Research Article

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# Efficacy and Safety of Multimodal Analgesic Therapy to Prevent Pain during Screening for Retinopathy of Prematurity

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## ABSTRACT

***Background:*** *Premature infants admitted to the Neonatal Intensive Care Unit are exposed on average to 14 painful procedures per day, as the retinopathy of prematurity screening. Neonatal pain is often underestimated and insufficiently treated, but there are short-term and long-term deleterious effects in premature infants exposed to repetitive pain. Since premature infants cannot verbalize the pain, the use of validated measurement tools is recommended for its evaluation and measurement of pain. The aim of this study was to determine the usefulness of a multimodal analgesic therapy proposed, to prevent pain in premature infants under retinal evaluation.*

***Methods:*** *We carried out a blinded, randomized clinical trial. Premature infants ≤ 34 weeks of gestational age received standard therapy (one drop of tetracaine in each eye) or proposed multimodal analgesic therapy (paracetamol oral at 15 mg/kg, 30 minutes prior to retinal evaluation, and intranasal fentanyl 2 µg/kg, 5 minutes prior to retinal screening, as well as warm containment and non-nutritional suction. The primary outcome was the score of Premature Infant Pain Profile-Revised (PIPP-R). The application of the score PIPP-R was performed 35 minutes before the procedure, during, and 15 minutes after the procedure.*

***Results:*** *There were no significant differences in PIPP-R score prior to the retinal screening, however, during the retinal evaluation the PIPP-R score was significantly lower in the proposed multimodal therapy group (14.0 vs 6.5, p=0.0001); and 15 minutes after the procedure, score remained lower in the proposed multimodal therapy group (2.9 vs 1.6 p=0.0001). No adverse effects were documented in neither group. In conclusion, retinal screening cause's deep pain, the topical tetracaine is insufficient to mitigate it. The proposed multimodal therapy can be useful to prevent the pain caused by the procedure and it does not cause adverse effects.*

## Keywords
Retinal screening, Children pain, Premature infants, PIPP-R, Analgesic therapy.

## Introduction
Growing evidence suggests that neonates experience pain like adults; nevertheless, many still believe that neonates perceive pain differently and the nociception is limited, especially shortly after birth [1].

Premature infants admitted to the Neonatal Intensive Care Unit (NICU), experience higher frequency of invasive and painful procedures, are exposed on average to 14 painful events per day, at least in the first two weeks of the stay in the NICU [2].

Unfortunately, neonatal pain is often underestimated and insufficiently treated, with the false argument that premature infants are unable to perceive and verbalize the magnitude of pain. There was a belief that they have immature cortical development and pain responses abolished, therefore it was believed that they did not perceive pain [3].

We currently know that before 28 weeks of gestation, painful stimuli are associated with physiological, hormonal, and metabolic markers of the stress response, and that neuroanatomical pathways for nociception from the periphery to the cortex are developed.

Preterm birth, defined as any birth before 37 completed weeks or 259 days of gestation, affects between 5 and 10% of all births, in the US it is reported in 8 to 11%, and in Europe, it varies 5 to 7%. The global rate of prematurity is approximately 15 million per year [4].

Some of the painful procedures that PI undergo, include heel stick, venipuncture, arterial puncture, lumbar puncture, chest tube insertion, central venous catheter insertion, endotracheal tube aspiration, surgery, and retinopathy of prematurity (ROP) screening [5].

There are short-term and long-term deleterious effects in premature infants exposed to repetitive pain; increase apoptosis, cause oxidative stress and alterations in the central and peripheral nervous system, leading to changes such as: decreased pain threshold, persistent hyperalgesia, greater and longer response and sensitivity to pain, increased pain response in the tissues surrounding the painful stimulus, arrest of the development of myelinating cells and neuro-behavioral disorders. In addition, it has been shown to decrease the growth and development of the cerebellum, altering the programming of the hypothalamic-adreno-pituitary axis [6-8].

Many painful procedures in premature infants with gestational age ≤ 29 weeks were associated with delayed postnatal growth, poor early neurological development, greater cortical activation, altered brain development, inadequate cognitive and motor development at one year of age, and changes in cortical thickness at 7 years of age [9].

Since premature infants cannot verbalize the pain, the use of validated measurement tools is recommended for its evaluation and measurement of pain [10].

Preterm Infant Pain Profile (PIPP) score was developed for preterm and term newborns but has limited validation in very low weight premature infants, for which the PIPP-revised score (PIPP-R), was created [11].

ROP is a disease that originates in the immature vasculature of the retina of premature newborns, if not diagnosed and treated opportunely, that could result in blindness. Serial evaluation of all newborns less than 34 weeks gestational age is recommended and necessary until the retina matures [12]. Retinal evaluation is a painful and stressful procedure; it requires the use of a blepharostat and the use of a scleral indenter, which has been shown to be very painful for premature infants [13]. Various interventions have been tried to reduce this pain response, but they have not been found to be very effective [14].

The American Academy of Pediatrics recommends that efforts be made to minimize the discomfort and painful systemic effect of the retinal evaluation, and it is imperative to investigate new approaches to reducing pain in this setting [15]. Therefore, in the present study we set out to determine the usefulness of a multimodal analgesic therapy proposed, to prevent pain in premature infants under retinal evaluation.

## Methods
### Participants
This was a randomized, blinded clinical trial, which included 104 PI ≤ 34 weeks of gestation in addition, ≤ 2000 g of weight, who underwent retinal evaluation from January to October 2019, admitted to the NICU of a level III Pediatric Hospital in Guadalajara, Jalisco, Mexico.

Patients with use of analgesic included in their management, with absolute contraindication of any of the proposed pharmacological and/or non-pharmacological analgesic therapies, omission of any of the three evaluations of the PIPP-R score; or with major congenital malformations were excluded from the study.

### Ethical considerations
The study was approved by the Ethics and Research Institutional Committees, *Instituto Mexicano del Seguro Social*, Guadalajara, Jalisco, Mexico (IMSS register number R-2020-1302-033). All methods and procedures were performed in accordance with government regulations and with the Institutional Guidelines of the *Instituto Mexicano del Seguro Social* (IMSS) in Guadalajara Jalisco, México (COFEPRIS register number 17 CI 14 039 045; CONBIOETICA register number 14 CEI 001 2018022), which comply with national and international guidelines and the Declaration of Helsinki.

All the parents of the participants signed an informed consent, and it was explained what their participation would consist of and the scope of the study. All data were handled according to ethical and confidentiality guidelines.

### Procedures and score determinations

After signing the informed consent, the patients were randomized using opaque envelopes, for assignment in either of two groups: a) standard management: application of one drop in each eye of phenylephrine and tropicamide ophthalmic solution, 1 hour prior to the retinal evaluation in order to dilate the pupil, and one drop in each eye of tetracaine ophthalmic solution at the time of evaluation, or b) a proposed multimodal analgesic intervention, which included: a dose of paracetamol at 15 mg/kg orally, 30 minutes before the procedure and single intranasal dose of fentanyl at 2 µg/kg, five minutes before; as well warm containment measures approach, and non-nutritive suction with a pacifier impregnated with 10% dextrose solution.

Pain was assessed using the PIPP-R score (Premature Infant Pain Profile-Revised), 35 minutes before the procedure, during the procedure, and 15 minutes after it was performed or finished [16].

### Statistical analysis

The methodological advisor who performed the statistical analysis of the data obtained, always ignored the assignment of the groups, which were identified by means of a pre-determined code or folio. The analysis was carried out with the SPSS package (Statistical Package for the Social Sciences) version 25. The frequencies were compared with $\chi^2$ and Fischer's exact test when necessary, and for quantitative data which are presented as mean ± standard deviation (SD). Student's *t* was used. The distribution of the data was evaluated, which did not present a normal distribution, for which they were analyzed with non-parametric inferential statistics, (Mann-Whitney test for independent samples, between the standard management groups versus the proposed multimodal analgesic intervention group). A statistically significant value was considered when the value of *p* was ≤ 0.05 with a confidence level of 95%.

## Results

104 premature infants were included in this study, 54 were assigned to standard management and 50 to a proposed multimodal analgesic intervention. We did not find significant differences in baseline characteristics of children (Table 1).

**Table 1:** Baseline characteristics of children.

| Variable | Standard therapy group, n=54 | Multimodal therapy group, n=50 | *p* value |
|---|---|---|---|
| Gestational age (weeks) | 30.3 ± 2.4 | 30.3 ± 2.1 | 0.921 |
| Birth weight (g) | 1399 ± 482 | 1365 ± 362 | 0.687 |
| Female (n, %) | 25 (46.2 %) | 16 (32 %) | 0.162 |
| Male (n, %) | 29 (53.7 %) | 34 (68 %) | |

The results of gestational age and birth weight are expressed as mean ± standard deviation and number of female or male are given on percentage.

The PIPP-R score prior to the retinal evaluation in the standard therapy group was 1.8 ± 1.9, and in the intervention group it was 1.5 ± 1.9 (*p*=0.415), which translates into the absence of pain prior to the procedure such as we expected. The PIPP-R score during the retinal evaluation in the standard therapy group was 14.0 ± 2.4 (which represents deep pain); while in the multimodal analgesic therapy group, it was 6.5 ± 2.9, (*p*=0.0001) (Table 2).

We were surprised that the PIPP-R score 15 minutes after retinal evaluation, stayed higher in the standard therapy group: 2.9 ± 1.9; in contrast to the intervention group, which was 1.6 ± 1.7, (*p*=0.001) (Table 2).

**Table 2:** PIPP-R score in both groups, previous, during and after retinal evaluation.

| Score | Standard therapy group, n=54 | Multimodal therapy group, n=50 | *p* value |
|---|---|---|---|
| Before PIPP-R score | 1.8 ± 1.9 | 1.5± 1.9 | 0.415 |
| During PIPP-R score | 14.0 ± 2.4 | 6.5 ± 2.9 | 0.0001 |
| After PIPP-R score | 2.9 ± 1.9 | 1.6± 1.7 | 0.0001 |

Pain was assessed using the PIPP-R score (Premature Infant Pain Profile-Revised).
The results of PIPP-R score in both groups are expressed as mean ± standard deviation

We analyzed the PIPP-R score by gestational age at birth, dividing patients into 3 subgroups (26-28.6 weeks, 29-31.6 weeks, and 32-34.6 weeks). We found that results remained unchanged with no significant differences in PIPP-R score prior to retinal evaluation; and with clearly significant differences during and after retinal evaluation (Table 3).

**Table 3:** PIPP-R score by subgroups of gestational age at birth.

| **Gestational age (weeks)** | **PIPP-R score** | **Standard therapy group, n=54** | **Multimodal therapy group, n=50** | ***p* value** |
|---|---|---|---|---|
| | Before | 1.9 ± 2.0 | 2.1 ± 2.0 | 0.781 |
| 26-28.6 | During | 15.3 ± 2.0 | 7.6 ± 2.4 | 0.0001 |
| | After | 3.1 ± 2.1 | 1.3 ± 1.4 | 0.014 |
| | Before | 1.8± 2.0 | 1.8± 2.1 | 0.947 |
| 29-31.6 | During | 13.5 ± 2.5 | 5.9 ± 3.2 | 0.0001 |
| | After | 2.9 ± 1.9 | 1.8 ± 1.9 | 0.090 |
| | Before | 1.7 ± 1.9 | 0.7 ± 1.1 | 0.065 |
| 32-34.6 | During | 13.5 ± 2.2 | 6.3 ± 2.9 | 0.0001 |
| | After | 2.7 ± 1.7 | 1.5 ± 1.7 | 0.038 |

Data are expressed as mean ± standard deviation. Pain was assessed using the PIPP-R score (Premature Infant Pain Profile-Revised).

Sometimes the retinologist required the use of an indenter to perform small mobilizations of the eyeball. Contrary to what we expected, there were no significant differences in the PIPP-R score between preterm infants in whom indentation was used and in those who did not (Table 4).

**Table 4:** PIPP-R score with and without use of indenter.

| PIPP-R score | Group | PIPP-R score with indenter Standard n=25 Multimodal n=26 | PIPP-R score without indenter Standard n=29 Multimodal n=24 | *p value* |
|---|---|---|---|---|
| Before | Standard | 2.08 ± 2.08 | 1.66 ± 1.89 | 0.43 |
| | Multimodal | 1.73 ±1.95 | 1.33 ± 1.88 | 0.46 |
| During | Standard | 14.44 ± 2.25 | 13.72 ± 2.53 | 0.28 |
| | Multimodal | 6.46 ± 3.17 | 6.63 ± 2.79 | 0.84 |
| After | Standard | 2.76 ± 2.20 | 3.14 ± 1.68 | 0.47 |
| | Multimodal | 2.04 ± 1.90 | 1.13 ± 1.48 | 0.06 |

Data are expressed as mean ± standard deviation. Pain was assessed using the PIPP-R score (Premature Infant Pain Profile-Revised).

Finally, no patient presented complications or adverse effects related to the administration of the pharmacological and non-pharmacological measures of the proposed multimodal analgesic therapy.

## Discussion

The screening for ROP is necessary in premature infants, in order to promptly diagnose ROP and thus avoid risk of compromising visual outcome. Screening is done by indirect ophthalmoscopy, a potentially painful procedure that involves the insertion of a speculum (blepharostat), use of an indenter, and a considerable amount of handling. Despite the use of local anesthetic drops before eye examination, screening remains a painful procedure [17].

For this reason, we consider that it is imperative to protocolize an effective preventive analgesic therapeutic approach for this vulnerable population.

In the present randomized clinical trial, we set out to compare the standard management that has been used in the NICU of the tertiary Hospital, *versus* the usefulness of the proposed multimodal analgesic therapy, to prevent pain during ROP screening. We enrolled 104 premature infants, randomly distributed into two groups: standard management group (n=54) and proposed multimodal therapy group (n=50); both groups were homogeneous in gestational age and birth weight (Table 1).

According to the results, we found a significant decrease in pain; evaluated by the PIPP-R score, during the retinal evaluation, in the intervention group who received the proposed multimodal analgesic therapy, furthermore, 15 minutes after the retinal evaluation, the standard group maintained a higher PIPP-R score than the intervention group; therefore, we confirmed that the standard group, not only presented more intense pain, but that they remained sore minutes after the procedure ended.

Recently, a clinical trial was reported with non-pharmacological measures to prevent pain during the Retinopathy of Prematurity (ROP) screening. They included 45 premature infants, undergoing ROP screening and were randomly assigned to one of the three groups that orally received either: expressed breast milk (n=14), 10% dextrose solution (n=14) or sterile water (n=17), one minute before retinal evaluation. They used the PIPP score to assess pain, and they found no significant differences between the tree groups; the mean PIPP scores were similar: 11.8 ± 2.8 *versus* 9.8 ± 3.3, *versus* 10.2 ± 2.9 ($p$=0.18). They concluded that the effects were similar in the three groups and do not relieve pain during the procedure [18].

Just as previously reported, non-pharmacological measures did not relieve pain during ROP screening; in the present study we found that tetracaine eye drops are not enough to prevent pain in this procedure, a situation that was confirmed in a meta-analysis by Disher *et al*. in which they analyzed 29 clinical trials that evaluated pain relieving interventions for ROP examinations; such as acetaminophen, expressed breast milk suction, sweetened solution suction, non-nutritive suction, and topical anesthetics. They observed that the use of topical anesthetic together with suction of expressed breast milk had better pain control than topical anesthetic alone, but the rest of the comparisons were not statistically significant. Combined treatments were more likely to mitigate pain but did not reach statistical significance. They concluded that the use of multisensory interventions, recognized as therapeutic measures that combine strategies directed at multiple sensory systems; provides better results in relieving pain during eye examinations in premature infants, which is comparable to our results [19].

The clinical trial by Sethi *et al.,* as well as our study, administered opioid analgesia. They compared the effect of low-dose fentanyl infusion (1 µg/kg/h) versus 24% oral sucrose during laser therapy for ROP. It should be noted that during the application of laser therapy it is necessary to place the blepharostat. They found that the mean PIPP-R score at any time during the procedure was significantly lower in the fentanyl group compared to the 24% oral sucrose group [(7.2 ± 6.1 *versus* 9.0 ± 7.9 ($p$=0.01)]. They concluded that low dose fentanyl infusion was found to be efficacious in reducing pain as compared with 24% sucrose, during laser por ROP [20].

Intranasal fentanyl has been considered an ideal analgesic option in emergency rooms, and additional evidence has increasingly been generated regarding the safety and efficacy of its intranasal administration in preventing pain during relatively rapid procedures such as retinal examination por ROP screening. As shown in the study by Sindhur *et al*., In which they used the same doses of intranasal fentanyl as in our study, they included a total of 111 premature infants, and like us, they found that the PIPP-R score during the retinal examination. Was significantly lower in the fentanyl group (8.3 ± 2.1 *versus* 11.5 ± 2.1, mean difference: 3.2 (95% CI 2.46-4.06), ($p$=0.001) [21].

However, it has also been associated with adverse effects, Sindhur *et al.*, reported apnea episodes in 2 patients who received intranasal fentanyl, as well as oxygen desaturation and consequently the need

to increase the inspired fraction of oxygen in 1 patient. These events occurred in the first 3-10 minutes after the retinal examination. They did not find a significant difference in the incidence of adverse effects [21]. In contrast, the multimodal therapy proposed in our study was useful and safe since we did not document any adverse effects.

Fentanyl is a synthetic opioid, very useful in neonates because it is relatively short time to peak analgesic effect (2-3 minutes) and the rapid termination of action after small doses.

Based on accumulating literature and experience with intranasal fentanyl in our NICU, and concern about providing neonates without intravenous access; we have included the use of intranasal fentanyl in our clinical practice.

Even though adverse effects have been described with the use of opiates, in the present study, we observed that fentanyl administered intranasally provides an adequate safety profile; however, there are currently limited published data in neonates. Harlos *et al*., reported on the use of intranasal fentanyl in a retrospective study including 11 neonates undergoing palliative care. They administered 1-2 µg/kg/doses, no complications were identified, including when it was used multiple times in the same infants, and they concluded that intranasal fentanyl can administered in a variety of care settings [22].

McNair *et al.*, documented their experience with intranasal fentanyl analgesia for procedural pain management in premature neonates in a surgical neonatal intensive care unit. They reported 23 premature infants of 31.8 ± 4.1 weeks, treated with intranasal fentanyl. The mean dose was 1.3 µg/kg, and most frequent indication was for peripheral insertion of a central catheter. They concluded it was useful to alleviate the pain, and there were six cases of cardio-respiratory depression, however, clinical factors could account for all of them [23].

It is considered that the use of the indenter increases pain during retinal revision, therefore, we carried out a sub-analysis of the scores of the PIPP-R score in preterm newborns who required its use; we found no differences between the group of preterm infants in whom the indenter was used in contrast to the group of preterm infants in whom it was not used.

## Conclusions

The pharmacological and non-pharmacological analgesic measures that constitute the multimodal analgesic therapy proposed in the present study, appropriately prevented the pain in the premature infants undergoing ROP screening, without adverse effects.

Topical tetra Caine as monotherapy is insufficient to prevent the pain caused during and after retinal examination. We need to continue to investigate better ways to prevent pain in preterm infants undergoing ROP screening.


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