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# 'NOPAIN-ROP' trial: Intravenous fentanyl and intravenous ketamine for pain relief during laser photocoagulation for retinopathy of prematurity (ROP) in preterm infants: A randomised trial

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## ABSTRACT

**Objectives** To investigate if intravenous fentanyl or intravenous ketamine can provide adequate analgesia in preterm infants undergoing laser photocoagulation for retinopathy of prematurity (ROP).

**Design** Open-label randomised trial.

**Setting** Tertiary care institution.

**Participants** Preterm infants who underwent laser photocoagulation for ROP.

**Interventions** Infants were randomised to receive fentanyl as intravenous bolus dose of 2 µg/kg, followed by an intravenous infusion of 1 µg/kg/hour increased to a maximum of 3 µg/kg/hour or intravenous ketamine as bolus dose of 0.5 mg/kg, followed by further intermittent intravenous bolus doses of 0.5 mg/kg to a maximum of 2 mg/kg in the initial phase and intravenous fentanyl (bolus of 2 µg/kg followed by infusion of 2 µg/kg/hour to a maximum of 5 µg/kg/hour) or intravenous ketamine (bolus dose of 1 mg/kg followed by intermittent bolus doses of 0.5 mg/kg to a maximum of 4 mg/kg) in the revised regimen phase.

**Main outcome measures** Proportion of infants with adequate analgesia defined as the presence of both: (1) all the Premature Infant Pain Profile-Revised scores measured every 15 min less than seven and (2) proportion of the procedure time the infant spent crying less than 5%. Secondary outcomes included apnoea, cardiorespiratory or haemodynamic instability, feed intolerance and urinary retention requiring catheterisation during and within 24 hours following the procedure.

**Results** A total of 97 infants were randomised (fentanyl=51, ketamine=46). The proportions of infants with adequate analgesia were 16.3% (95% CI 8.5% to 29%) with fentanyl and 4.5% (95% CI 1.3% to 15.1%) with ketamine. Ten infants (19.6%) in the fentanyl group and seven infants (15.2%) in the ketamine group had one or more side effects. In view of inadequate analgesia with both the regimens, the study steering committee recommended using a higher dose of intravenous fentanyl and intravenous ketamine. Consequently, we enrolled 27 infants (fentanyl=13, ketamine=14). With revised regimens, the proportions of infants with adequate analgesia were higher: 23.1% (95% CI 8.2% to 50.2%) with fentanyl and 7.1% (95% CI 1.3% to 31.5%) with ketamine. However, higher proportions of infants developed apnoea (n=4; 30.7%), need for supplemental oxygen (n=5, 38.4%) and change in cardiorespiratory scores (n=7; 53.8%) with fentanyl but none with ketamine.

**Conclusions** Fentanyl-based and ketamine-based drug regimens provided adequate analgesia only in a minority of infants undergoing laser photocoagulation for ROP. More research is needed to find safe and effective regimens that can be employed in resource constrained settings.

**Trial registration number** CTRI/2018/03/012878.

## Strengths and limitations of this study

- ► Largest trial addressing the issue of analgesia during laser photocoagulation for treatment of retinopathy of prematurity in preterm infants.
- ► Robust methodology and high-quality implementation of the study.
- ► Outcome measures were clinically relevant and measured in a highly objectivised manner.
- ► Small number of infants in the second phase due to logistical constraints.
- ► Incomplete birth and caregiving data as the cohort of enrolled infants were predominantly outborn.

## INTRODUCTION

Retinopathy of prematurity (ROP), a vasoproliferative disorder of developing retinal vessels of premature infants, is a leading cause of potentially avoidable childhood blindness. Lower birth weight, lower gestational age (GA) and exposure to supplemental oxygen are established risk factors for ROP.[1] The standard of treatment for ROP is ablation of retinal vessels by laser photocoagulation, which is a

painful procedure. In high-income countries, it is carried out as a major procedure under general anaesthesia or a combination of sedation, analgesia and paralysis ensuring adequate procedural analgesia in the infant.[2 3] However, in low-income to middle-income countries, with limited availability of resources for providing general anaesthesia or deep sedation, the ophthalmologists are compelled to carry out this procedure under topical anaesthesia, often on an outpatient basis. This practice not only subjects the infant to severe and prolonged pain but also adverse long-term neurodevelopmental consequences like impairment in cognition, learning disorders, attentional disorders, behavioural problems and motor abnormalities.[4 5]

Opioid analgesics (morphine, fentanyl and remifentanil) and ketamine have been found to be useful for providing sedation and analgesia during laser photocoagulation in multiple studies[6–12]; however, their optimal dosage and safety profile have not been well studied in neonates. Recently, we conducted a randomised trial comparing intravenous fentanyl (continuous infusion of 1 µg/kg/hour throughout the procedure) and oral 24% dextrose in providing analgesia to the infants undergoing laser photocoagulation.[13] The study found that fentanyl was superior to 24% dextrose in reducing the pain. However, on post hoc analysis of study data for adequate analgesia (as defined in the present study: Premature Infant Pain Profile-Revised (PIPP-R) less than 7 and proportion of the procedure time the infant spent crying less than 5%), we found that none of the enrolled infants (0/58, 0%) had adequate analgesia during the procedure. There is an urgent need to find an optimum regimen that can effectively alleviate unnecessary procedure-related severe and prolonged pain with adequate safety margin.[14]

## METHODOLOGY

### Setting

The study was conducted in a day care facility of a tertiary care hospital in North India. This facility is jointly run by the Departments of Ophthalmology and Paediatrics; manned by a nurse and a paediatrics fellow and includes facility for ventilation as well as continuous haemodynamic monitoring of the infant. It caters to outborn infants (<3 months of age) referred from neonatal and ophthalmic centres in north India for laser photocoagulation, intravitreal injections or surgery for advanced ROP (~400 cases per year).

The protocol for laser photocoagulation prior to the study was to admit the infant in the morning. The ophthalmology team performed the procedure with assistance from the paediatrics fellow and the nurse. The infant was given intravenous fentanyl infusion in the dose of 1 µg per kg per hour started 15 min before and continued through the procedure for analgesia along with topical ophthalmic anaesthetic drops. After the procedure, infants were discharged most often to home or back to referring hospital same day itself, once they were stable following a few hours of observation. If an infant developed any complications or required prolonged observation, they were transferred to the neonatal intensive care unit (NICU) for further management.

### Study design and participants

This was an open-label randomised trial with two intervention arms. A control arm was not included in the study design since it would be considered unethical to not provide analgesia for this procedure. Assuming no pain at all during the procedure as the standard of care, we wished to test how well the study regimens achieved that goal.

All infants with type 1 ROP requiring laser photocoagulation were eligible for inclusion if they were haemodynamically stable; did not have anaemia (packed cell volume more than 30%), grade III–IV intraventricular haemorrhage, patent ductus arteriosus or necrotising enterocolitis and the anticipated duration of procedure was more than 30 min. Infants were excluded if they were already receiving any respiratory support (continuous positive airway pressure or mechanical ventilation), sick enough to require NICU care or had any known congenital malformations.

### Randomisation and masking

An independent investigator generated random sequence to allocate the study participants into one of the two study groups. We used serially numbered, sealed and opaque envelopes for allocation concealment. The unit nurse opened the envelope and assigned the infant to a group. Blinding could not be done due to the obvious nature of the intervention (infusion vs intermittent boluses); however, the outcome assessors were blinded to the groups.

### Intervention

The intervention consisted of intravenous fentanyl bolus, followed by infusion in one group and intravenous ketamine intermittent boluses in the other. In addition, infants in both the groups received 0.5% ophthalmic paracaine drops for topical anaesthesia every 20 min during the procedure and non-pharmacological measures, namely swaddling and containment. Inadequate response was defined as one of the following: (1) increased crying from baseline, (2) restlessness, (3) tachycardia defined as persistent change in heart rate of more than 24 beats per minute from the baseline and (4) facial expression suggestive of pain.

#### Fentanyl group

We administered intravenous fentanyl in a bolus dose of 2 µg/kg over 5 min, 15 min prior to the procedure, followed by a continuous infusion of 1 µg/kg/hour until the end of the procedure. The study team continuously evaluated the infant for adequacy of analgesia during the procedure. If the response was inadequate, the infusion rate was titrated by 0.5 µg/kg/hour every 15 min to a maximum of 3 µg/kg/hour.

### Ketamine group

We administered a bolus dose of 0.5 mg/kg of ketamine 1 min prior to the procedure. If there was inadequate response as described above, further intermittent bolus doses of 0.5 mg/kg were given every 10 min till a maximum of 2 mg/kg (total of four boluses).

## Outcomes

The primary outcome was proportion of infants with adequate analgesia, defined as the presence of both: (1) all the PIPP-R[15] scores measured every 15 min less than seven and (2) proportion of the procedure time the infant spent crying less than 5%.

PIPP-R is a standard pain scale used for quantification of acute procedural pain in neonates. It consists of seven items: three parameters of facial expression of pain (brow bulge, eye squeeze and nasolabial furrow), two physiological (heart rate and oxygen saturation) and two contextual (GA and behavioural state parameters scored at three levels) (online supplemental table 1). Each item is scored from zero to three after an observation period of 30 s. A cumulative score of all items less than seven is generally considered to be indicative of minimal or no pain; score of 7–12 indicating mild to moderate pain and more than 12 indicative of severe pain.

Proportion of the procedure time the infant spent crying was calculated from the duration of cry and total duration of procedure (duration the infant cried divided by total duration of the procedure).

The secondary outcomes included any event during the procedure and a period of 24 hours following the procedure: apnoea during and post procedure (defined as cessation of breathing for more than 20 s or of lesser duration if associated with bradycardia or desaturation (<85%)), need for supplemental oxygen during and post procedure, change in mean cardiorespiratory stability scores requiring upgradation of respiratory support, haemodynamic instability requiring fluid boluses or vasoactive support, feed intolerance (defined as increase in prefeed abdominal girth by more than 2 cm along with gastric residuals of more than 50% of the feed volume, presence of haemorrhagic aspirates, recurrent vomiting, blood in stools or abdominal tenderness), urinary retention (defined as non-passage of urine for 12 hours, presence of full bladder on manual palpation that required catheterisation) and need for NICU admission for 24 hours or longer as decided by the clinical team.

The cardiorespiratory stability score devised by Haigh *et al* (online supplemental table 2) is a widely accepted scoring method used to depict the change in the overall systemic status of an infant on a 24-hour basis. It is recorded by assessing the change in level of respiratory support, frequency of apnoeic or bradycardic episodes and need for emergency resuscitation over a 24-hour period.[16]

## Procedure

The laser photocoagulation was carried out in the paediatric high-dependency unit. We monitored the infants continuously during the procedure using multipara monitor (EDAN iM50, Edan instruments, USA). During the procedure, if the infant developed haemodynamic instability, apnoea or bradycardia at any point, the fentanyl infusion or subsequent doses of ketamine were not given. If there were recurrent apnoea and desaturations, then supplemental oxygen by nasal prongs with a flow of 0.5–1 L/min was started and requirement of supplemental oxygen was noted. After the procedure, all the enrolled infants were transferred to neonatology facility for a mandatory 24 hours observation.

### Measurement of PIPP-R score during the procedure

We performed intermittent video recording of the infant focusing on the face (Sony HDR-XR150E) prior to the procedure (for baseline score), followed by every 15 min until the end of the procedure. Each recording was done for a duration of 30 s. Two independent assessors blinded to the group allocation analysed all the recorded videos by comparing the infant's reaction with that of the 'reference' videos specially prepared for the study (online supplemental table 3) and assigned PIPP-R scores. The discrepancies were resolved through mutual discussions.

### Cry during the procedure

We performed continuous voice recording of the infant during the entire procedure duration (Sony ICD-PX240 MP3 Digital Voice IC Recorder). One independent assessor analysed the recordings and calculated the proportion of time spent crying during the procedure.

## Additional data collection

We collected baseline details such as GA, post menstrual age (PMA) at enrolment, antenatal risk factors (eg, pregnancy-induced hypertension, gestational diabetes mellitus), requirement of delivery room resuscitation, presence of postnatal morbidities like respiratory morbidity, hypotension requiring inotropes, culture positive sepsis and anaemia requiring blood transfusions retrospectively from the neonatal discharge or referral summaries provided by the families.

GA was calculated from the first day of last menstrual period, by the first trimester ultrasound or by hospital records if other two were not available. PMA was calculated by adding postnatal age (period after birth) to GA at birth. Appropriateness of birth weight for GA was assigned as per the published reference.[17 18] The worst stage of ROP was recorded from previous retinal examination records. In cases where both eyes were affected, the greatest severity of disease was documented.

## Sample size

The standard of care for retinal ablation is general anaesthesia or deep sedation providing complete relief of pain during the procedure as practised in well-resourced setting. Since that option did not exist in our setting, we

choose not to take any control arm but to evaluate the proportion of infants in two study arms who had adequate analgesia as per the study definition. We calculated sample size for both the arms separately hypothesising that 90% of the infants would achieve adequate analgesia. For an absolute precision of 7.5% and 95% CI, we needed 62 infants in each group.

### Statistical analysis

The baseline and outcome data were collected in case recording form and concurrently entered into the electronic database (MS Access) with inbuilt range check. We periodically checked for completeness and accuracy of the data. We analysed the data by Stata V.15.1. The outcomes were expressed in terms of percentages and 95% CI. We did not plan any interim analysis.

### Patient and public involvement

Patients or the public were not involved in the design, conduct, reporting or dissemination plans of our research.

## RESULTS

Between 16 April 2018 and 5 May 2019, we screened 297 infants. During this study period after enrolling 97 infants (51 in fentanyl group and 46 in ketamine group), study team noted inadequate analgesia with both the study regimens. Accordingly, the study steering committee recommended revision of the regimens: higher dose of intravenous fentanyl (intravenous bolus dose of 2 µg/kg followed by an intravenous infusion of 2 µg/kg/hour to maximum of 5 µg/kg/hour) and intravenous ketamine (bolus dose of 1 mg/kg followed by intermittent bolus doses of 0.5 mg/kg to a maximum of 4 mg/kg) were recommended. Subsequently, we enrolled 27 more infants (13 in fentanyl group and 14 in ketamine group). The results are described separately as initial phase and revised regimen phase (figure 1).

### Initial phase

The mean weight at birth and randomisation were 1227 g and 2165 g in fentanyl group and 1202 g and 2258 g in

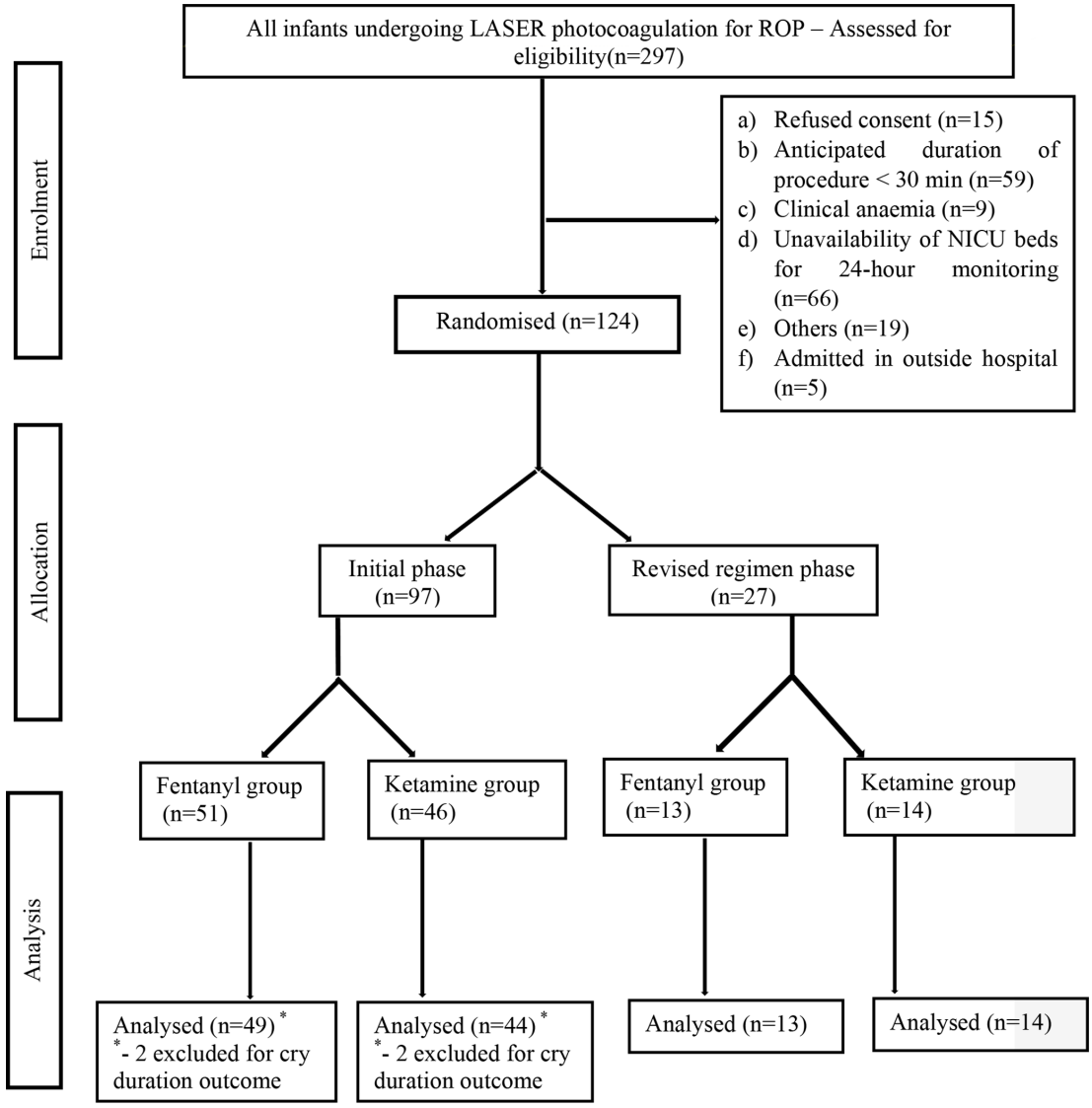


**Figure 1** Study flow of enrolled infants. NICU, neonatal intensive care unit; ROP, retinopathy of prematurity.

Table 1 Baseline characteristics of enrolled infants with initial regimens*

| Characteristic | Fentanyl (N=51) | Ketamine (N=46) |
|---|---|---|
| Gestational age at birth (week)† | 29.7 (1.9) | 29.8 (1.5) |
| PMA at randomisation (week)† | 37.8 (2.7) | 39.2 (3.1) |
| Birth weight (g)† | 1227.8 (280) | 1202.9 (254) |
| Weight at randomisation (g)† | 2165.8 (582) | 2258.1 (658) |
| Male gender | 36 (70.5) | 24 (52.1) |
| Antenatl steroid‡ | | |
| Complete | 12 (23.5) | 7 (15.2) |
| Incomplete | 3 (5.9) | 7 (15.2) |
| None | 16 (31.4) | 9 (19.6) |
| Not known | 20 (39.2) | 23 (50) |
| Caesarean delivery | 19 (37.2) | 21 (45.6) |
| Morbidities during neonatal period | | |
| RDS | 19 (37.2) | 26 (56.5) |
| Delayed adaptation | 10 (19.6) | 7 (15.2) |
| Pneumonia | 9 (17.6) | 5 (10.9) |
| AOP | 14 (27.4) | 8 (17.4) |
| Any sepsis | 43 (84.3) | 39 (84.7) |
| Hypotension requiring inotropes | 5 (9.8) | 6 (13) |
| Any blood product transfusion | 21 (41.1) | 23 (50) |
| Stage of ROP§ | | |
| APROP | 6 (11.7) | 6 (13.0) |
| Stage 2±plus | 13 (25.5) | 9 (19.5) |
| Stage 3±plus | 25 (49) | 22 (47.8) |
| Stage 4±plus | 6 (11.7) | 9 (20.4) |
| ROP sequelae | 1 (1.9) | – |
| Eye lasered | | |
| Both | 47 (92.1) | 42 (91.3) |
| Right | 3 (5.9) | 2 (4.3) |
| Left | 1 (1.9) | 2 (4.3) |
| Duration of procedure (min) | 75 (48–90) | 59.1 (40–91) |

*Data depicted as n (%).
†Indicates data as mean (SD).
‡Only in infants with available data.
§Worst stage of ROP was taken in cases where both eyes affected.
AOP, apnoea of prematurity; APROP, aggressive posterior retinopathy of prematurity; PMA, post menstrual age; RDS, respiratory distress syndrome; ROP, retinopathy of prematurity.

ketamine group (table 1). The baseline characteristics were similar in both the groups except slight male preponderance in fentanyl and higher PMA at randomisation in ketamine group. Most common stage of ROP warranting laser in the initial phase was stage three with or without plus disease.

The proportions of infants with adequate analgesia were 16.3% (8/49; 95% CI 8.5% to 29%) in fentanyl group and 4.5% (2/44; 95% CI 1.3% to 15.1%) in ketamine group. Need for supplemental oxygen was higher during the procedure with both fentanyl (9/51; 95% CI 9.6% to 30.2%) and ketamine (4/46; 95% CI 3.4% to 20.3%) compared with postprocedure (n=1; 1.9% with fentanyl and n=1; 2.1% with ketamine). In addition, more infants had apnoea during the procedure in both the groups compared with the 24 hours postprocedure. Both the regimens were well tolerated with no difference in side effects postprocedure between the groups (table 2, online supplemental figure 1).

### Revised regimen phase

The mean weight at birth and randomisation were 1281 g and 2061 g in fentanyl group and 1301 g and 2505 g in ketamine group (online supplemental table 4). Most common stage of ROP warranting laser was stage 3 with/without plus and aggressive posterior retinopathy of prematurity in equal proportion.

The proportions of infants with adequate analgesia with revised regimens were higher: 23.1% (3/13; 95% CI 8.2% to 50.2%) in fentanyl and 7.1% (1/14; 95% CI 1.3% to 31.5%) in ketamine groups. However, greater proportion of infants developed apnoea (n=4, 30.7%), oxygen requirement (n=5, 38.4%) and change in cardiorespiratory scores (n=7, 53.8%) with fentanyl but none with ketamine (table 3, online supplemental figure 2).

### Post hoc analysis

Since, we wanted to see in quantitative terms whether there was a lesser degree of pain control or no pain control at all, we performed post hoc analysis to see the degree of pain control with different regimens using an alternative definition of adequate analgesia as well as the PIPP-R scores at all time points (table 4).

On analysis of proportion of infants with adequate analgesia based on procedure duration, we did not find any difference in proportion of infants with adequate analgesia at different duration of procedure (<45 min, 45–60 min and >60 min; online supplemental table 5).

## DISCUSSION

Most low-income and middle-income countries including India are currently experiencing the third epidemic of ROP due to improved survival of preterm neonates and poor quality of care.[19] It has been estimated that 490 000 preterm infants are born with a GA of <32 weeks in India, and at least 5000 preterm infants require laser photocoagulation treatment for ROP every year.[20 21]

The ophthalmic centres performing laser photocoagulation are far and few compared with the large number of preterm infants being referred for screening and treatment in these settings. These ophthalmic centres often do not have the required support from anaesthesia and neonatology services due to their limited capacity to cater to these referred infants. Consequently, they act in a hyperefficient way and carry out the procedures in manners that require minimal monitoring and hospital stay of these infants. The incessant cry of the infants due to pain provides reassurance to many that the infant is breathing during the procedure.

Table 2 Study outcomes of enrolled infants with initial regimens*

| Characteristic | Fentanyl | | Ketamine | |
|---|---|---|---|---|
| | No (%) | 95% CI | No (%) | 95% CI |
| Primary | (N=49) | | (N=44) | |
| Infants achieving adequate analgesia | 8 (16.3) | 8.5 to 29 | 2 (4.5) | 1.25 to 15.1 |
| 1. All the PIPP-R scores less than seven | 20 (39.2) | 27 to 52.9 | 10 (21.7) | 12.2 to 35.5 |
| 2. % of the procedure time infants spent crying† | 9.5 | 4.6 to 20.2 | 18.4 | 8.8 to 34.4 |
| Secondary | (N=51) | | (N=46) | |
| Apnoea | | | | |
| During the procedure | 4 (7.8) | 2.2 to 18.9 | 2 (4.3) | 1.2 to 14.5 |
| After the procedure | 1 (1.9) | 0.05 to 10.4 | 0 | |
| Need for supplemental oxygen | | | | |
| During the procedure | 9 (17.6) | 9.6 to 30.2 | 4 (8.6) | 3.4 to 20.3 |
| After the procedure | 1 (1.9) | 0.35 to 10.3 | 1 (2.1) | 0.38 to 11.3 |
| Change in cardiorespiratory stability scores‡ | | | | |
| No change from baseline | 41 (80.4) | 66.9 to 90.2 | 39 (84.8) | 71.1 to 93.7 |
| Improved from baseline | 0 | | 0 | |
| More instability from baseline | 10 (19.6) | 11 to 2.5 | 7 (15.2) | 7.6 to 28.2 |
| Haemodynamic instability requiring inotropes | 0 | – | 2 (4.3) | 0.5 to 14.2 |
| Need for NICU admission for >24 hours | 0 | – | 2 (4.3) | 0.5 to 14.2 |

*Data represented as n (%).
†Data represented as median (IQR).
‡Cardiorespiratory stability score was defined as score 0—improved from baseline, score 1—no change from baseline, score 2—mild instability, score 3—marked instability and score 4—life-threatening event.
NICU, neonatal intensive care unit; PIPP-R, Premature Infant Pain Profile-Revised.

Additionally, as the infant has not received any sedative drugs, it facilitates discharging infant with more confidence. Despite the worrisome consequences of leaving pain untreated, the reasoning for lack of treatment has become widely accepted in lieu of limited resources. However, pain relief is an important ethical consideration even in resource abundant settings. Adequate pain relief also allows to perform the procedure safely and with precision.

There is lack of high-quality data from low-income to middle-income countries regarding pain relief during treatment for ROP. We chose fentanyl and ketamine because the previous Randomised Controlled Trial (RCT) from the same unit by Sethi *et al*[13] failed to demonstrate adequate analgesia with low dose fentanyl infusion without bolus as well as oral dextrose.

### Analgesic efficacy and adverse effects: fentanyl and ketamine

Compared with morphine, fentanyl offers equal level of analgesia although with fewer adverse events.[7 22] Common side effects with fentanyl include bradycardia, desaturation, tolerance and chest wall rigidity. Chest wall rigidity usually occurs after rapid intravenous bolus injections.

Ketamine is a unique agent with three actions—sedation, analgesia and amnesia; however, it is not well studied in neonatal population. Short-term increase in heart rate, blood pressure, intraocular and intracranial pressure are notable side effects. Ketamine can also cause laryngospasm, respiratory depression, increased respiratory secretions and emesis. Although animal studies have raised concerns with ketamine use (neuronal apoptosis in rat brain), this has been reported with doses that are 100 times of those used in clinical practice.

### Statement of principal findings

The study regimens of intravenous fentanyl (bolus of 2 µg/kg followed by infusion of 1 µg/kg/hour to a maximum of 3 µg/kg/hour) and intravenous ketamine (intermittent intravenous bolus doses of 0.5 mg/kg to maximum of 2 mg/kg) provided adequate analgesia in only a minority of infants (16.3% and 4.5%, respectively). Even the revised regimens of fentanyl (intravenous bolus dose of 2 µg/kg followed by an intravenous infusion of 2 µg/kg/hour to maximum of 5 µg/kg/hour) and ketamine (intermittent intravenous bolus doses of 1 mg/kg to maximum of 4 mg/kg) did not improve these proportions (23.1% and 7.1%) in a very clinically meaningful way. Though, in general, the drugs were well tolerated but a minority did experience significant side effects that required prolonged monitoring (>24 hours) in the ketamine group (n=2; 4.3%). A possible explanation for inadequate analgesia even with

**Table 3** Study outcomes in enrolled infants receiving revised regimen*

| Characteristic | Fentanyl (n=13) | | Ketamine (n=14) | |
|---|---|---|---|---|
| | No (%) | 95% CI | No (%) | 95% CI |
| Primary | | | | |
| Infants achieving adequate analgesia | 3 (23.1) | 8.2 to 50.2 | 1 (7.1) | 1.3 to 31.5 |
| 1. All the PIPP-R scores less than 7 | 6 (46.1) | 23.2 to 70.8 | 4 (28.5) | 11.7 to 54.6 |
| 2. % of the procedure time infants spent crying† | 7.9 | 3.1 to 13.8 | 10.1 | 5.5 to 12.5 |
| Secondary | | | | |
| Apnoea | | | | |
| During the procedure | 4 (30.7) | 12.7 to 57.6 | 0 | – |
| After the procedure | 0 | – | 0 | |
| Need for supplemental oxygen | | | | |
| During the procedure | 5 (38.4) | 17.7 to 64.5 | 0 | – |
| After the procedure | 0 | | 0 | – |
| Change in cardiorespiratory stability scores‡ | | | | |
| No change from baseline | 6 (46.1) | 19.2 to 74.8 | 14 (100) | |
| Improved from baseline | 0 | 0 | 0 | |
| More instability from baseline | 7 (53.8) | 29.1 to 76.8 | 0 | |
| Haemodynamic instability requiring inotropes | 0 | | 0 | |
| Need for NICU admission for >24 hours | 0 | | 0 | |

*Data represented as n (%).
†Data represented as median (IQR).
‡Cardiorespiratory stability score was defined as score 0—improved from baseline, score 1—no change from baseline, score 2—mild instability, score 3—marked instability and score 4—life-threatening event.
NICU, neonatal intensive care unit; PIPP-R, Premature Infant Pain Profile-Revised.

higher doses of both agents may be that the neonates experience additional multitude of stimuli during the laser procedure (physical restraining, use of eyelid retractor, indenter and the bright laser beam itself). We did find control of pain at instance when babies were experiencing mild to moderate pain (PIPP-R ≤12) as indicated by the PIPP-R scores at all time points. Also, the cry duration was considerably better with more

**Table 4** Post hoc analysis for degree of control of analgesia with different study drug regimens

| Characteristics | Fentanyl Initial dose (n=49) | Ketamine Initial dose (n=44) | Fentanyl Revised dose (n=13) | Ketamine Revised dose (n=14) |
|---|---|---|---|---|
| Proportion of time spent crying | | | | |
| <5% | 13 (26.5) | 5 (11.4) | 5 (38.4) | 3 (21.4) |
| 5%–14.9% | 21 (42.8) | 13 (29.5) | 5 (38.4) | 8 (57.1) |
| 15%–40% | 12 (24.5) | 20 (45.4) | 3 (23.1) | 3 (21.4) |
| >40% | 3 (6.1) | 6 (13.6) | 0 | 0 |
| PIPP-R scores | | | | |
| N* | 244 | 214 | 51 | 48 |
| Less than 7 | 165 (67.6) | 108 (50.4) | 34 (66.6) | 25 (52.1) |
| 7–12 | 69 (28.3) | 89 (41.5) | 11 (21.5) | 13 (27.1) |
| 13 to 21 | 10 (4.1) | 17 (7.9) | 6 (11.7) | 10 (20.8) |
| Neonates with maximum PIPP-R ≤12 and <15% of time spent crying | 32 (65.3) | 17 (38.6) | 10 (76.9) | 11 (78.5) |

Data represented as n (%)
*PIPP-R score represents total no of occasions for which PIPP-R score was assessed.
PIPP-R, Premature Infant Pain Profile-Revised.

than 90% infants having proportion of time spent crying <40% indicating at least some pain control with the study regimens.

### Strengths and weaknesses of the study

Our study addresses a critical gap in humane care of the vulnerable preterm infants in resource-constrained setting. To our best knowledge, this is the largest trial addressing the issue of analgesia during laser photocoagulation for treatment of ROP in preterm infants. We employed a robust methodology and ensured high-quality implementation of the study. Our outcome measures were clinically relevant and measured in a highly objectivised manner.

Our study is limited by the fact that it enrolled referred babies with incomplete birth and caregiving data. However, we believe, this should not have affected internal or external validity of the study.

### Strengths and weaknesses in relation to other studies

Overall, there is a paucity of studies addressing the issue of pain during retinal ablation for ROP in preterm infants. Kataria *et al* in his RCT demonstrated that oral dextrose hardly provided any analgesia compared with a placebo.[23] In the previous RCT from our own unit, Sethi *et al*[13] used a continuous fentanyl infusion of 1 µg/kg/hour without any prior bolus and reported mean PIPP-R scores of 7.2 (±1.1) and proportion of time spent crying during procedure of 62.5% (95% CI 50.7% to 74.2%) indicating poor control of the pain. The regimens in our study provided better control of pain compared with the regimen used in previous study but still fell considerably short of achieving adequate analgesia in majority of the infants. However, the PIPP-R scores and percentage cry duration were considerably better with the four regimens used in the study. This means that the degree of analgesia offered by our study regimens was near adequate and may be used as reasonable alternatives until an ideal regimen is identified.

With regard to safety profile, all the regimens used in the study were well tolerated except for slight increase in side effects with higher dose fentanyl regimen implying that a minimum observation of 24 hours in the hospital following the procedure is mandatory. In the study by Örge *et al*[7] using fentanyl at a dose of 1 µg /kg over 20 min (less than lower dose fentanyl regimen used in our study), it was observed that 11% (2/18) infants had apnoea, 28% (5/18) had bradycardia and 67% (12/18) had desaturation events with fentanyl. They also suggested that the higher incidence of desaturation events was not severe or prolonged enough to warrant change in level of respiratory support as only 6% required change in respiratory support. In a multicentric observational study conducted by Sato *et al*[8] in Japan, a higher dose of fentanyl was used (5 µg/kg bolus followed by intermittent boluses at 2.5 µg/kg) and found a higher proportion of desaturation 45% (5/11) and bradycardia 54% (6/11) during the procedure with no incidence of apnoea (defined as >150% frequency from baseline or >6 times a day in infants who had no apnoea prior to procedure, probably explaining the zero incidence) and feed intolerance. Sample sizes were significantly small in both the above studies.

In the previous study using ketamine as an analgesic agent by Lyon *et al*[12] (intermittent ketamine doses ranging from 0.5 mg/kg to 4 mg/kg), main outcome assessed was change in the cardiac or respiratory status during or post laser therapy. They found that 27.2% infants (3/11) developed intraprocedural complications and 18.1% infants (2/11) developed postprocedure complications requiring hiking of respiratory support although small sample size. Above study did not use any pain scores or other parameters of systemic instability postprocedure.

### Limitations of the study

We acknowledge certain limitations of our study. As our study population was a predominantly out born cohort, there was variable quality and completeness of data on baseline characteristics. We could not analyse outcome of cry duration/proportion of cry in four infants during the first phase of the study due to inadequate cry recordings. Small number of infants enrolled in the second phase of the study due to logistical constraints as we had to stop the trial after achieving the target sample size. Also, since the majority of infants enrolled in the study were infants with birth weight ≥1500 g, our study results may not be applicable to very low birthweight population.

### Meaning of the study: implications for clinicians

Our study regimens did not find a concrete option for adequate procedural analgesia. Therefore, we recommend that general anaesthesia or deep sedation and analgesia must remain the standard of care for carrying out laser photocoagulation in infants. Use of additional sedative agent like midazolam alone or in combination with opioids may be considered for optimal sedation during laser therapy.[9 24 25] However, in absence of such option and until we find a better regimen, the clinicians may consider using fentanyl-based regimen for providing analgesia during the procedure. As the study regimens may have important side effects in a few infants, these infants need to be observed for at least 24 hours in the hospital after the procedure.

### Unanswered questions and future research

There is a need for studies addressing the issue of optimal analgesia during laser therapy for ROP in preterm infants in resource-constrained settings. Studies among neonates admitted in NICU and requiring laser before discharge are also integral to understand the delayed adverse effects of analgesic agents.

## CONCLUSION

Our study demonstrated that the regimens involving intravenous fentanyl and ketamine provided adequate analgesia only in a minority of preterm infants undergoing laser photocoagulation for ROP. There is an urgent

need to address the issue of pain relief during retinal ablation in order to alleviate the unnecessary suffering of a sizeable population of preterm infants in resource-constrained countries. Till an effective regimen is identified, our study regimens based on fentanyl may be used for providing pain relief in resource-constrained settings.

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