

SCIENTIFIC CORRESPONDENCE

Entonox as an analgesic agent during panretinal photocoagulation

H L Cook, R S B Newsom, E Mensah, M Saeed, D James, T J ffytche

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Background/aims: Panretinal photocoagulation (PRP) reduces the risk of visual loss in proliferative diabetic retinopathy but some patients cannot tolerate PRP because of pain. Inhaled Entonox was evaluated as an analgesic during PRP.

Methods: A randomised, crossover, double masked pilot study was performed. Patients inhaled either air or Entonox and half the PRP was applied. The treatment was completed with the alternate inhaled gas. Patients graded pain experienced during both stages of the treatment using a visual analogue scale. Pain scores were compared using a paired *t* test.

Results: 20 patients participated. Mean pain scores from the Entonox and air treatments were 2.94 (SD 2.73) versus 3.73 (SD 3.20) respectively ($p < 0.03$).

Conclusion: Entonox can be used as a safe and effective analgesic agent during PRP treatment.

The World Health Organization (WHO) recently reported that 2.2% of the UK population have diabetes mellitus.¹ Furthermore, the prevalence of diabetes is predicted to double by the year 2010.¹ The annual incidence of new cases of proliferative diabetic retinopathy (PDR) is 2.7–4% for patients with type 1 diabetes and 0.6–3.2% for those with type 2 diabetes.² Untreated high risk characteristic PDR results in a 33% risk of severe visual loss at 3 years.³ The risk of severe visual loss, however, is reduced by 50% by adequate laser PRP.³

The Diabetic Retinopathy Study (DRS) recommended that between 800 and 1600 argon laser burns of 500 μm size should be applied to the peripheral retina in a scatter fashion.³ However, a recent study found that 64.1% of eyes treated received less than the DRS recommendation treatment.⁴ Therefore, a large number of diabetic patients with PDR are being undertreated, with a consequent risk of significant visual loss. A possible reason for this undertreatment is patient intolerance because of pain. We therefore describe the use of a new analgesic method for PRP treatment, inhaled Entonox.

METHODS

A randomised, crossover, double masked study was performed to evaluate the efficacy of Entonox as an analgesic agent during PRP treatment. All patients undergoing PRP were eligible for inclusion. Ethics committee permission was obtained and all patients gave informed consent.

Entonox was administered through a disposable mouthpiece attached to a portable Entonox cylinder via a one way demand valve system. The patients were randomised to two groups. Group 1 received Entonox for the first half of the treatment (approximately 500 burns) and air for the second half (approximately 500 burns). Group 2 received air for the first half of the treatment and Entonox for the second half.

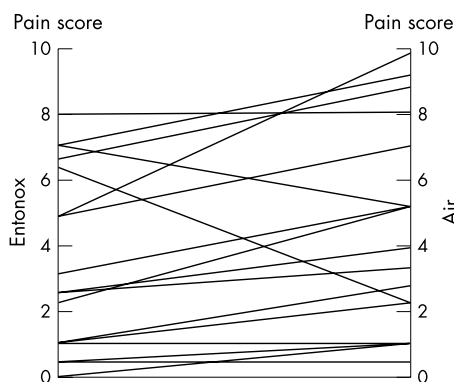


Figure 1 Graphic representation of pain scores (scale 0–10) obtained for all patients during the two halves of panretinal photocoagulation treatment. Each line represents one patient and shows the difference in the pain scores obtained during the two phases of treatment with Entonox and air. Note that patients in groups 1 and 2 are combined, so that this graph does not represent the order of treatment.

Treatment was performed using a slit lamp mounted argon green laser with topical amethocaine and a panretinal contact lens. Both the patient and the surgeon were masked to the type of gas being administered. There was a 2 minute washout period after half the total planned treatment had been applied, during which the patient completed a visual analogue score chart to indicate the extent of pain experienced during the preceding treatment. A score of 0 represented no pain and a score of 10 represented the worst pain imaginable by the patient. Treatment was then completed using the alternative inhaled gas, and a further visual analogue score was completed at the end of treatment. Pain scores were compared using paired *t* tests.

RESULTS

Twenty patients participated in the study, 11 in group 1 and nine in group 2. Patients tolerated the administration of Entonox and air via the mouthpiece well and there were no adverse effects.

There were a range of analgesic responses to both the Entonox and the placebo; however, the majority of patients experienced less pain with Entonox administration (Fig 1). The mean pain score for Entonox was 2.94 (SD 2.73) and for air 3.73 (SD 3.20) ($p = 0.03$). The mean pain scores for group 1 were 2.5 (SD 2.75) for the initial half of the treatment with Entonox and 3.89 (SD 3.86) for the second half of the treatment with air ($p = 0.008$). The mean pain scores for group 2 were 3.52 (SD 2.39) for the initial half of the treatment with air and 3.46 (SD 2.76) for the second half of the treatment with Entonox ($p > 0.5$).

DISCUSSION

Pain experienced during PRP is very variable but appears to be more common with retreatment and with treatment applied

anterior to the equator, especially in the 3, 6, 9, and 12 o'clock positions (corresponding to the location of the long ciliary nerves).⁵ We found a mean pain score of 3.73 on placebo for PRP treatment. This confirms that PRP is a painful ophthalmic procedure. Weinberger⁶ previously found a mean pain score of 5.3 in his PRP control group (compared to pain scores of 1.46 for cataract surgery⁷ and 1.73 for vitreoretinal surgery⁸). Some patients respond to pretreatment oral analgesia; however, others require local anaesthetic blockade or even general anaesthesia in order to tolerate treatment. These forms of anaesthesia carry the risk of side effects and require additional monitoring of the patient.⁹⁻¹⁰ There is also a small risk of ocular perforation with sharp needle techniques.¹¹⁻¹³ This study therefore evaluated a new analgesic technique for PRP treatment.

Entonox is a mixture of 50% nitrous oxide and 50% oxygen. Inhalation produces an analgesic effect without loss of consciousness.¹⁴ Self administration of Entonox as an analgesic has been widely used for many years, particularly in obstetric practice¹⁵ and by paramedics for prehospital care.¹⁶ Entonox has a good safety record, with no serious side effects recorded for intermittent use,¹⁴ and is rapidly cleared from the circulation by exhalation.¹⁷ There were no adverse effects during this study. It is unlikely that occupational safety limits for Entonox exposure would be exceeded if Entonox analgesia was used only in selected cases.¹⁸ However, it would be good practice to ensure adequate ventilation of the treatment room between cases and consider the introduction of scavenging equipment if large numbers of patients were to be treated consecutively.

The perception of pain is a unique experience to an individual. Many factors influence perception of pain, including age, sex, cultural differences, past experience, and anxiety levels. It is therefore notoriously difficult to compare analgesic effect and pain perception across a group of patients. Our study attempted to overcome this problem by performing a crossover study, whereby the same individual evaluated a change in acute pain perception at two stages in the same treatment.

Our study found that inhaled Entonox was an effective analgesic for PRP treatment when compared to a placebo (air). However, a statistical difference in analgesic effect may not be clinically significant. Attempts have been made to evaluate the minimum clinically significant difference (MCSD) in visual analogue pain scores for acute pain.¹⁹⁻²⁰ These studies found that the MCSD is in the region of 10 mm—that is, 1.0, for acute pain in an accident and emergency setting. We found a difference of 1.39 (13.9 mm) for the two halves of treatment in group 1—that is, Entonox followed by placebo, which achieves the MCSD quoted. However, the type of pain perceived by patients in our study may not be directly comparable to the acute pain evaluated in these studies. Furthermore, our study was a small pilot study and larger studies would be required to evaluate this more fully.

In our study, there was a greater analgesic effect when Entonox was administered from commencement of PRP treatment—that is, patients in group 1. Overall, only two patients experienced more pain while using Entonox. Both these patients were in group 2—that is, patients using air for the first half of the treatment and Entonox for the second half of the treatment. These findings can be explained by the pre-emptive analgesia theory that suggests that analgesic agents administered before the onset of pain prevent perception of pain by the patient.²¹ The same theory suggests that once pain is experienced subsequent administration of analgesia will be less effective due to both local hyperalgesia and central pain centre sensitisation ("wind up").²¹

Pre-emptive analgesic mechanisms of action remain poorly understood. However, from our study it would appear that Entonox should be administered at commencement of

treatment in order to have a maximal analgesic effect during PRP treatment. Inhaled Entonox is a useful addition to the current methods available to facilitate adequate PRP treatment in selected patients who have a greater pain perception—that is, younger patients and those undergoing retreatment, who have previously not been able to tolerate the full planned treatment because of pain and this could hence help reduce the risk of visual loss in diabetic patients.

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