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## Efficacy of Topical Anesthetics to Reduce Pain in Premature Infants During Eye Examinations for Retinopathy of Prematurity

Virginia A Marsh, William O Young, Kimberly K Dunaway, Grace E Kissling, Rita Q Carlos, Susan M Jones, Dawn H Shockley, Nicole L Weaver, J Laurence Ransom, and Peter Gal

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**BACKGROUND:** Eye examinations for retinopathy of prematurity (ROP) are stressful and probably painful, but many ophthalmologists do not apply topical anesthetics because their efficacy in reducing pain has not been established.

**OBJECTIVE:** To evaluate the potential benefits of topical anesthetic eye drops in reducing pain during neonatal eye examination for ROP.

**METHODS:** Neonates born at  $\leq 30$  weeks' gestation and expected to have at least 2 examinations for ROP were included. Patients were randomly assigned to receive either proparacaine HCl ophthalmic solution 0.5% or NaCl 0.9% (saline) eye drops prior to an eye examination. In a subsequent examination, each patient received the alternate treatment. Eye drops were prepared in the pharmacy in identical tuberculin syringes, and physicians, nurses, and pharmacists were blinded to the treatment given. Pain was measured using a scoring system with both physical and physiologic measures of pain (Premature Infant Pain Profile [PIPP], possible range 1–21), which has been validated in preterm infants. PIPP scoring was performed simultaneously by 2 nurses: 1 and 5 minutes before and after the eye examination and during initial placement of the eye speculum. The same ophthalmologist performed all examinations.

**RESULTS:** Twenty-two patients were studied, with 11 infants receiving proparacaine and 11 receiving saline as the first treatment. Crossover was performed with a median of 17.5 days between treatments. Patients experienced significantly less pain at speculum insertion with proparacaine than with saline (paired difference  $-2.5 \pm 3.4$ ;  $p = 0.001$ ).

**CONCLUSIONS:** Topical anesthetic pretreatment reduces the pain response to eye examination for ROP and should become routine practice. Because this is not effective in all infants, additional measures to reduce pain should be taken.

**KEY WORDS:** proparacaine, retinopathy of prematurity.

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Sick premature infants are exposed to many stressful and painful stimuli during their stay in the neonatal intensive care unit (NICU). Among these noxious stimuli is the neonatal eye examination required to evaluate for the presence of retinopathy of prematurity (ROP). These eye examinations are associated with physiologic consequences, such as changes in pulse rate and oxygen desaturation.<sup>1,2</sup> The benefits of analgesics and topical anesthetics to minimize the painful response associated with the ROP eye examina-

tion are unclear. A study using proparacaine HCl 0.5% failed to demonstrate reduced pain markers compared with a parallel placebo-treated NaCl 0.9% (saline) group.<sup>3</sup> With the parallel design, pain response was compared in patients who may intrinsically have different pain sensitivity. All infants in that study were reported to exhibit a stress response. Anecdotally, it has been stated elsewhere that local anesthetics do not reduce pain response when instilled prior to an eye examination for ROP,<sup>4</sup> while others suggest it is essential to use a topical anesthetic.<sup>2</sup> Consequently, while ophthalmologists typically administer topical anesthetics to children and adults, preterm infant eye examinations are of-

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Author information provided at the end of the text.

ten performed without topical anesthetic pretreatment. We have been working to minimize pain in our NICU and designed a placebo-controlled, double-blind, crossover study to determine whether this source of neonatal pain can be minimized. Since patients act as their own controls, we feel this is a more appropriate method of determining the efficacy of a pain prevention strategy.

## Methods

Premature infants  $\leq 30$  weeks' gestation and who required at least 2 eye examinations to monitor for ROP were admitted to the study. Patients were required to be sufficiently clinically stable to tolerate the eye examination based on the neonatologist's clinical assessment and could not require analgesia (fentanyl) or sedation (lorazepam) for at least 12 hours prior to the procedure. The study was approved by the hospital's institutional review board. The nature of the procedure was explained to the parents and consent obtained. The ROP eye examinations were clinically necessary as part of routine monitoring for preterm infants. Patients were enrolled by the study nurses. Examinations were performed by a single consultant pediatric ophthalmologist with 10 years of experience performing premature infant eye examinations. He was assisted by the NICU nurse responsible for the patient's care on that day and 2 pain study nurses who had gone through special training with the Premature Infant Pain Profile (PIPP) scoring system<sup>5</sup> to promote interobserver consistency.

Mydriatic eye drops (phenylephrine HCl 1%, cyclopentolate HCl 0.2%) were administered approximately 60–90 minutes before the examination. The patient was swaddled several minutes before the procedure and held by a nurse during the eye examination. The ophthalmologist inserted a spring-loaded wire Sauer premature infant eyelid speculum to hold the eyelids open. The retina of each eye was examined with an indirect ophthalmoscope through dilated pupils using a thimble-type Schepens scleral depressor to rotate the eye and indent the sclera to allow thorough examination of the retina.

The study observation interval began 5 minutes prior to the procedure and ended 5 minutes after completion of examination of the second eye. For each procedure, 2 pain study nurses performed pain assessments using the PIPP scale and reached consensus scores that were recorded on a study form at 5 different times throughout the observation period. All individuals involved in the direct care or assessment of the patient were blinded to the eye drops (anesthetic or saline) administered during the procedure.

A standard procedure was followed for each eye examination. The ophthalmologist evaluated patients in the order prescribed by the nurse investigators. This allowed the pain study nurses to record baseline PIPP scores on each infant 5 minutes and 1 minute prior to the procedure. The ophthalmologist administered the study eye drops, 2 drops in each eye, prior to examination of the first eye, then about 30 seconds later inserted an eyelid speculum to facilitate keeping the eye open and performed an examination lasting about 5 minutes to complete both eyes. The study nurses recorded PIPP scores during initial insertion of the wire eyelid speculum and 1 and 5 minutes after completion of the entire examination of both eyes.

The eye drops administered for the ROP examination were prepared by the hospital pharmacist in tuberculin syringes and labeled as study drug. The local anesthetic used was proparacaine HCl ophthalmic solution 0.5% (Bausch & Lomb, Tampa, FL) and the placebo was normal saline prepared under a sterile hood. The dose administered was 2 drops in each eye just prior to the examination. The delay from the administration of eye drops to the insertion of the speculum for examination of the first eye was approximately 30 seconds. The proparacaine package insert recommends instilling 1–2 drops and notes that anesthesia occurs 30 seconds after instillation and lasts approximately 15 minutes. Treatment allocation was made in groups of 6 based on the results from a dice roll. The hospital pharmacist was the only one familiar with the individual treatment assignments. One investigator who was never present during eye examination studies (PG) reviewed interim results after 12 patients were treated to ensure that infants were not unnecessarily administered saline if proparacaine proved beneficial. The study was stopped after 22 patients because a new ophthalmologist was scheduled to rotate onto the

service and we did not want to confound the study by altered examination technique.

The PIPP scale used to evaluate pain measures both physical and physiologic pain indicators and has been validated in prior publications.<sup>5–8</sup> The PIPP score is determined by assigning 0–3 points for various factors including gestational age at the time of observation; behavioral state (eg, quiet or active); increase in maximum heart rate; decrease in oxygen saturation; and facial features involving brow bulge, eye squeeze, and nasolabial furrow. Possible scores can range from 1 to 21. Scales that consider both aspects of clinical pain presentation are considered superior to those that utilize a single marker, because pain presentation in newborns may vary so that some patients react with more physiologic changes, while others present with more physical signs.<sup>6,7</sup> PIPP scores  $\geq 10$  and increases in scores of  $\geq 4$  points are considered to be a pain response that justifies intervention. This is based on data from the initial validation study for the PIPP score, which observed that infants 28–30 weeks' gestational age had mean PIPP scores of 10.3 during a real heelstick versus 6.3 during a sham heelstick procedure.<sup>5</sup> A subsequent validation study in which nonpainful stimuli resulted in mean  $\pm$  SD scores of  $9 \pm 0.8$  and painful stimuli resulted in mean scores of  $11.0 \pm 1.3$  suggested the PIPP score cutoff of 10.<sup>8</sup>

Four study nurses underwent special training to ensure reliable PIPP scores. For each ROP examination, 2 of the study nurses observed the infant as described above and recorded their consensus scores 5 minutes and 1 minute before the examination, at wire eyelid speculum insertion, and 1 minute and 5 minutes after the examination.

A double-blind crossover design was used in which each patient received the anesthetic and the placebo on different days in random order. The study was designed assuming that, without intervention, 80% of infants would have a pain response associated with the eye examination, and we sought to reduce this to 40% with the anesthetic. We estimated that 24 patients would be needed to detect this effect, with a  $p$  value  $< 0.05$  and a power of 80%.

Statistical analyses of PIPP scores were performed several different ways because definitions of pain in premature infants are somewhat arbitrary and may vary. Consequently, analyses were performed to consider (1) higher absolute PIPP scores, (2) number of PIPP scores increasing by  $\geq 4$  points from baseline (average of 1 and 5 min pre-examination), (3) number of PIPP scores  $\geq 10$ , (4) number of PIPP score differences of  $\geq 4$  points between treatment and placebo conditions, and (5) areas under the PIPP score curves from 5 minutes before the examination to eyelid speculum insertion and from lid speculum insertion to 5 minutes after the examination. AUCs were calculated using the trapezoidal rule. Statistical analyses compared proparacaine HCl 0.5% and saline treatments.

For statistical comparisons of the numbers of patients with PIPP scores  $\geq 10$ , the numbers of patients with increases in PIPP scores  $\geq 4$  points from baseline, and the numbers of patients with differences of  $\geq 4$  points between treatment and placebo, the binomial test was used. For comparisons of actual PIPP scores and of AUCs, paired  $t$ -tests were used. Paired  $t$ -tests were also used to compare postnatal ages between the proparacaine HCl 0.5% and saline treatments. The influences of post-conceptual age at time of examination and of the order of treatment on PIPP score were examined with a mixed-model repeated-measures ANCOVA. The number needed to treat to expect one patient to benefit from the anesthetic was estimated as the reciprocal of the absolute risk reduction for patients who experience pain with the anesthetic than with the placebo. Data are reported as mean  $\pm$  SD.

## Results

Twenty-two patients were enrolled in the study from October 2002 through May 2003. All patients completed the study without deviation from the protocol. Eleven infants received topical anesthetic first and 11 received saline drops first. The length of time between each patient's 2 eye examinations ranged from 4 to 21 days (median 17.5). Gestational ages ranged from 24 to 32 weeks, and postnatal ages at time of treatment ranged from 27 to 60 days. Postnatal ages at time of examination were not significantly different between the anesthetic and placebo conditions (Table 1).

PIPP scores at 1 minute and 5 minutes prior to the eye examination were similar in the anesthetic and placebo conditions. However, PIPP scores during placement of the wire eyelid speculum were significantly higher for the placebo than anesthetic treatment (Table 1). PIPP scores, while generally higher with placebo, were not statistically significantly higher than those in the anesthetic condition 1 and 5 minutes after completion of the eye examination.

Defining pain as an increase in a PIPP score of  $\geq 4$  points from baseline (the average of scores at 5 and 1 min before examination), all of the 22 patients had a painful reaction with eyelid speculum insertion when saline was administered, while 19 (86%) of the patients had a painful reaction with eyelid speculum insertion when the anesthetic was administered. Using this definition of pain, the anesthetic and placebo conditions did not differ significantly.

Alternatively, defining a painful reaction as a PIPP score  $\geq 10$ , no patients had a painful reaction 5 minutes before the examination and 2 placebo- and 2 anesthetic-treated patients had painful reactions 1 minute before the examination. During the examination, painful reactions occurred in 20 (91%) placebo- and 15 (68%) anesthetic-treated patients. Five infants had painful reactions with the placebo but not the anesthetic, while none had painful reactions with the anesthetic but not the placebo at eyelid speculum insertion (binomial test,  $p = 0.03$ ). At 1 minute after the examination, painful reactions were observed in 6 patients with the placebo but not the anesthetic and in 3 patients with the anesthetic but not the placebo (binomial test,  $p = 0.25$ ). Five minutes after the examination, painful reactions occurred in 3 patients with the placebo but not the anesthetic and in 1 patient with the anesthetic but not the placebo (binomial test,  $p = 0.31$ ).

Defining a painful reaction as a difference of  $\geq 4$  points in PIPP scores between the anesthetic and placebo conditions, at placement of the eyelid speculum, 9 patients had a

painful reaction with placebo and 2 had a painful reaction with the anesthetic (binomial test,  $p = 0.03$ ). One minute after the procedure, 8 patients had a painful reaction with treatment with placebo and 2 had a painful reaction with the anesthetic (binomial test,  $p = 0.06$ ). Five minutes after the procedure, 5 patients had painful reactions with placebo and 2 had painful reactions with the anesthetic (binomial test,  $p = 0.23$ ).

The AUC for PIPP score was used as a global marker of pain for the 5-minute interval from beginning the eye examination. Before insertion of the speculum, the AUC for PIPP scores did not differ between the placebo and anesthetic conditions ( $p = 0.21$ ). After insertion of the speculum, the AUC for PIPP scores was significantly greater with the placebo than the anesthetic treatment ( $p = 0.02$ ) (Table 1). Table 2 contains a summary of the results for all 5 definitions of pain response.

As a separate issue, the effect of postconceptional age on PIPP score was examined. Postconceptional age, defined as gestational age plus day of life at treatment expressed in weeks, was inversely related to PIPP score as assessed with bivariate correlations. In a mixed-model repeated-measures ANCOVA, an interaction (postconceptional age  $\times$  treatment) indicated that the inverse relationship was steeper for the anesthetic condition than for the placebo condition. However, even after adjusting for postconceptional age, significant differences between the anesthetic and placebo conditions remained ( $F [1, 6.84] = 10.76$ ,  $p = 0.014$ ). A similar repeated-measures ANCOVA showed no order effect of the treatments.

Table 3 gives the numbers of patients who experienced less pain with the anesthetic than with the placebo using each of the 5 possible definitions of pain response. Depending on the definition of pain response, the number needed to treat to expect one patient to benefit from the anesthetic ranges from 1.3 to 7.4 (Table 3).

Table 1. Demographic Information and PIPP Scores for the 22 Neonates

Parameter	Anesthetic <sup>a</sup>	Placebo <sup>a</sup>	Paired Difference <sup>a</sup>	p Value <sup>b</sup>
Gestational age (wk)	27.4 $\pm$ 1.9	27.4 $\pm$ 1.9	0	
Day of life	39.2 $\pm$ 12.1	39.4 $\pm$ 12.1	-0.2 $\pm$ 17.7	0.48
PIPP score				
5 min pre-examination	2.7 $\pm$ 0.9	3.0 $\pm$ 1.3	-0.3 $\pm$ 1.4	0.19
1 min pre-examination	4.6 $\pm$ 2.9	4.8 $\pm$ 3.4	-0.2 $\pm$ 4.8	0.41
wire insertion	11.0 $\pm$ 3.2	13.5 $\pm$ 3.5	-2.5 $\pm$ 3.4	0.001
1 min post-examination	9.3 $\pm$ 3.7	10.5 $\pm$ 3.5	-1.2 $\pm$ 4.0	0.09
5 min post-examination	4.5 $\pm$ 2.5	5.8 $\pm$ 3.2	-1.3 $\pm$ 3.6	0.06
AUC (cumulative pain)				
pre-examination	26.2 $\pm$ 13.5	28.4 $\pm$ 16.0	-2.2 $\pm$ 21.5	0.20
post-examination	37.8 $\pm$ 13.2	44.5 $\pm$ 14.2	-6.7 $\pm$ 14.3	0.02
O <sub>2</sub> desaturation $\geq 10\%$ on PIPP score, n pts. (%)				
pre-examination	2 (9.1)	3 (13.6)		1.00
eye speculum insertion	6 (27.3)	13 (59.1)		0.045
post-examination	6 (27.3)	3 (13.6)		0.371

PIPP = Premature Infant Pain Profile.  
<sup>a</sup>Mean  $\pm$  SD.  
<sup>b</sup>One-sided paired *t*-tests.

No adverse events, except pain response due to the eye examination, were associated with either placebo or proparacaine eye drops.

## Discussion

Clinicians generally agree that the neonatal eye examination for ROP produces a pain response in premature infants.<sup>1-4</sup> This is consistent with other publications, which recognize that premature infants have exaggerated pain reactions rather than muted sensitivity to pain as previously believed.<sup>9,10</sup> The examination for ROP, which is carried out in neonates <32 weeks' gestation or 1500 g birth weight, is painful and elicits a significant pain response.<sup>1,2</sup> This is substantiated in our study by the marked increase in PIPP scores during the eye examination, with 100% of patients receiving placebo having increases in PIPP scores  $\geq 4$  points above baseline. The physiologic importance of the painful reactions

is highlighted by the high rate of oxygen desaturation by  $\geq 10\%$  during and after the eye examination (Table 1).

Previously published experiences did not observe a beneficial effect of topical anesthetics in reducing this painful reaction.<sup>3,4</sup> Consequently, the use of topical anesthetic prior to the eye examination has been somewhat arbitrary and inconsistent. However, these reports are based on anecdotal experience and on a randomized trial comparing topical anesthetic or saline treatments using parallel but different patient populations, rather than a crossover design.<sup>3</sup> Our study used a blinded crossover approach in which patients functioned as their own control, thus increasing the statistical power to detect any differences. One theoretical issue in our design is that the infants may alter their sensitivity and reaction to painful stimuli, thus negating the proposed advantage of patients being their own control. However, in our study, as well as in prior studies,<sup>1,2</sup> no correlation was seen between markers of neonatal pain and stress and gestational age, making the issue of maturation altering pain response unlikely.

Because neonatal pain may present in many different ways, single markers of neonatal distress (eg, heart rate or blood pressure) are not as reliable as a pain score that reflects both physiologic and physical findings. We selected the PIPP scale as a measure of pain because it has been demonstrated to meet the standards of a good scale (ie, good inter-rater reliability, internal consistency, construct validity) and it was developed for premature infants.<sup>5-10</sup> The PIPP scale has also been used successfully in pain studies by other investigators.<sup>11-13</sup> With this scale, we found that pain, as defined by several different criteria, was significantly lower at lid speculum insertion with topical anesthetic than with saline eye drops, thus supporting the argument that topical anesthetic agents can reduce pain associated with neonatal eye examinations for ROP. Because the effects that we observed are not large, it is unlikely that they would be noticed in anecdotal observation. It is also apparent that not all patients benefit from this intervention.

## Conclusions

Our study supports a statistically and clinically significant benefit to using topical anesthetics during neonatal eye examinations for ROP. Although the number needed to treat may vary with pain definition, using the most widely accepted pain definition (ie, PIPP  $\geq 10$ ), 4.4 patients would need to receive topical proparacaine for one patient to benefit.

It is possible that patients may benefit from additional interventions. This study shows that preterm infants experience pain during eye examinations for ROP and that topical anesthetics should routinely be used.

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**Table 2.** Summary of Results Based on Different Definitions for Pain Response

Definition of Pain Response	One-Sided p Values for Placebo vs Anesthetic		
	Before Examination	At Wire Insertion	After Examination
Actual PIPP score	0.19, 0.41	0.001	0.09, 0.06
Increase in PIPP score by $\geq 4$ points above baseline score		0.13	0.50, 0.50
PIPP score $\geq 10$	NA, 0.69	0.03	0.25, 0.31
PIPP scores for placebo and anesthetic conditions differ by $\geq 4$ points	1.00, 0.50	0.03	0.06, 0.23
PIPP AUC	0.21		0.02

NA = not applicable; PIPP = Premature Infant Pain Profile.  
<sup>a</sup>p < 0.05 considered significant. The 2 p values in the Before Examination column apply, respectively, to the scores for 5-minutes and 1-minute pre-examination and the 2 p values in the After Examination column apply, respectively, to the scores for 1- and 5-minute post-examination, except for the AUC, which was calculated for the entire periods of time before and after examination.

**Table 3.** NNT to Expect One Patient to Benefit from the Anesthetic

Definition of Pain Response	Pts. with Less Pain with Anesthetic vs Placebo at Wire Insertion, n (%)	NNT
Actual PIPP score	17 (77)	1.3
Increase in PIPP score by $\geq 4$ points above baseline score	3 (14)	7.4
PIPP score $\geq 10$	5 (23)	4.4
PIPP scores for placebo and anesthetic conditions differ by $\geq 4$ points	9 (41)	2.4
PIPP AUC after lid speculum insertion	13 (59)	1.7

NNT = number needed to treat; PIPP = Premature Infant Pain Profile.

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## EXTRACTO

**INTRODUCCIÓN:** Los exámenes oculares de la retinopatía del prematuro (ROP) resultan estresantes y probablemente dolorosos para el recién nacido, pero muchos oftalmólogos no aplican anestésicos tópicos porque

diversos estudios no han conseguido establecer su eficacia en la reducción del dolor.

**OBJETIVO:** Este estudio se diseñó con el fin de evaluar los beneficios potenciales de los colirios anestésicos tópicos en la reducción del dolor durante el examen ocular de ROP en el neonato.

**MÉTODOS:** Se incluyeron neonatos nacidos con  $\leq 30$  semanas de gestación y a los que se les practicó al menos 2 exámenes de ROP. Se diseñó un estudio con asignación aleatoria, doble ciego, controlado con placebo, y cruzado, utilizando previamente al examen ocular bien solución oftálmica de clorhidrato de proparacaína al 0.5% o bien un colirio con un placebo de suero salino normal. En el examen subsiguiente, cada paciente recibió el tratamiento alterno. El colirio se preparó en la farmacia en jeringas de tuberculina similares y los médicos, enfermeras y farmacéuticos de la Unidad Neonatal de Cuidados Intensivos (NICU) desconocían el tratamiento administrado en cada caso. La medición del dolor se realizó mediante un sistema de puntuación que incluye la medición física y psicológica del dolor (escala PIPP [Premature Infant Pain Profile], rango posible = 1 a 21), que ha sido validado en prematuros. La puntuación del dolor (escala PIPP) se realizó simultáneamente por 2 enfermeras 1 y 5 minutos antes y después del examen ocular y durante la colocación inicial del espéculo ocular. Todos los exámenes oculares fueron realizados por el mismo oftalmólogo.

**RESULTADOS:** El estudio incluyó 22 pacientes, de los cuales 11 pacientes recibieron inicialmente como tratamiento proparacaína y otros 11 pacientes recibieron suero salino. El dolor fue significativamente inferior durante la colocación del espéculo en aquellos pacientes que recibieron proparacaína en vez de suero salino.

**CONCLUSIONES:** La premedicación con anestésicos tópicos reduce la respuesta al dolor en el examen ocular de retinopatía del prematuro y debería convertirse en una práctica habitual. Debido a que esta medida no es efectiva en todos los pacientes, deben llevarse a cabo medidas adicionales para la reducción del dolor.

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## RÉSUMÉ

**OBJECTIF:** Il semble que plusieurs ophtalmologistes n'appliquent aucun anesthésique topique lors d'un examen oculaire pour diagnostiquer une rétinopathie associée à la prématurité (RAP) puisque plusieurs études n'ont pas documenté l'efficacité d'un tel traitement. L'objectif de cette étude était d'évaluer si l'administration d'une solution anesthésique peut réduire la douleur durant l'examen oculaire chez les nouveaux-nés.

**MÉTHODOLOGIE:** Les nouveaux-nés d'un âge gestationnel de 30 semaines et moins, chez qui 2 examens oculaires pour une RAP étaient anticipés, ont été inclus dans cette étude à double-insu avec permutation et contrôlée par placebo. Les patients, assignés de façon aléatoire à une solution placebo saline ou à une solution ophtalmique d'hydrochlorure de proparacaïne 0.5%, recevaient le traitement avant le premier examen oculaire puis le traitement alternatif était administré durant l'examen oculaire subséquent. Les solutions oculaires étaient préparées par le département de pharmacie dans des seringues à tuberculine d'apparence identique. Les médecins, les pharmaciens, et les infirmières de l'unité néonatale n'étaient pas informés de la nature de la solution administrée. La douleur était mesurée par une échelle validée (Premature Infant Pain Profile) qui utilise des mesures physiologiques et physiques pour établir un score variant entre 1 et 21. Le score de la douleur était mesuré de façon simultanée par 2 infirmières 1 et 5 minutes avant l'examen oculaire et durant le placement initial du spéculum. Tous les examens oculaires étaient faits par le même ophtalmologiste.

**RESULTS:** Vingt-deux patients ont été recrutés pour cette étude. Une douleur moins intense a été notée lors de l'insertion du spéculum chez les patients ayant reçu la proparacaïne par rapport à la solution saline.

**CONCLUSIONS:** L'utilisation d'un anesthésique topique semble réduire la réponse douloureuse associée à un examen oculaire lors du diagnostic d'une RAP et devrait devenir une pratique courante lors de telles procédures. Toutefois, puisque ce traitement n'est pas efficace chez tous les patients, des mesures additionnelles pour contrôler la douleur devraient être utilisées.

Sylvie Robert