SCIENTIFIC REPORT

Double masked randomised controlled trial to assess the effectiveness of paracetamol in reducing pain in panretinal photocoagulation

D Vaideanu, P Taylor, P McAndrew, A Hildreth, J P Deady, D H Steel

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Aim: To assess the effectiveness of pre-emptive analgesia with paracetamol in reducing pain associated with panretinal photocoagulation (PRP) in a prospective, double masked, randomised controlled trial.

Method: 60 patients undergoing PRP for the first time were enrolled and randomised to paracetamol or placebo, taken for 2 days starting 24 hours before the laser treatment. The laser treatment was performed following a standardised protocol. Pain during and after treatment was assessed using the McGill pain questionnaire (MPQ) and visual analogue scales (VAS).

Results: The statistical analysis looked for differences between the two study groups immediately after the laser surgery and 24 hours later. There was no statistically significant difference in the primary outcome measure of perception of pain during and 24 hours after PRP, between the paracetamol and placebo group. However, none of the patients in the paracetamol group reported increased total pain at 24 hours, whereas six patients in the placebo group reported increased pain; this difference (21%) was significant to $p=0.01$.

Conclusions: Pre-emptive analgesia with paracetamol did not significantly reduce pain associated with PRP. This study has described for the first time the type of pain associated with PRP, which is perceived mainly as a discomfort. The main attributes of the pain that patients described, were sharp, flashing, tiring, intense, piercing, intermittent, and brief.

Diabetic retinopathy is the commonest cause of blindness in the working age group in United Kingdom.^{1,2} Panretinal photocoagulation (PRP) using argon laser has been shown to reduce the risk of blindness in patients with proliferative diabetic retinopathy by 50%.³ It has been recognised that most patients experience some degree of pain during and, to a lesser extent, after the laser treatment.⁴ This can range from mild to severe. In a few cases it can be intolerable necessitating the laser to be delivered either under general anaesthesia or with a local anaesthetic block. Both of these alternatives run the risk of further morbidity and even mortality.⁵

Oral analgesia is used on a variable basis just before and after laser in an attempt to reduce the severity of pain.

Pre-emptive analgesia uses the concept that sustained excitation of dorsal horn neurons may be eliminated or reduced if the afferent barrage is prevented or reduced from reaching the CNS by either pre-injury neural block with local anaesthetics or the use of other analgesics (for example,

opioids, non-steroidal anti-inflammatory drugs) before it receives a nociceptive input.^{6,7}

Paracetamol is a widely used and effective analgesic. Although the mechanism of action of paracetamol is still not clearly understood, its safety profile in therapeutic doses is well established.^{8,9} The use of paracetamol before painful stimuli as pre-emptive analgesia is known to enhance its effect.¹⁰ The quality of pain in PRP is undefined and the best analgesic to target the pain is unknown.

To our knowledge no studies have addressed the role of oral analgesia in pain relief during PRP. Our study addresses this question and also defines the type of pain in PRP.

METHOD

The study was a prospective double masked, randomised controlled trial. We compared the effectiveness of paracetamol versus placebo as pre-emptive analgesia in PRP in patients with diabetic retinopathy. The McGill pain questionnaire (MPQ) and visual analogue scales (VAS) were used to grade the pain.

Ethics committee approval was obtained and all participants gave informed consent.

Sequential patients with newly diagnosed proliferative diabetic retinopathy, attending medical retina clinics at Sunderland Eye Infirmary, were invited to participate in the study.

Exclusion criteria for the study were history of paracetamol sensitivity or allergy, severe liver disease, pregnancy, patients on regular analgesics, previous PRP, and age less than 18 years old.

Sixty patients were enrolled in the study. The patients were randomised to paracetamol or placebo via an electronic randomisation function (SPSS 12.1). The randomisation tables were sent to the pharmacist who allocated the patient a randomisation number and gave the patient the appropriate medication. The patients were instructed to take the medication every 6 hours, for 3 days, starting 1 day before the laser treatment. Non-compliant patients were excluded from the study. The participants, nursing staff, and medical staff were masked to the type of trial medication the patient received.

Two consultant ophthalmologists with an interest in retinal disease performed the laser treatment.

The treatment was standardised as follows: PRP, total of 1200 burns, 400 μ m spot size, duration of pulse 0.1 seconds, aiming for a moderately grey burn, avoiding the horizontal midlines, maximum treatment time of 30 minutes, mean treatment time 15 minute (as recommended by EDTRS).¹¹

Abbreviations: PPI, present pain intensity; PRI, pain rate index; PRI-T, total pain rate index; PRP, panretinal photocoagulation; MPQ, McGill pain questionnaire; VAS, visual analogue scale

MCGILL XLS

McGill Pain Questionnaire

Patient's Name _____ Date _____ Time _____ am/pm

PRI: S _____ A _____ E _____ M _____ PRI(T) _____ PPI _____

(1-10) (11-15) (16) (17-20) (1-20)

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Figure 1 MPQ administered to the patients included in trial.

Benoxinate drops 0.4% were used for topical anaesthesia, before contact lens use.

Pain was assessed at two points following the laser treatment:

- Immediately (within 15 minutes) after the laser treatment to evaluate the pain experienced during laser
- Twenty four hours after the laser treatment to evaluate pain experienced following the laser treatment.

The pain was assessed using, at both time points, two techniques.

Firstly, an MPQ was used. The MPQ was designed to enable the patient to specify both the quality and degree of pain experienced.¹² It is based on the observation that each type of pain is characterised by a distinctive constellation of words. It analyses four major aspects of pain: sensory (1–10), affective (11–15), evaluative (16), and miscellaneous (17–20) (fig 1). The pain rate index (PRI) is based on the rank values of the words. The word in each subclass implying the least pain is given a value of 1, the next word is given a value of 2, etc. The rank values of the words chosen by a patient are summed to obtain a score separately for the sensory, affective, evaluative, and miscellaneous words, in addition to providing a total score (subclass 1–20, which is PRI-T).¹² Present pain intensity (PPI) represents the number-word

combination chosen as the indicator of overall pain intensity at the time of administration of the questionnaire.¹² Secondly, a VAS, from 0 to 10 was used.

A nurse trained to guide the patient through the MPQ and VAS supervised the first assessment. The same nurse conducted a second pain assessment over the telephone, 24 hours after the first pain assessment.

The patients were provided with 30 mg codeine phosphate tablets to use in case of breakthrough pain.

Statistical analysis

The primary outcome of the study was the assessment of pain immediately after the laser treatment and at 24 hours after laser, as expressed by the total pain rate index (PRI-T). The secondary outcomes were: MPQ subgroup results analysis and VAS results analysis immediately after laser and analysis of pain at 24 hours after laser as assessed by both MPQ and VAS.

Statistical power was set at 80% (5% significance level) in order to detect a difference of 30% in reported pain (PRI-T) between paracetamol and placebo groups for the primary outcome.

The Mann-Whitney test for two independent samples was used to test between group differences, while the Wilcoxon matched pairs test was used to measure change over time within groups. Frequency data were examined via Fisher's

Figure 2 Consort flow chart for the study.

exact test for two proportions, with the addition of 95% (exact) confidence intervals where appropriate.

RESULTS

Sixty patients were recruited for the study. Four patients were excluded: two eligible patients decided not to participate after enrolment but before randomisation. Two further patients who were enrolled and randomised (one in each arm of the study) refused to take the study medication. Unfortunately, we were unable to collect data on them because they declined to complete the pain assessment. We therefore conducted an available case analysis rather than intent to treat analysis. Each arm of the study thus had 28 patients (fig 2). Forty one of the patients were male and 15 were female. Mean age was 51 years (median 42 years, range 24–79 years).

The statistical analysis looked for differences between the two study groups immediately after the laser surgery and at 24 hours after laser. The total pain rate index (PRI-T), the PPI (present pain intensity), as well as the individual subgroups and VAS were examined. All data distributions were non-normally distributed within and between the study groups, as confirmed via the Shapiro-Wilk distributional test. Results are presented in table 1.

There were no statistically significant differences observed between the paracetamol and placebo group for any of the items studied. Subset analysis failed to demonstrate a sex difference.

Figures 3 and 4 illustrate the distribution of the PRI-T scores in the two study groups via box-and-whisker plots, immediately after laser (fig 3) and at 24 hours after laser (fig 4).

None of the patients in the paracetamol group reported increased total pain (PRI-T) at 24 hours, whereas six patients in the placebo group reported increased pain. This difference (21%) was significant to $p=0.01$, and a 95% confidence interval for the difference runs from 6.5% to 41.0%. More patients in the paracetamol group reported reduced pain at 24 hours after laser for the sensory, affective, and evaluatory types of pain; however, these were not statistically significant (table 2).

Correlation between the PRI-T and VAS was moderate for the first questionnaire (Spearman's $R=0.49$, $p<0.001$) and good for the second questionnaire (0.80, $p<0.001$).

After laser treatment, 8/56 patients had to take breakthrough pain medication. Of these, 2/28 (15%) were in the paracetamol group and 6/28 (85%) in the placebo group, ($p<0.13$).

The MPQ was designed as a tool to reproducibly differentiate various pain syndromes.¹²

By analysing the words the patients participating in this trial used to describe their pain during the laser treatment, we were able to characterise the pain in PRP.

The pain descriptors that are most characteristic of the pain associated with PRP in our study group were sensory: sharp (50%), flashing (41%), pricking (40%); affective: tiring

Table 1 Summary table of pain scores

	Paracetamol	Placebo	p Value
PRI-T immediately after laser			
Mean	23.8	24.8	0.92
Median	21	21	
SD	14.2	15.2	
Range	(2–49)	(4–55)	
PRI-T 24 hours after laser			
Mean	7.7	12	0.91
Median	3	2	
SD	10.2	16.4	
Range	(0–38)	(0–55)	
VAS immediately after laser			
Mean	4	5.2	0.11
Median	3.5	5	
SD	2.3	2.7	
Range	(0–8)	(1–10)	
VAS 24 hours after laser			
Mean	2.4	2.7	0.92
Median	2	2	
SD	2.2	2.6	
Range	(0–8)	(0–10)	
PPI immediately after laser			
Mean	1.9	2.4	0.16
Median	2	2	
SD	0.9	1	
Range	(0–4)	(1–5)	
PPI 24 hours after laser			
Mean	1	1.1	0.69
Median	0.5	1	
SD	1.2	1.3	
Range	(0–4)	(0–5)	

(38%), blinding (29%), evaluative: intense (23%), annoying (21%); miscellaneous: piercing (33%), nagging (26%).

DISCUSSION

Our study evaluated the analgesic effect of pre-emptive analgesia with paracetamol during and after PRP and describes the characteristics of pain patients experience during the laser treatment.

Pre-emptive analgesia aims to attenuate the severity of pain from starting by blocking the nervous system's usual response to pain. By preventing the sensitising reaction to surgical treatment, the postoperative pain may be reduced.¹³ However, reviews of trials assessing pre-emptive analgesia in the treatment of postoperative pain show that the results are variable.^{7–14} We chose a dosage regimen to maximise the analgesic action of paracetamol during and after laser treatment, as suggested in literature.^{8–9}

The pain perception is a personal experience to each individual. Many factors can influence the perception of pain

including sex difference, cultural differences, past experiences, and anxiety levels. The MPQ provides us with an insight into the qualities of pain that are experienced and we therefore chose this tool to evaluate the pain associated with PRP.

Studies to evaluate the best analgesic in PRP are limited.^{15–18} This study can be used as a useful baseline for future, larger studies to target pain associated with PRP with specific analgesic agent. Furthermore an important observation in this study was the description of the quality and type of pain patients experience during PRP using the MPQ. It was perceived mainly as a discomfort, and the main attributes patients awarded to this pain were sharp, flashing, tiring, intense, piercing, intermittent, and brief.

The occurrence of pain in PRP may be influenced by many parameters. In an attempt to try and reduce the pain during PRP, the laser operative can alter some laser parameters—for example, shorter duration, lower intensity. In this study we standardised the laser parameters as much as possible to try to keep the pain stimulus as constant as possible.

Figure 3 Box plots showing the distribution of PRI-T scores in both groups, immediately after laser.

Figure 4 Box plots showing the distribution of PRI-T scores in the both groups, 24 hours after laser.

Table 2 Relative reduction in pain at 24 after laser treatment

Item	Patients with reduced pain taking paracetamol	Patients with reduced pain taking placebo	p Value (χ^2)
Total score	100%	78.6%	0.01
Sensory	92.9%	78.6%	0.13
Affective	53.6%	46.4%	0.59
Evaluatory	35.7%	32.1%	0.78
Miscellaneous	60.7%	60.7%	1.0

CONCLUSION

This study did not show any statistically significant difference in the perception of pain during PRP between the paracetamol and placebo group. One reason for not showing any statistical significant difference between the two study groups may be that the sample size was insufficient in relation to the actual degree of difference in the population, and therefore a larger study would be needed to demonstrate a statistically significant difference of a smaller magnitude. As can be seen in the results the experience of pain during PRP is a very variable experience between patients. It may also be the case that the concept of pre-emptive analgesia needs revisiting, as the various trial results are variable.⁷⁻¹⁴ Two patients (one patient in each arm of the study) refused to take the study medication after randomisation and both declined to complete the pain assessments. We were thus unable to carry out an "intent to treat" analysis and had to use the weaker methodology of an available case analysis.

When comparing the amount of pain at 24 hours after laser treatment, more patients in the paracetamol group reported a reduction in pain compared to the placebo group. Also, only 2/28 patients in the paracetamol group took breakthrough pain medication compared with 6/28 in the placebo group. The study was not designed to look for a difference in this outcome and it needs to be interpreted with caution. It is however an interesting result and perhaps deserves further investigation.

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REFERENCES

- 1 **British Diabetic Association/Department of Health.** *St Vincent Joint Task Force for Diabetes: report of the Visual Impairment Subgroup.* London: British Diabetic Association/Department of Health, 1994.
- 2 **Kohner EM, Stratton IM, Aldington SJ.** Prevalence of diabetic retinopathy at diagnosis of NIDDM in the UKPDS. *Invest Ophthalmol and Vis Sci* 1993;**34**:713.
- 3 **Diabetic Retinopathy Study Research Group.** Preliminary report on the effects of photocoagulation therapy. *Am J Ophthalmol* 1976;**81**:383-96.
- 4 **Tamai M, Mizuno K.** Distribution of intra- and extraocular pain induced by argon laser photocoagulation. *Tahoku J Exp Med* 1984;**142**:427-35.
- 5 **Kallio H, Puska P, Summanen P, et al.** Retrobulbar/peribulbar block with 0.2% ropivacaine or 1% lidocaine for transcleral cyclophotocoagulation or retinal pan-photocoagulation. *Reg Anaesth Pain Med* 1999;**24**:342-6.
- 6 **Wall PD.** The prevention of postoperative pain. *Pain* 1988;**33**:289-90.
- 7 **Dahl JB, Kehlet H.** The value of pre-emptive analgesia in the treatment of post-operative pain. *Br J Anaesth* 1993;**70**:434-9.
- 8 **Ward B, Alexander-Williams MJ.** Paracetamol revisited: a review of the pharmacokinetics and Pharmacodynamics. *Acute Pain* 1999;**2**:139-49.
- 9 **Bonnefont J, Courade JP, Alloui A, et al.** Antinociceptive mechanism of action of paracetamol. *Drugs* 2003;**63**(Spec No 2):1-4.
- 10 **Moore A, Collins S, Carroll D, et al.** Paracetamol with and without codeine in acute pain: a quantitative systematic review. *Pain* 1997;**70**:193-201.
- 11 **Early Treatment Diabetic Retinopathy Study Research Group.** Early photocoagulation for diabetic retinopathy. EDTRS report number 9. *Ophthalmol* 1991;**98**(suppl):766-85.
- 12 **Melzack R.** The McGill Pain Questionnaire: major properties and scoring methods. *Pain* 1975;**1**:277-99.
- 13 **Woolf CJ, Chong MS.** Preemptive analgesia—treating post-operative pain by preventing the establishment of central sensitization. *Anesth Analg* 1993;**77**:362-79.
- 14 **McQuay HJ.** Pre-emptive analgesia: a systematic review of clinical studies. *Ann Med* 1995;**27**:249-56.
- 15 **Whitacre MM.** The effect of transcutaneous electrical nerve stimulation on ocular pain. *Ophthalmic Surg* 1991;**22**:462-6.
- 16 **Richardson C, Hollinghurst A.** the use of entonox for pain relief during argon laser therapy for proliferative diabetic retinopathy. *Ophthalmic Nurs* 1999;**3**:16-18.
- 17 **Cook HL, Newsom RSB, Mensah E, et al.** Entonox as an analgesic agent during panretinal photocoagulation. *Br J Ophthalmol* 2002;**86**:1107-8.
- 18 **Weinberger D, Ron Y, Lichter H, et al.** Analgesic effect of topical diclofenac 0.1% drops during retinal laser photocoagulation. *Br J Ophthalmol* 2000;**84**:135-7.