treatment*	8(50)	7(43.8)	1.14 (0.53 to 2.44)	0.730
Bronchopulmonary dysplasia*	5 (31.3)	3 (18.9)	1.67 (0.47 to 5.89)	0.685
Bronchopulmonary dysplasia/mortality before discharge*	6 (35.3)	4 (23.5)	1.50 (0.51 to 4.38)	0.708
Duration of non-invasive ventilation [†]	17.95 (20.02)	13.64 (18.69)		0.522

Data are presented as *n (%), †Mean (SD)

Figures

Figure 1

Consolidated Standards of Reporting trials flow diagram

Figure 2

multiple dot plots indicating close agreement between the three raters with respect to R-PIPP